Holistic Integrative Oncology

GUIDELINE

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CACA guidelines for holistic integrative management of prostate cancer

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Abstract

Prostate cancer (PC) is an epithelial malignancy occurring in the prostate. PC ranks second in incidence among all male malignancies globally by the latest statistics from the World Health Organization. Notably, China has seen a more rapid increase in PC incidence compared to developed European and American nations. By 2022, the newly reported cases and deaths due to PC in China increased to 134,200 and 47,500, respectively. Thus, early diagnosis and standardized treatment for prostate cancer in China remain far-reaching objectives. Burgeoning research on advanced PC and castration-resistant prostate cancer in recent years have paved the way for a new era of integrated treatment methods including novel endocrine drugs, chemotherapy, targeted therapy, and immunotherapy. Future therapies involve precision treatment guided by genetic testing and individualized integrated treatment as part of a multidisciplinary integrated diagnosis and treatment model for PC. The Genitourinary Oncology Committee of the China Anti-Cancer Association (CACA-GU) has invited multidisciplinary experts across fields including surgery, oncology, pathology, radiology, herbal medicine, physiatry, and psychology to collaboratively write, discuss, and revise guidelines on managing PC. The CACA Guidelines for Holistic Integrative Management of Prostate Cancer includes epidemiology, screening and diagnosis, treatment for localized PC, diagnosis and treatment of PC recurrence after radical prostatectomy, management of metastatic PC, traditional Chinese medicine diagnosis and treatment of PC, and rehabilitation from PC. This guideline aims to standardize the clinical diagnosis and treatment management of PC in China. It is more aligned with China's clinical practice, highlights Chinese characteristics, and bears significant clinical importance.

Keywords Prostate cancer, Clinical guideline, Holistic integrative medicine

1 Epidemiology

Prostate cancer (PC) refers to an epithelial malignancy occurring in the prostate. According to the 2018 GLOBOCAN statistics by the World Health Organization (WHO), PC ranks second in incidence among all male malignancies worldwide. The incidence of PC in China is much lower than that in European and American countries, but it has shown an upward trend in recent years, with a more rapid growth rate than in developed European and American countries. It is estimated that there were 72,000 new cases and approximately 30,700 deaths from PC in China in 2015 [1]. By 2022, the number of new cases and deaths from PC in China had increased to 134,200 and 47,500 respectively [2]. Early diagnosis and standardized treatment of PC still have a long way to go in China.

PC has a very high incidence among elderly males. The incidence of this disease is relatively low before the age

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of 50, and gradually increases with age, with 80% of cases occurring in males over 65 years old. There is a significant difference in the staging composition of PC patients between China and developed Western countries. Taking the United States as an example, nearly 91% of newly diagnosed PC cases there are clinically localized, with radical surgery or radical radiotherapy as the first-line treatment. These patients have a good prognosis after receiving standard treatment, with a 5-year overall survival (OS) rate close to 100%. However, only 30% of newly diagnosed cases in China are clinically localized, while the rest are locally advanced or metastatic patients who cannot receive local radical treatment and have a poor prognosis [3].

Early-stage PC can achieve good outcomes, even cure, through radical surgery or radical radiotherapy. Due to the slow growth of the tumor itself, some low-risk, elderly patients can also choose active monitoring based on specific circumstances and receive further treatment when the disease progresses. For locally advanced and metastatic PC, androgen deprivation therapy is generally selected to prolong survival and improve quality of life; some patients may choose surgical resection or multimodality integrated treatment based on radiotherapy. In recent years, with the deep research on advanced PC and castration-resistant PC, a new era has been opened up with integrated treatment modes such as novel endocrine drugs, chemotherapy, targeted therapy, and immunotherapy. Precision treatment guided by genetic testing and individualized integrated treatment under a multidisciplinary integrated diagnosis and treatment model point to the future direction for PC [4, 5].

2 Screening and diagnosis of PC

2.1 PC screening

Before performing prostate-specific antigen (PSA) screening in male populations, potential risks and benefits should be disclosed.

Class I Recommendation	Class II Recommendation
Men > 50 years old should undergo PSA follow-up every 2 years. Men > 45 years old with a family history of PC (either paternal or maternal) should undergo PSA follow-up every 2 years. Men > 40 years old with PSA > 1 ng/mL should undergo PSA follow-up every 2 years. Men > 40 years old carrying the BRCA2 gene mutation should undergo PSA follow-up every 2 years. [b]	Men < 40 years old with PSA > 1 ng/mL are recommended to undergo PSA follow-up every 2 years. [a] Men < 60 years old with PSA > 2 ng/mL are recommended to undergo PSA follow-up every 2 years.[a]

Note: a. For men without risk factors, the interval between PSA follow-ups can be extended to 8 years [4].

b. Some domestic scholars have pointed out that the proportion of germline mutations in DNA damage repair genes among Chinese patients is 9.8%, with BRCA2 accounting for 6.3% of these mutations [6]. Among these genes, germline mutations in BRCA2, ATM, MSH2, and PALB2 are significantly associated with the risk of prostate cancer [7].

2.2 Symptoms of PC

Urinary Obstruction Symptoms [a]	Voiding Difficulties, Urinary Hesitancy, Weak Urinary Stream, Intermittent Urination, Urinary Retention
Lower Urinary Tract Irritative Symptoms	Frequent Urination, Urgency, Nocturia, Urge Incontinence
Local Invasive Symptoms [b]	Testicular Pain, Ejaculatory Pain, Hematuria, Renal Function Decline, Back Pain, Hematospermia, Erectile Dysfunction
Systemic Symptoms [c]	Bone Pain, Pathological Fractures, Paraplegia, Anemia, Lower Extremity Edema, Retroperitoneal Fibrosis, Paraneoplastic Syndrome, Disseminated Intravascular

Note: a. Invasion of the urethra or bladder neck may cause obstructive symptoms, such as dysuria manifested as hesitancy, weak stream, intermittent flow and even urinary retention. A tumor that obviously compresses the rectum may cause difficulty in defecation or ileus.

b. Tumor invasion and compression of the vas deferens may cause testicular pain and ejaculatory pain on the affected side; invasion of the bladder may cause hematuria; invasion of the trigone of the bladder, such as the openings of the bilateral ureters, may cause renal dysfunction and lumbar soreness; local invasion of the vas deferens may cause hemospermia; erectile dysfunction will occur when the tumor breaks through the prostatic fibrous capsule and invades the pelvic plexus branch that dominates the cavernous body of the penis.

c. PC is prone to bone metastasis, causing bone pain or pathological fracture and paraplegia; PC may invade bone marrow and cause anemia or pancytopenia; tumor compression of the iliac vein or pelvic lymph node metastasis can cause double lower limb edema. Other rare clinical findings include retroperitoneal fibrosis due to lymphatic spread of tumor cells along the ureter, paraneoplastic syndrome due to ectopic hormone secretion, and disseminated intravascular coagulation.

2.3 Diagnostic methods for PC

Class I Recommendation	Class II Recommendation	Class III Recommendation
Prostate-Specific Antigen (PSA)[a]	Digital Rectal Examination (DRE)	p2PSA and PHI Index[c]
Prostate Biopsy[b]	Transrectal Ultrasound (TRUS)	PCA3[d]
Prostate Magnetic Resonance Imaging (MRI)		4K Score[e]
		ConfirmeMDX[f]

Note: a. PSA is organ-specific, not tumor-specific. Elevations in PSA can also occur in benign prostatic hyperplasia (BPH), prostatitis, and other non-malignant prostate conditions. As an independent variable, PSA offers a better predictive indicator of the disease compared to digital rectal examination (DRE) and transrectal ultrasonography (TRUS). PSA levels can be influenced by various factors, such as DRE, prostate biopsy, and administration of finasteride (which typically halves PSA levels).

b. The decision for prostate biopsy should be based on PSA levels and/or suspicious findings from DRE and/or imaging studies, with consideration given to age, underlying comorbidities, and treatment response. Ultrasound-guided transrectal or transperineal biopsy is the standard approach. For baseline biopsy in patients with smaller prostate volumes, a minimum of eight-core systematic biopsy is recommended, while for larger prostates, 10 to 12 cores are advised. In repeat biopsies, saturation biopsy (with more than 20 needle cores) can enhance the detection rate of PC.

MRI-TRUS fusion targeted biopsy represents a novel technology in prostate biopsy, integrating multiparametric MRI (mpMRI) with transrectal ultrasound imaging (TRUS). This technique targets suspicious lesions for biopsy, thereby enhancing the detection rate of clinically significant prostate cancer (PC) while reducing the identification of clinically insignificant, low-risk PC. MRI-TRUS fusion targeted biopsy can be categorized into three types: cognitive fusion biopsy, software fusion, and MR-directed biopsy.

Cognitive Fusion Biopsy: This method involves a preliminary mpMRI scan, where the surgeon identifies suspicious lesions or regions of interest based on the MRI images. Subsequently, under conventional ultrasound guidance, targeted biopsy is performed on the corresponding suspicious lesions or regions on the TRUS images.

Software Fusion: In this approach, the mpMRI scan is performed prior to the biopsy, and the MRI images are imported into specialized software. The target region and prostate contour are outlined, and the corresponding images in TRUS and MRI are matched and locked. This allows the suspicious target area highlighted by MRI and the prostate image to change in real-time as the ultrasound probe moves, facilitating targeted biopsy.

MR-Directed Biopsy: This technique requires the use of specific biopsy needles and multiple real-time MRI scans during the biopsy procedure to precisely locate the biopsy needle relative to the suspicious lesion.

Current research indicates that cognitive fusion and software fusion targeted biopsies do not significantly differ in terms of biopsy positivity rates. However, cognitive fusion biopsy necessitates a more experienced operator. In practical prostate biopsy procedures, a combined approach of targeted and systematic biopsy can further improve biopsy accuracy [8–10].

c. p2PSA is a truncated isoform of PSA precursors, which is the most stable and has the highest tumor specificity among the isoforms. The Prostate Health Index (PHI) is a multi-factor integrated model parameter that incorporates serum PSA, fPSA, and p2PSA concentrations. Its clinical application has been approved by regulatory agencies such as the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and the China Food and Drug Administration (CFDA). Multiple studies, both domestic and international, have reached a consensus that PHI demonstrates better diagnostic performance for PC compared to PSA and %fPSA. Specifically, for individuals over 50 years old with a negative digital rectal examination (DRE) and a PSA level of 4–10 ng/mL, PHI exhibits superior efficacy in increasing the positive rate of prostate biopsy and predicting high-grade PC [10, 11]. Additionally, some studies suggest that PHI density may also offer advantages over PSA density in diagnosing clinically significant prostate cancer [12].

d. PCA3, or Prostate Cancer Antigen 3, is a non-coding messenger RNA (mRNA) fragment located on chromosome 9 (9q21-22). Large-scale retrospective clinical studies of prostate biopsies have shown that PCA3 has good positive (48%-75%) and negative (74–90%) predictive values [13].

e. The 4Kscore is an indicator that integrates total PSA, free PSA, intact PSA, and hK2 [14].

f. The ConfirmeMDX test is based on the concept that benign prostate tissue adjacent to PC lesions exhibits unique epigenetic changes. It quantifies the methylation levels of the promoter regions of three genes—APC, RASSF1, and GSTP1—in benign prostate tissue. If PC is missed during biopsy, the epigenetic changes in benign tissue may indicate the presence of the tumor [15].

2.4 Prostate biopsy

Indications for Initial Prostate Biopsy
Suspicious nodule detected on Digital Rectal Examination (DRE) regardless of PSA value
Suspicious lesion detected on Transrectal Ultrasound (TRUS) or Magnetic Resonance Imaging (MRI) regardless of PSA value
PSA value > 4 ng/ml

Procedure for Prostate Biopsy	
Pre-biopsy Examination[a]	Class I Recommendation
Transrectal/transperineal biopsy under antibiotic protection[b]	Class I Recommendation
Local infiltration anesthesia around the prostate[c]	Class I Recommendation
Use of anticoagulants and antiplatelet drugs during the perioperative period [d]	Class I Recommendation
Initial biopsy with 10–12 core systematic/targeted biopsy via transrectal/transperineal approach[e]	Class I Recommendation

Note: a. mpMRI improves the detection rate of clinically significant prostate cancer (csPC). If mpMRI is positive, MRI-guided targeted prostate biopsy (MRI-TBx) should be included in the systematic prostate biopsy. If mpMRI is negative, systematic prostate biopsy can be performed.

b. Antibiotic prophylaxis (oral or intravenous) is recommended before the biopsy. Quinolones are the first choice, with ciprofloxacin preferred over ofloxacin. Antibiotic selection should consider drug resistance.

c. For transperineal biopsy, ultrasound-guided periprostatic nerve block is recommended. For transrectal biopsy, local anesthesia can be administered through rectal instillation.

d. For patients with cardiovascular or cerebrovascular disease risk, history of stent implantation, or long-term use of anticoagulants or antiplatelet drugs, comprehensive assessment of bleeding risk and cardiovascular/cerebrovascular risk is necessary during the perioperative period, and decisions regarding the use of these medications should be made carefully.

e. For baseline biopsy, a minimum of 8 core systematic biopsy is recommended for prostates smaller than 30 ml. For larger prostates, 10–12 core systematic biopsy is recommended. Increasing the number of biopsy cores does not significantly increase the complication rate. Recent studies have confirmed that MRI-guided fusion targeted biopsy improves the detection rate of clinically significant PC (by 12%) and reduces the detection rate of clinically insignificant low-risk PC (by 13%), therefore, MRI examination and MRI-guided targeted prostate biopsy are encouraged before initial biopsy.

Indications for Repeat Prostate Biopsy[a]
Non-atypical hyperplasia or high-grade prostatic intraepithelial neoplasia (PIN) identified on initial biopsy pathology
PSA > 10 ng/ml on repeat testing, regardless of f/t PSA and PSAD values
PSA 4–10 ng/ml on repeat testing, with abnormal f/t PSA, PSAD values, DRE, or imaging findings[b]
PSA 4–10 ng/ml on repeat testing, with normal f/t PSA, PSAD values, DRE, and imaging findings[c, d,e]

Note: a. MRI-TBx (MRI-guided targeted biopsy) is the preferred method for repeat biopsy.

b. If TRUS or MRI suggests suspicious lesions (e.g., PI-RADS > 3), mpMRI examination is recommended. MRI-guided targeted biopsy based on mpMRI can significantly improve the positive rate of repeat biopsy and avoid missed diagnoses.

c. PSA should be reviewed every 3 months. Repeat biopsy is indicated if PSA is > 10 ng/ml for two consecutive tests or PSAV > 0.75 ng/ml.

d. The f/t PSA ratio still has some predictive value in the lower PSA range [16].

e. Some domestic scholars suggest that combining PSAD and PI-RADS results can assist in the selection of biopsy method [17].

2.5 Pathological evaluation of PC

2.5.1 Gleason scoring system[a]

Grade	Histological Features
1	Well-formed glands arranged in compact but separate nodules with distinct borders
2	Nodules with microscopic infiltration into surrounding normal tissue, glands arranged loosely with more than grade 1 atypia
3	Varying sizes of glandular elements with irregular shapes, distinct infiltrating growth pattern, but each gland remains independent with clear lumens
4	Glands fused to form cribriform patterns or arranged in rings without central lumens
5	Poorly differentiated carcinoma with no distinct gland formation, arranged in solid nests or single and double cell cords

Note: a. The Gleason scoring system is recommended for the pathological grading of prostate adenocarcinoma. The PC tissue is divided into primary and secondary grading areas, each scored on a scale of 1 to 5. The total Gleason score, obtained by adding the scores of the two areas, represents the degree of differentiation.

PC Grading Groups System[a]

Grading Groups System	
Grading Group 1	Gleason score ≤ 6, composed solely of individually separated, well-formed glands
Grading Group 2	Gleason score 3 + 4 = 7, primarily well-formed glands with fewer poorly formed glands/fused glands/cribriform glands
Grading Group 3	Gleason score 4 + 3 = 7, primarily poorly formed glands/fused glands/cribriform glands with a few well-formed glands
Grading Group 4	Gleason score 4 + 4 = 8; 3 + 5 = 8; 5 + 3 = 8, composed solely of poorly formed glands/fused glands/cribriform glands; or predominantly well-formed glands with a few non-glandular differentiation components; or predominantly non-glandular differentiation components with a few well-formed glands[b]
Grading Group 5	Gleason score 5 + 5 = 10; 5 + 4 = 9; 4 + 5 = 9, lack of glandular formation (with or without necrosis), with or without poorly formed glands/fused glands/cribriform glands[c]

Note: a. In 2014 and 2019, the International Society of Urological Pathology (ISUP) proposed a new grading system called the PC Grading Groups system, which classifies PC into five distinct groups based on the Gleason total score and disease risk [4].

b. Composed of even fewer poorly formed glands/fused glands/cribriform glands.

c. For more than 95% poorly formed glands/fused glands/cribriform glands, or lack of glandular formation in biopsy or RP specimens, with less than 5% well-formed glands, these factors are not considered in grading.

2.6 Staging of PC

2.6.1 PC TNM staging system [a, b]

Primary Tumor (T) [c]			
Clinical		**Pathological**	**(pT) [d]**
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Clinically occult tumor not palpable or visible on imaging		
	Incidental tumor in ≤ 5% of resected tissue		
	Incidental tumor in > 5% of resected tissue		
	Tumor demonstrated by needle biopsy (e.g., due to elevated PSA), involving one or both lobes, but not palpable		
T2	Tumor palpable, confined within the prostate	pT2	confined within the prostate
	T2a Tumor involves ≤ 1/2 of one lobe		
	T2b Tumor involves > 1/2 of one lobe but remains within that lobe		
	T2c Tumor involves both lobes		
T3	Tumor extends through the prostatic capsule but is not fixed or involves adjacent structures	pT3	Tumor extends through the prostatic capsule
	T3a Extension through the prostatic capsule (unilateral or bilateral)		pT3a Prostatic invasion (unilateral or bilateral) or microscopic invasion of the bladder neck
	T3b Tumor involves the seminal vesicles (unilateral or bilateral)		pT3b Tumor involves the seminal vesicles
T4	Tumor is fixed or involves other adjacent structures other than seminal vesicles: e.g., external sphincter, rectum, bladder, levator ani muscle, and/or pelvic wall	pT4	Tumor involves other adjacent structures other than seminal vesicles: e.g., external sphincter, rectum, bladder, levator ani muscle, and/or pelvic wall

Note: a. The most widely adopted staging system for PC is the TNM staging system established by the American Joint Committee on Cancer (AJCC), using the 8th edition from 2017 [18].

b. The European Association of Nuclear Medicine (EANM) proposed a "miTNM" (molecular imaging TNM) classification based on PSMA PET/CT results. The prognosis of miT, miN, and miM stages may be better than that of T, N, and M stages, but the extent of this prognostic change and its practical significance remain to be evaluated. UICC or AJCC currently do not support this reclassification [19, 20].

c. T staging represents the primary tumor, which relies primarily on DRE, TRUS, MRI, and biopsy results, with pathological grade and PSA also serving as aids.

d. There is no pathological T1 classification.

Regional Lymph Nodes (N)[a]			
Clinical		**Pathological**	**(pN)**
NX	Regional lymph nodes cannot be evaluated	pNX	No regional lymph node sampling specimen

Regional Lymph Nodes (N)[a]

Clinical		Pathological	(pN)
N0	No regional lymph node metastasis	pN0	No regional lymph node metastasis
N1	Regional lymph node metastasis	pN1	Regional lymph node metastasis

Note: a. N staging represents the status of regional lymph nodes. The gold standard for N staging is dependent on post-lymphadenectomy pathology, though CT, MRI, and ultrasound can also serve as auxiliary methods. Metastasis ≤ 0.2 cm can be diagnosed as pNmi [4].

Distant Metastasis(M)[a]

Clinical	
MX	Metastasis cannot be evaluated
M0	No metastasis disease
M1	Metastasis disease [b, c]
	M1a Metastasis of non regional lymph nodes
	M1b Bone metastasis
	M1c Metastasis to other parts, with or without bone metastasis

Note: a. M staging represents distant metastasis, mainly focusing on bone metastasis. Staging is dependent on imaging examinations such as ECT, PSMA-SPECT/CT, PSMA-PET/CT, MRI, CT, and X-rays.

b. PSMA-PET/CT and MRI have complementary roles in determining the T staging of prostate cancer. PSMA-PET/CT exhibits better efficacy in detecting smaller metastatic lymph nodes compared to traditional imaging modalities and shows high sensitivity and specificity in M staging [21, 22].

c. Domestic studies have shown that SUVmax-PSMA is an independent predictor of the accuracy of PSMA-PET detection in prostate cancer [23].

Prognostic Grouping

Subgroup	T	N	M	PSA	Grade Group
I	cT1a-c	N0	M0	PSA < 10	1
	cT2a	N0	M0	PSA < 10	1
	pT2	N0	M0	PSA < 10	1
IIA	cT1a-c	N0	M0	10 ≤ PSA < 20	1
	cT2a	N0	M0	10 ≤ PSA < 20	1
	pT2	N0	M0	10 ≤ PSA < 20	1
	cT2b	N0	M0	PSA < 20	1
	cT2c	N0	M0	PSA < 20	1
IIB	T1-2	N0	M0	PSA < 20	2
IIC	T1-2	N0	M0	PSA < 20	3
	T1-2	N0	M0	PSA < 20	4

Prognostic Grouping

Subgroup	T	N	M	PSA	Grade Group
IIIA	T1-2	N0	M0	PSA ≥ 20	1–4
IIIB	T3-4	N0	M0	Any PSA	1–4
IIIC	Any T	N0	M0	Any PSA	5
IVA	Any T	N1	M0	Any PSA	Any
IVB	Any T	Any N	M1	Any PSA	Any

2.7 Traditional Chinese Medicine (TCM) diagnosis of PC

TCM diagnosis

Disease diagnosis[a]

Syndrome diagnosis (before local and systemic treatment)[b]

Syndrome diagnosis (after local and systemic treatment)[c]

Note: a. Disease diagnosis: PC is caused by the combined action of various factors such as external pathogen, internal damage, diet, and visceral dysfunction, resulting in disorders of "yin" and "yang", deficiency of healthy "qi", and obstruction of "qi" and blood to meridians and collaterals, causing local "qi" stagnation, blood stasis, phlegm coagulation, dampness accumulation, and heat toxin. Spleen-kidney deficiency is the primary cause; the pouring of dampness or heat, phlegm and blood stasis, and other factors can accelerate the progress of the disease.

b. Syndrome diagnosis (before local and systemic treatment).

(1) Syndrome of liver "qi" depression: chest distress and discomfort, hypochondriac pain, abdominal distension, no appetite for food, or "qi" ascending in a counterflow to the throat, limb fatigue, light red tongue with a white and thick coating, and a wiry pulse.

(2) Syndrome of "qi" depression transforming into fire: chest distress and discomfort, hypochondriac pain, abdominal distension, no appetite for food, red face and eyes, vexing heat in the chest, dark urine with burning pain, red tongue with a yellow coating, and a wiry pulse.

(3) Syndrome of malnutrition of the heart spirit: trance, restless mind, being suspicious and easily startled, feeling sad and easily crying, being temperamental, or always stretching and yawning, having a pale tongue with a thin coating, and having a wiry pulse.

(4) Syndrome of heart-spleen deficiency: severe palpitations; insomnia, dreaminess, dizziness and amnesia; sallow complexion; inappetence; abdominal distension and loose stool; fatigue and weakness; pale and tender tongue or teeth-marked tongue, with a thin coating; and thready-weak pulse.

(5) Syndrome of heart-kidney "yin" deficiency: heartache, palpitation, night sweats, insomnia, soreness and weakness

of the waist and knees, dizziness and tinnitus, frequent and urgent urination, frequent nocturnal urination, dry mouth and constipation, red tongue with fluid inadequacy and a thin or peeling coating, thready and rapid pulse or regularly intermittent pulse, and irregular or rapid pulse.

c. Syndrome diagnosis (after local and systemic treatment).

(1) Syndrome of stasis-heat injuring fluid: pain in the surgical wound, no aversion to cold, fever, dry mouth, dark red tongue with a sparse coating, and wiry and thready pulse.

(2) Syndrome of spleen deficiency and "qi" stagnation: weakness, shortage of "qi", abdominal distension, poor appetite, constipation, light red tongue with a thick or yellow and greasing coating, and wiry and thready pulse.

(3) Syndrome of kidney deficiency with dampness and fever: urinary pain, dribbling, even incontinence, light red tongue with a yellow coating, deep and thready pulse.

(4) Syndrome of "qi"-blood deficiency: fatigue, physical deficiency and weak "qi", pale tongue with a thin or sparse coating, and thready pulse.

3 Treatment of localized PC

3.1 Very low risk

Definition: clinical stage T1c, Gleason score ≤ 6, PSA < 10 ng/mL, presence of disease in fewer than 3 biopsy cores, ≤ 50% PC involvement in any core, and PSA density < 0.15 ng/mL/g.

Options	Level I Recommendations	Level II Recommendations
Initial therapy	Radical prostatectomy only[a,b] (for patients tolerating surgical side effects)	Radical prostatectomy + lymph node dissection
	EBRT or brachytherapy [c]	Other local treatments for prostate [d]
	Active surveillance [e]	
	Watchful waiting: for asymptomatic patients with expected survival < 10 years (based on complications)	
Adjuvant Therapy	EBRT (no lymph node metastasis after radical surgery, but with adverse prognostic pathological features)[f]	Follow-up
	ADT (with lymph node metastasis after radical surgery)	EBRT
	Follow-up (no adverse prognostic features and no lymph node metastasis after radical surgery, or initial treatment with EBRT or brachytherapy)	

Note: a. Radical prostatectomy can be performed via open, laparoscopic, or robot-assisted approaches. For patients with a life expectancy > 10 years, sexual activity requirements, and low risk of extracapsular extension, nerve-sparing surgery is recommended. The robotic surgical platform, with its high-definition 3D visual field and flexible robotic arm system, has demonstrated advantages in robot-assisted laparoscopic radical prostatectomy (RARP), particularly for elderly patients, due to its reduced trauma and earlier recovery of urinary continence [24, 25]. Studies by Chen et al. [26] have shown that with standard rehabilitation training and nursing, RARP patients regain urinary control earlier, with most achieving control within 1–6 months, significantly higher than the control group.

b. Predicted risk of lymph node metastasis < 2%.

c. EBRT is recommended at 74–80 Gy in 2 Gy fractions; hypofractionated regimens (68 Gy/20fx over 4 weeks or 70 Gy/28fx over 6 weeks) can be considered as alternatives. Low-dose brachytherapy may be feasible for patients who have not undergone TURP, have good IPSS scores, and have a prostate volume < 50 mL [27].

d. Other local treatments for the prostate include cryotherapy and high-intensity focused ultrasound (HIFU) therapy.

e. Active surveillance involves monitoring every 6 months with PSA tests, DRE every 12 months, and possible mpMRI and repeat biopsy as necessary. If PSA elevation, Gleason score increase, or MRI-indicated progression occurs during follow-up, radical treatment should be promptly initiated [28–30].

f. Poor prognostic features include positive surgical margins, seminal vesicle invasion, extracapsular extension, or postoperative PSA failing to drop below undetectable levels (< 0.1 ng/ml).

3.2 Low risk

Definition: T1-T2a, Gleason score ≤ 6/prognosis group 1, and PSA < 10 ng/mL.

	Level I Recommendations	Level II Recommendations
Initial therapy	Radical prostatectomy only [a, b] (for patients who can tolerate the surgical side effects)	Radical prostatectomy + lymph node dissection
	EBRT or brachytherapy [c]	Other local treatments for prostate [d]
		Active surveillance [e]

	Level I Recommendations	Level II Recommendations
Adjuvant Therapy	EBRT (adverse prognostic pathological features after radical surgery [f] and no lymph node metastasis)	Follow-up
	ADT (with lymph node metastasis)	EBRT
	Follow-up (no adverse prognostic features and no lymph node metastasis after radical surgery)	
	Follow-up (for patients receiving intensity- modulated radiotherapy)	ADT

Note: a. Radical prostatectomy can be performed by open surgery using laparoscopic or robotic assistance, with nerve-sparing surgery in patients with a life expectancy > 10 years or at a low risk of extracapsular extension [31].

b. Lymph node dissection can be excluded in patients with a < 2% predicated probability of nodal metastases.

c. For external beam radiotherapy (EBRT), intensity-modulated RT of 74 ~ -80 Gy at 2 Gy per fraction is recommended; low-dose split-course regimens (68 Gy/20 fx over 4 weeks or 70 Gy/28 fx over 6 weeks) may act as an alternative; low-dose brachytherapy is an option for TURP-naïve patients with good IPSS scores and a prostate volume less than 50 mL [32].

d. Cryotherapy, HIFU, etc [33].

e. Dynamic follow-ups include PSA testing every 6 months and a DRE every 12 months, only for patients with a life expectancy less than 10 years [31]. It is still recommended to perform the BRAC1/2 test when appropriate.

f. Pathologic features with poor prognosis include positive surgical margins, seminal vesicle invasion, extracapsular extension, or detectable PSA postoperatively (not PSA < 0.1 ng/mL).

3.3 Intermediate risk

Definition: cT2b-T2c, or Gleason score at 7, or PSA at 10 ~ 20 ng/mL.

	Level I Recommendations	Level II Recommendations
Initial therapy	Radical prostatectomy [a] + pelvic lymph node dissection [b]	Radical prostatectomy + standard lymph node dissection
	EBRT (76 ~ 78 Gy) + 4 ~ 6 months of concurrent ADT [c]	EBRT (76 ~ 80 Gy) without concurrent ADT
		EBRT (76 ~ 78 Gy) combined with brachytherapy, with or without concurrent ADT
		Brachytherapy[d] or other localized therapy for the prostate [e]
		Active surveillance [f]
Adjuvant Therapy	EBRT (no lymph node metastasis after RP, but with the presence of adverse prognostic pathological features [g])	Follow-up (no lymph node metastasis after RP, but with adverse prognostic pathological features [g])
	ADT (lymph node metastasis after RP)	EBRT (Lymph node metastasis after RP)
	Follow-up (no adverse prognostic features and no lymph node metastasis after radical surgery)	
	Short-course ADT for 4 ~ 6 months after radiotherapy	Higher radiotherapy dose required for patients not accepting ADT

Note: a. Radical prostatectomy can be performed by open surgery using laparoscopic or robotic assistance, with nerve-sparing surgery in patients with a life expectancy > 10 years or at a low risk of extracapsular extension.

b. Lymph node dissection can be excluded in patients with a < 2% predicated probability of nodal metastases.

c. For external beam radiotherapy (EBRT), it is recommended to perform intensity-modulated RT of 76–78 Gy at 2 Gy per fraction combined with concurrent ADT for 4–6 months; the recommended duration for ADT is based on two RCT studies [34, 35].

d. Low-dose brachytherapy is an option for TURP-naïve patients with good IPSS scores and a prostate volume less than 50 mL, such as 125I at 145 Gy, 103Pd at125 Gy, and Cs at 115 Gy.

e. Cryotherapy, HIFU, etc.

f. Dynamic follow-ups include a PSA test every 6 months; a DRE every 12 months; only for highly selected patients (GS4 < 10%) who have a life expectancy less than 10 years and accept an increased potential risk of disease metastasis.

g. Pathologic features with poor prognosis include positive surgical margin(s), seminal vesicle invasion, extracapsular extension, or detectable PSA postoperatively (PSA > 0.1 ng/mL).

3.4 High and very high risk

Definition: T3a, pathological grade group 4 or 5, or PSA > 20 ng/mL; very high-risk definition: T3b-T4,

primary pathological grade group 5, or > 4 cores of histopathological grade group 4–5.

Initial Clinical Assessment	Stratification	Level I Recommendations	Level II Recommendations	Level III Recommendations
Life expectancy > 5 years, or with symptoms	Initial therapy	External beam radiotherapy + androgen deprivation therapy [a]		External Beam Radiotherapy (EBRT) + Androgen Deprivation Therapy (ADT) + Abiraterone [j]
		External beam radiotherapy + brachytherapy + androgen deprivation therapy [b]		
		Radical prostatectomy + pelvic lymph node dissection [c]		
	Postoperative adjuvant therapy	External beam radiotherapy or observation[d] (adverse features [e] but without lymph node metastasis confirmed after surgery)		
		Androgen deprivation therapy or observation [f] (lymph node metastasis confirmed after surgery)	Plus external beam radiotherapy [g] (lymph node metastasis confirmed after surgery)	
	Subsequent treatment	Active surveillance [h] (undetectable PSA or its nadir after initial treatment)		
		See the sections below for the diagnosis and treatment of recurrent PC after radiotherapy or surgery (recurrence after initial treatment as per PSA)		
Life expectancy ≤ 5 yearand asymptomatic	Treatment options [i]	Observation		
		Androgen deprivation therapy		
		External beam radiotherapy		

Note: a. For patients with high-risk and very high-risk prostate cancer (PC), external beam radiotherapy (EBRT) combined with 2–3 years of androgen deprivation therapy (ADT) (using luteinizing hormone-releasing hormone (LHRH) agonists alone or in combination with first-generation anti-androgens such as flutamide or bicalutamide) has been proven effective.

One study randomized 415 patients to receive EBRT alone or EBRT integrated with 3 years of ADT. Another study (RTOG 8531) randomized 933 patients with T3 PC who underwent EBRT to receive adjuvant ADT or ADT upon recurrence. Two additional phase 3 clinical trials evaluated the long-term efficacy of ADT with or without EBRT for T3 PC. Across all four studies, EBRT combined with ADT improved disease-specific survival and overall survival (OS) compared to monotherapy [36]. For suitable patients, consideration can be given to administering 6 cycles of docetaxel chemotherapy integrated with steroids after EBRT completion, while continuing ADT. The GETUG 12 study [37] randomized 413 patients with high-risk/very high-risk PC to receive intensity-modulated radiation therapy (IMRT) + ADT or IMRT + ADT + docetaxel + estramustine. After a median follow-up of 8.8 years, the latter group had a non-recurrence rate of 62%, compared to 50% in the former group.

b. EBRT combined with brachytherapy and 1–3 years of ADT (using LHRH agonists alone or in combination with first-generation anti-androgens such as flutamide or bicalutamide) is commonly used in patients with high-risk/very high-risk PC. This treatment modality has demonstrated excellent prognoses, with 9-year progression-free survival (PFS) and disease-free survival (DFS) rates reaching 87% and 91%, respectively. A multicenter retrospective study of 1809 patients with Gleason scores of 9–10 PC found that EBRT + brachytherapy + ADT was associated with improved prostate-specific survival and metastasis-free survival compared to radical prostatectomy or EBRT + ADT. Furthermore, an analysis of 43,000 high-risk PC cases from the National Cancer Database found that EBRT + brachytherapy + ADT had similar mortality rates compared to radical prostatectomy but lower mortality rates than EBRT + ADT.

c. For high-risk/very high-risk prostate cancer (PC) that is not fixed to the pelvic wall, and in younger patients with good general health, radical prostatectomy (RP) combined with pelvic lymph node dissection (PLND) can be performed. Some patients with high-risk/very high-risk PC may benefit from RP. An analysis of 822 patients who underwent RP with Gleason scores of 8–10 on biopsy found that PSA levels greater than 10 ng/mL, a clinical stage of T2b or higher, Gleason scores of 9–10, more biopsy cores with high-grade tumor, and tumor involvement of more than 50% of the prostate tissue indicated poor postoperative survival. Patients without these adverse factors had significantly better 10-year biochemical recurrence-free survival (BCRFS) and disease-specific survival compared to those with adverse factors. Therefore, RP is an option for high-risk and some very high-risk patients. PLND should include all lymph node-bearing areas, namely the anterior external iliac vein, lateral pelvic wall, mid-bladder wall, posterior pelvic floor, distal Cooper's ligament, and proximal internal iliac artery. Several studies suggest that a more extensive PLND may provide better survival benefits by removing micrometastases, although definitive evidence is still lacking. Currently, most experts advocate for extended PLND in high-risk/very high-risk PC, including the external iliac, internal iliac, and obturator lymph nodes, and some propose extending the dissection superiorly to the crossing of the common iliac artery and ureter and including presacral

lymph nodes. This approach can provide more accurate staging information and remove micrometastases, which is beneficial for PC treatment, but the procedure requires high surgical skills and has more complications. One study retrospectively collected clinical data from 54 patients who underwent PLND or salvage lymph node dissection guided by 99mTc-PSMA SPECT/CT. In six patients, PSMA SPECT/CT detected more lymph node metastases that were missed by MRI and helped modify the extent of lymph node dissection. Compared to mpMRI, 99mTc-PSMA SPECT/CT-guided surgery can effectively detect and remove lymph node metastases with high sensitivity and specificity, delaying disease progression in prostate cancer patients [38]. Another study compared the diagnostic performance of 18F-prostate-specific membrane antigen (PSMA)-1007 PET/CT and multiparametric MRI (mpMRI) for pelvic lymph node metastases in prostate cancer [39]. 18F-PSMA-1007 PET/CT had higher sensitivity and negative predictive value than mpMRI for diagnosing lymph node metastases, while mpMRI had higher specificity and positive predictive value than 18F-PSMA-1007 PET/CT.

For high-risk localized prostate cancer patients, neoadjuvant therapy prior to surgery can help reduce the difficulty of laparoscopic radical prostatectomy, decrease the rate of positive surgical margins, lower surgical complication rates, and aid in early recovery of urinary control [40–42]. For very high-risk localized prostate cancer, compared to ADT alone, neoadjuvant ADT combined with docetaxel or abiraterone results in better pathological outcomes (pCR or MRD) [43]. Neoadjuvant docetaxel + cisplatin chemotherapy combined with androgen deprivation therapy can prolong progression-free survival (PFS) in patients with germline DNA damage repair gene (gDDR) deficient locally advanced prostate cancer (PCa), and is tolerable for patients [44].

d. After radical prostatectomy for high-risk/very high-risk PC, there are two treatment options: 1) initiate adjuvant external beam radiotherapy (EBRT) to the surgical area once urinary function recovers within 6 months post-surgery, or 2) opt for observation and follow-up with clinical and biological monitoring.

e. Adverse features include: positive surgical margins, seminal vesicle invasion, extraprostatic extension, or detectable PSA.

f. For PC patients with confirmed lymph node metastasis after radical prostatectomy, postoperative adjuvant androgen deprivation therapy (ADT) (orchiectomy or LHRH agonist monotherapy) is one option [36]. Another option is observation and follow-up with clinical and biological monitoring. A study comparing 98 patients with confirmed lymph node metastasis who underwent immediate postoperative ADT versus observation found significantly improved overall survival (OS) in the ADT group. However, another SEER study comparing 120 days of ADT versus observation in prostatectomy patients with lymph node metastasis showed similar OS and cancer-specific survival between groups. A retrospective study of 731 lymph node metastasis patients did not confirm better postoperative survival benefits with initial ADT compared to observation. Retrospective studies suggest that initial observation may be safe for N1 patients after radical prostatectomy, as 28% of 369 patients remained biochemical recurrence-free at 10 years.

g. For PC patients with lymph node metastasis after radical prostatectomy, a third option is ADT (orchiectomy or LHRH agonist monotherapy) combined with pelvic EBRT [45]. This recommendation is based on a retrospective study from the National Cancer Database showing that ADT plus EBRT improves biochemical recurrence-free survival, cancer-specific survival, and OS compared to ADT alone in patients with lymph node metastasis after radical prostatectomy.

h. For the first 5 years after initial treatment, PSA should be checked every 3 months, and then annually thereafter. Digital rectal examination (DRE) should be performed annually, which can be omitted if PSA is undetectable.

i. Palliative androgen deprivation therapy (ADT) (orchiectomy or LHRH agonist monotherapy) or external beam radiotherapy (EBRT) can be used in high-risk/very high-risk PC patients with a life expectancy of ≤ 5 years, although renal hydronephrosis or tumor metastasis may occur within 5 years. If the risks of relevant treatments outweigh the benefits, observation and follow-up with clinical and biological monitoring may be considered.

j. The STAMPEDE study indicates that for very high-risk prostate cancer patients, the use of EBRT combined with ADT and abiraterone significantly prolongs the treatment failure survival rate compared to EBRT/ADT alone, with an HR of 0.21 (95% CI, 0.15–0.31).

3.5 Regional lymph node metastasis (any T, N1, and M0)

Stratification	Level I Recommendations	Level II Recommendations
	ADT (2–3 years) [a] + radiotherapy [b] ± abiraterone [c] + prednisone/methylprednisolone ADT [a] ± abiraterone [c] + prednisone/methylprednisolone	Radical prostatectomy + pelvic lymph node dissection [d]

Stratification	Level I Recommendations	Level II Recommendations
Postoperative adjuvant therapy	Androgen deprivation therapy or observation [e]	Plus EBRT [e]

Note: a. Regimen: (1) Orchiectomy (testicular removal); (2) LHRH agonists, such as leuprorelin acetate, triptorelin acetate, goserelin acetate, and histrelin acetate.

b. Regimen: (1) External beam radiotherapy(EBRT): 72 Gy ~ 80 Gy at 2 Gy per fraction; 75.6 Gy ~ 81 Gy at 1.8 Gy per fraction; 70.2 Gy at 2.7 Gy per fraction; 70 Gy at 2.5 Gy per fraction; 60 Gy at 3 Gy per fraction. (2) Brachytherapy: 125I, 110 ~ 115 Gy; 103Pd, 90 ~ 100 Gy; 137Cs, 85 Gy; High-dose brachytherapy at 21.5 Gy (10.75 Gy*2); intensity-modulated radiotherapy at 37.5 Gy (2.5 Gy per fraction) + 12–15 Gy high-dose brachytherapy [46].

c. Abiraterone regimen: abiraterone 1000 mg po qd + prednisone 5 mg (or methylprednisolone 4 mg) po bid. Abiraterone should be administered on an empty stomach, i.e., without eating from at least 2 h pre-dose and at least 1 h post-dose. Combination with castration therapy is required. Prednisone or Methylprednisolone should be taken after meals. Common adverse reactions include hypertension, electrolyte disturbances, adrenal insufficiency, hepatotoxicity, and dyslipidemia.

d. Refer to the management of very high-risk prostate cancer undergoing radical prostatectomy.

e. Refer to the postoperative management of very high-risk prostate cancer with confirmed lymph node metastases after radical prostatectomy.

4 Diagnosis and treatment of PC recurrence after radical prostatectomy

4.1 Diagnosis and treatment of recurrence after radical prostatectomy

4.1.1 Examination and evaluation of recurrence after radical prostatectomy

	General Principles
General Condition Assessment	1. Medical History [a]
	2. Physical Examination
	3. Hematological Tests [b]
	4. PSA and Testosterone Tests [c]
	5. Psychological Evaluation and Counseling
Confirmatory Examinations[d]	1. Pathological review of the Primary Tumor[e]
	2. Chest X-ray or CT
	3. Bone Scan[f]
	4. Abdominal and Pelvic CT or MRI[g]
	5. 11C-Choline PET/CT or 18F PET/CT[h]
	6. PSMA PET/CT[i]
	7. Prostate Bed Biopsy (if imaging suggests local recurrence)

Note: a. Thoroughly inquire about the patient's past treatment history, especially the surgical method, postoperative pathology including Gleason score, staging, surgical margins, neoadjuvant or adjuvant endocrine therapy, and other important treatment-related medical history. Several studies have reported risk factors related to biochemical failure after radical prostatectomy for localized high-risk prostate cancer, such as diabetes [47], PSA density, positive surgical margins, and postoperative adjuvant therapy [48]. A study reviewed the clinical data of 166 patients with localized high-risk prostate cancer who underwent radical prostatectomy. Multivariate Cox regression analysis showed that postoperative adjuvant therapy, PSA density, and positive surgical margins were independent predictors of biochemical failure.

b. Since most anti-androgen and novel endocrine therapy drugs are metabolized by the liver, liver and kidney function tests are crucial for assessing drug contraindications.

c. Generally, after radical prostatectomy, PSA is reduced to undetectable levels (PSA < 0.1 ng/mL). Under the premise of negative imaging examinations, continuous PSA levels ≥ 0.2 ng/mL on two occasions are defined as the standard for biochemical recurrence. However, some scholars believe that increasing the PSA baseline to 0.4 ng/mL may better indicate the risk of distant metastasis [49–51].

d. All imaging examinations should only be used when guiding subsequent treatment.

e. After confirming recurrence or metastasis, pathological reassessment of the primary tumor, including pathological consultation, is essential. Especially when the previous Gleason score or surgical margins are unknown, further clarification of special pathological types such as neuroendocrine differentiation is important. It is also recommended to perform biopsy of the metastatic site to determine the characteristics of the lesion.

f. In asymptomatic patients, the diagnostic rate of bone scan and abdominal and pelvic CT is low [52]. Among patients with PSA recurrence after radical prostatectomy (RP), when PSA < 7 ng/ml, the positive rate of bone scan is < 5% [53, 54]. Bone scan should be considered when PSA cannot be reduced to undetectable levels after RP or when PSA decreases to undetectable levels but then increases twice consecutively. The bone scan may have a "flare phenomenon" or false-positive uptake, which

should be considered in combination with the patient's PSA levels and symptoms.

g. CT can well display anatomical structures and evaluate lymph node, bone, or visceral metastases. MRI can better display soft tissue and can also perform multiparametric and functional imaging. Local MRI can be considered to assess local recurrence when PSA cannot be reduced to undetectable levels after RP or when PSA decreases to undetectable levels but then increases twice consecutively.

h. PET/CT has higher sensitivity than bone scan for detecting bone metastases, with a sensitivity and specificity of 86–89% and 89–93% in patients with biochemical recurrence.

i. PSMA PET/CT, also known as Prostate-specific membrane antigen-based PET/CT, is a novel radionuclide imaging modality using PSMA as a marker. After radical prostatectomy (RP), PSMA PET/CT is the most sensitive imaging method at low PSA levels (< 0.5 ng/mL) and can help distinguish patients with local recurrence confined to the prostatic fossa from those with distant metastases, thereby influencing subsequent treatment decisions. In patients with biochemical recurrence (BCR), the detection rates of lesions in PSA levels ranging from 0.2–0.49 ng/mL, 0.5–0.99 ng/mL, 1.0–1.99 ng/mL, and > 2.0 ng/mL are 39–52%, 25–73%, 66–84%, and 92–97% [55], respectively, which are all higher than other traditional detection methods. A meta-analysis of 37 studies compared the combined detection rates of 68 Ga-PSMA-11 PET/CT and 68 Ga-PSMA-11 PET/MRI [56]. There was no significant difference in the overall detection rate of BCR between the two imaging modalities. However, the authors emphasized that not all studies included in the analysis used pathological biopsy as the gold standard. Therefore, larger-scale prospective studies are still needed to address this issue. Another study retrospectively included 35 patients who underwent mpMRI or 18F-PSMA-1007 PET/CT. All patients were confirmed to have adenocarcinoma by preoperative prostate biopsy and underwent RP surgery combined with ePLND. For pelvic lymph node metastases of prostate cancer (PCa), the sensitivity and negative predictive value of 18F-PSMA-1007 PET/CT were higher than those of mpMRI, while the specificity and positive predictive value of mpMRI were higher than those of 18F-PSMA-1007 PET/CT [39].

4.1.2 Treatment for recurrent PC after radical prostatectomy

Stratification	Category I Recommendation	Category II Recommendation	Category III Recommendation
Biochemical Recurrence/ Local Recurrence	Salvage radiotherapy combined with long-term endocrine therapy[a]	Salvage radiotherapy[b]	Salvage lymph node dissection [d]
		Observation and follow-up [c]	
Distant Metastasis		Systemic therapy [e]	
		Metastasis directed therapy [f]	
Subsequent Treatment [g]	ADT therapy ± bicalutamide	Olaparib (in cases with HRR pathway gene mutation)	Other chemotherapy regimens
	Abiraterone (or after failure of first-line other drugs)	Radium-223 (for bone metastasis only)	Addition of AR inhibitors
	Docetaxel (or after failure of first-line other drugs)	Cabazitaxel (for mCRPC after Docetaxel chemotherapy)	Anti-androgen withdrawal therapy
	Enzalutamide (or after failure of first-line other drugs)		Interchange of anti-androgen drugs
	Apalutamide (or after failure of first-line other drugs)		Ketoconazole
	Clinical trials		Glucocorticoid Low-dose estrogen

Note: a. After radical prostatectomy, the biochemical recurrence can be cured through early salvage radiotherapy, which is most effective before PSA rises to 0.5 ng/ml [57–60]. Through salvage radiotherapy, PSA can be reduced to below the detectable level in over 60% of patients, and the risk of progression within 5 years can be reduced by 80% [61]. Currently, there is no clear recommendation for the irradiation target area and dose of salvage radiotherapy after radical prostatectomy, but it should at least include the prostate cancer bed and may also include the entire pelvic cavity. The generally recommended dose is 64–72 Gy. The main adverse reactions are radioactive cystitis, urinary incontinence, and radiation enteritis, with a 2-grade adverse reaction rate of 4.7%-16.6% and a 3-grade rate of 0.6%-1.7%, which increase with increasing dose [62, 63].

b. According to the results of the RTOG 9601 clinical trial, adding 2 years of bicalutamide anti-androgen therapy to SRT can prolong disease-specific survival and OS [64]. Based on the GETUG-AFU 16 clinical trial, adding 6 months of LHRH analogues to SRT can significantly

prolong PFS [65]. For patients with contraindications to radiotherapy, those who cannot recover from urinary control after prostatectomy, or those who are unwilling to receive radiotherapy, endocrine therapy alone can also be used. In the phase III clinical trial EMBARK, the efficacy of enzalutamide combined with leuprolide, enzalutamide alone, and leuprolide alone in treating high-risk patients with biochemical recurrence (PSA ≥ 1 ng/ml after RP or PSA above nadir ≥ 2 ng/ml after EBRT; PSA doubling time PSADT ≤ 9 months) was compared. The results showed that after a median follow-up of 5 years, the risk of metastasis or death in the enzalutamide combined with leuprolide group was significantly reduced by 58% compared to the leuprolide group, with a reduced risk of death and prolonged PSA progression time [66]. The combination regimen also demonstrated high safety. Although the EMBARK data are not yet mature, they have already suggested the clinical value of enzalutamide combined with ADT in treating recurrent patients.

c. For low-risk patients (PSA doubling time > 12 months, time from surgery to biochemical recurrence > 3 years, GS ≤ 7, and T stage ≤ T3a), observation and follow-up may be performed for those with an expected lifespan of less than 10 years or who refuse salvage treatment.

d. Currently, the research on salvage lymph node dissection for local lymph node metastasis after radical prostatectomy is mainly retrospective. It is reported that the 2-year and 5-year biochemical progression-free survival rates for patients receiving salvage lymph node dissection are 23–64% and 6–31%, respectively, and the 5-year overall survival rate is 84% [67].

e. See the chapter on diagnosis and treatment of metastatic prostate cancer for details.

f. Palliative radiotherapy can be performed on weight-bearing bones or symptomatic bone metastases, with a single dose of 8 Gy effectively relieving symptoms. For patients with oligometastatic disease, SBRT can be administered to metastases in the form of clinical trials.

g. For patients who experience disease progression after salvage radiotherapy but without endocrine therapy, the subsequent treatment for metastasis is detailed in the diagnosis and treatment of metastatic hormone-sensitive prostate cancer (4.1). For patients who have undergone endocrine therapy and maintain castrate levels of testosterone but still experience disease progression, the subsequent treatment for metastasis is detailed in the diagnosis and treatment of metastatic castration-resistant prostate cancer (4.2). After endocrine therapy, some patients may experience symptoms such as hot flushes, chills, spontaneous sweating, night sweats, fatigue, and insomnia. These symptoms often cannot be relieved with Western medicine, and traditional Chinese medicine can be considered for adjustment. Based on clinical manifestations, the symptoms after endocrine therapy for prostate cancer can be classified into categories such as "internal agitation", "deficiency", "palpitation", "sweating", "depression", and "insomnia". In the early stage, the main symptoms are hot flushes, sweating, and irritability, which are manifestations of deficiency of kidney yin and hyperactivity of heart fire. The treatment should focus on nourishing the kidney and clearing the heart, with a combination of nourishing and clearing. The prescription may include Liuwei Dihuang Pills combined with Erzhi Pills and ingredients that clear the heart and reduce fire. In the later stage, as kidney essence gradually depletes, the heart and kidney fail to communicate, and qi and blood become deficient, leading to symptoms such as fatigue, anemia, forgetfulness, and other related functional decline. The treatment should prioritize nourishing the kidney and heart, replenishing qi and blood, with a prescription that may include Wuzi Yanzong Pills combined with ingredients that nourish the heart qi [68–70].

4.2 Management of PC recurrence after radical radiation therapy

After radical radiotherapy, whether or not endocrine therapy is administered, a PSA increase of 2 ng/mL above the nadir value is defined as biochemical recurrence.

4.2.1 Examination and accessment of PC recurrence after radical RT

Stratification	Category I Recommendation	Category II Recommendation	Category III Recommendation
Suitable for Local Treatment [a]	PSA Doubling Time Chest X-ray or CT PSMA PET/CT[b] PSMA SPECT/CT Prostate MRI[c] TRUS biopsy[d]	Abdominal/Pelvic CT or MRI [e] 11C-Choline PET/CT[f] or 18F PET/CT[g]	
Unsuitable for Local Treatment		PSMA PET/CT PSMA SPECT/CT Bone Scan	

Note: a. Definition of suitability for local treatment: Initial clinical stage T1-T2, Nx or N0; life expectancy > 10 years; PSA < 10 ng/ml before treatment; no evidence of LN involvement or distant metastatic disease before treatment; initial clinical stage T1 or T2 [71].

b. For patients with biochemical recurrence, the sensitivity of PSMA PET/CT in detecting distant metastases is significantly better than bone scan and choline PET/CT. Due to the high incidence of complications associated with salvage therapy after RT, patients suitable for salvage therapy should first undergo PSMA PET/CT, choline PET/CT, or 18F PET/CT to exclude distant metastases.

If distant metastases are present, salvage therapy is not recommended.

c. Multi-parametric MRI is currently the best method for localizing local recurrence and can guide prostate biopsy and subsequent local salvage therapy [72–75].

d. Whether the biopsy is positive is the main prognostic factor for biochemical recurrence after RT. Due to the high incidence of complications associated with local salvage therapy, obtaining pathological evidence before treatment is necessary.

e. It takes 7–8 years for biochemical recurrence to progress to clinical metastasis, and the positive rate of bone scan and abdominal-pelvic CT in asymptomatic patients is very low.

f. Choline PET/CT has better sensitivity in detecting bone metastases than bone scan, but it depends on PSA level and dynamics.

g. 18F PET/CT has an advantage over bone scan in detecting bone metastases, but it cannot evaluate soft tissue metastases.

4.2.2 Treatment of PC recurrence after radical RT

	Stratification	Category I	Category II	Category III
Suitable for localized therapy	TRUS biopsy positive, without metastasis		Active suvillence [a] Salvage radicalprostatectomy with pelvic lymphnode dessestion [b]	Salvage cryotherapy[c] Brachy therapy[d] HIFU[e]
	TRUS biopsy negative, without metastasis		Active suvillence; Hormonal therapy; Clinical trials	
	With metastasis		Systemic therapy[f]	
unsuitable for localized therapy			Hormonal therapy; Active suvillence;	

Note: a. For low-risk patients (PSA doubling time > 12 months; biochemical recurrence time > 3 years; Gleason score ≤ 7 and pathological stage ≤ T3a), observation can be performed until there are significant metastases. Unhealthy patients with a life expectancy of less than 10 years or who are unwilling to undergo salvage therapy can also be observed. The median time from biochemical recurrence to metastasis is approximately 8 years, and from metastasis to death is approximately 5 years.

b. Compared to other treatment modalities, salvage prostatectomy has the longest history and the highest potential for achieving local control. However, the implementation of salvage prostatectomy must consider the higher incidence of complications, as radiation therapy may increase the risk of fibrosis and poor wound healing. The 5-year and 10-year biochemical recurrence-free survival rates after salvage prostatectomy are approximately 47–82% and 28–53%, respectively, with 10-year DFS and OS rates of 70–83% and 54–89%, respectively. Compared to initial PC radical prostatectomy, the risks of complications such as anastomotic stricture (47 vs. 5.8%), urinary retention (25.3% vs. 3.5%), urinary fistula (4.1% vs. 0.06%), abscess (3.2% vs. 0.7%), and rectal injury (9.2 vs. 0.6%) are higher after salvage prostatectomy [76]. Additionally, the incidence of urinary incontinence ranges from 21 to 90%, and almost all patients experience erectile dysfunction [77–79]. Therefore, patient selection should be extremely cautious, and the procedure should be performed in experienced centers.

c. Prostate cryoablation has been proposed as an alternative to salvage radical prostatectomy due to its similar efficacy but lower complication rate. The 5-year biochemical recurrence-free survival rate after cryoablation is approximately 50% to 70% [80–83].

d. Although external beam radiation therapy is not recommended for local recurrence after radiation therapy, high-dose-rate (HDR) or low-dose-rate (LDR) brachytherapy can still be an effective treatment option for certain eligible patients (good performance status, primary localized prostate cancer, good urinary function, histologically confirmed local recurrence). In a systematic review, the reported 5-year BCR-free survival rate for HDR was 60% (95% CI: 52–67%), and for LDH was 56% (95% CI: 48–63%) [84]. The toxicity of brachytherapy is also within acceptable limits. However, there are relatively few published studies, and it should only be performed in experienced centers.

e. Most of the current research data on high-intensity focused ultrasound (HIFU) treatment comes from the same center. The median follow-up time is still short, and the outcome evaluation is not standardized. The incidence of important complications is roughly the same as other salvage treatments.

f. See the section on the diagnosis and treatment of metastatic PC for more details.

5 Mangement of metastatic PC

5.1 Mangement of metastatic hormonal sensitive PC(mHSPC)

5.1.1 Examainations and accessment of mHSPC

	General principles
General status accessment	1. History 2. Family history[a] 3. PSA [b] 4. Blood tests 5. Organ function accessment (Liver,Kindey, Heart)[c] 6. DRE
Confirmation examinations	Prosate biopsy[a] Metastatic biopys[a] ECT[b] MRI, CT[c] Abdominal ultrasound PET/CT[d]

1) General Status Assessment:

Note: a. The following conditions indicate a strong familial genetic predisposition: brothers, fathers, or multiple family members with a blood relationship who have been diagnosed with PC before age 60. Known familial genetic DNA repair gene abnormalities, especially BRCA2 mutations or lynch syndrome. More than one relative with breast cancer, ovarian cancer, pancreatic cancer (indicating BRCA2 mutation), or colorectal cancer, endometrial cancer, gastric cancer, ovarian cancer, pancreatic cancer, small intestine tumors, urothelial cancer, kidney cancer, or cholangiocarcinoma (lynch syndrome).

b. PSA should be rechecked every 3 months to promptly confirm the disease status and adjust the treatment plan. According to the SWOG 9346 study, PSA levels after 7 months of endocrine therapy can categorize patients into three different prognostic groups: 1) PSA < 0.2 ng/mL: median survival time of 75 months; 2) PSA 0.2 < 4 ng/mL: median survival time of 44 months; 3) PSA > 4 ng/mL: median survival time of 13 months [85].

c. Patients expected to undergo chemotherapy or abiraterone treatment, elderly patients, and patients with a history of hypertension, cardiovascular and cerebrovascular diseases should undergo functional assessments of important organs such as heart, liver, and kidneys before systemic treatment.

2) Diagnostic Examinations:

a. Pathological confirmation is crucial for subsequent treatment. Adenocarcinoma of the prostatic acini is the most common type, and other types of prostate tumors include sarcomas, squamous cell carcinomas, small cell carcinomas, urothelial carcinomas, and basal cell carcinomas. The treatment methods for different pathological types of prostate malignancies vary significantly. If neuroendocrine differentiation is suspected after CRPC, biopsy of recurrent metastases or second biopsy of the primary tumor can help confirm the diagnosis.

b. Bone scans are helpful in assessing the extent of bone metastases and the effectiveness of systemic treatment. Note: If new lesions are found on bone scans after systemic treatment but PSA levels decrease or soft tissue lesions improve, a repeat bone scan should be performed after 8–12 weeks to exclude the "flare phenomenon" or bone healing response. The "flare" phenomenon in bone scans is relatively common, especially when LHRH analogues are first used or when new endocrine drugs (such as enzalutamide or abiraterone) are switched.

c. CT/MRI provides high-resolution anatomical imaging results, which have considerable advantages in assessing visceral metastases, soft tissue metastases, and the biological activity of metastatic lesions.

d. The sensitivity of 18F-NaF PET/CT is better than bone scans, but its specificity is slightly lower. However, compared to choline PET/CT, 18F-NaF PET/CT has insufficient diagnostic ability for lymph node and visceral metastases. PSMA PET/CT has ideal diagnostic ability for PC recurrence when PSA levels are still low and can assist in evaluating treatment effectiveness. However, it is currently not recommended for staging PC at the time of initial diagnosis.

5.1.2 Stratification of mHSPC[a]

High volume mHSPC	Low volume mHSPC
The presence of ≥ 4 bone metastases (with ≥ 1 bone metastasis located outside the pelvis or spine) and/or the presence of visceral metastases.	Not suitable for high volume mHSPC

Note: a. According to the CHAARTED study, disease burden can serve as a potential predictor [86–88]. Subsequently, a subgroup analysis in the STAMPEDE study showed that ADT combined with prostate radiation therapy can benefit patients with low volume mHSPC.

5.1.3 Treatment of mHSPC

	Category I recommendations	Category II recommendations	Category III recommendations
new diagnosed mHSPC		ADT + bicaluatmide[c]	ADT + flutamide [c]
	ADT(LHRH agonist [a] or LHRH antagonist[b]) + abiraterone + predisone [d]	ADT + radical localized therapy (RP or RT)[e]	Intermittent ADT[f]
	ADT + docetaxel ± predisone [g]	ADT + abiraterone + docetaxcel[l]	Metastasis directed therapy, MDT[h]
	ADT + enzalutamide[i]		castration surgery[o]
	ADT + apalutamide [j]		
	ADT + Rezvilutamide[k]		
	ADT + daroluta-mide + docetaxol [n]		
	ADT + EBRT[m]		

Note: a. If the patient has weight-bearing bone metastases, the first-generation anti-androgen drugs should be used for ≥ 7 days before the first application of LHRH agonists to avoid or reduce the "flare" effect of testosterone [89].

Commonly used LHRH agonists include: Goserelin, Leuprorelin, Triptorelin.

b. LHRH antagonists: Degarelix.

c. First-generation anti-androgen drugs: Bicalutamide, Flutamide [90]. A randomized controlled clinical study involving 1,286 patients found no significant survival difference between simple surgical ablation or surgical ablation combined with Flutamide. However, subsequent retrospective analysis and small randomized controlled clinical studies suggest that the integration of first-generation anti-androgen drugs on the basis of ablation can bring smaller survival benefits (< 5%). Therefore, an individual assessment needs to be made between the possible increase in side effects and clinical benefits. In a randomized controlled double-blind clinical trial for advanced PC, Bicalutamide has a longer time from the beginning of treatment to resistance compared to Flutamide, so it has a higher recommendation level.

Attention: Avoid providing anti-androgen monotherapy only to M1 patients [91].

d. Two large randomized controlled clinical studies, STAMPEDE and LATITUDE, suggest that Abiraterone combined with prednisone can effectively prolong the overall survival time for metastatic hormone-sensitive PC [92–94].

The LATITUDE study enrolled 1,199 patients with high-risk metastatic PC. The 3-year OS of the Abiraterone group increased by 38% compared to the control group.

The STAMPEDE study enrolled 1,917 patients with high-risk locally advanced or distant metastatic or lymph node metastatic PC. The 3-year OS of the Abiraterone group increased by 37% compared to the control group. It is worth mentioning that the STAMPEDE study conducted a subgroup analysis of M1 and M0 patients and found that M1 patients had survival benefits, while M0 patients did not have significant survival benefits.

Abiraterone acetate tablets (II) are 2.2 modified new drugs synthesized using nanocrystal technology based on the original Abiraterone. Compared with 1,000 mg of Abiraterone acetate tablets, 300 mg of Abiraterone acetate tablets (II) meet the bioequivalence standards for Cmax, AUC0-t, and AUC0-∞, and Abiraterone acetate tablets (II) have higher bioavailability. In phase II clinical trials for mHSPC and mCRPC, Abiraterone acetate tablets (II) have passed the equivalence verification compared to Abiraterone acetate tablets. Currently, mHSPC and mCRPC indications have been approved in China [95, 96].

In addition, the latest international multicenter study in Asian populations showed that among Asian mHSPC patients, Abiraterone combined with ADT had a longer PFS compared to Docetaxel combined with ADT (NR vs. 15.1 months, 95%CI = 0.280–0.500, P < 0.001), but there was no significant difference in OS. Moreover, the proportion of patients who terminated the trial due to adverse reactions in the Abiraterone treatment group was significantly lower than that in the Docetaxel treatment group (0.6% vs. 3.6%). This study fully demonstrates the effectiveness and safety of Abiraterone in Asian patients [97].

e. Some cohort studies and retrospective studies suggest that newly diagnosed metastatic PC may benefit from primary tumor surgery or brachytherapy. Domestic clinical studies have also confirmed the effectiveness and safety of radical surgery for oligometastatic PC [98, 99]. This study enrolled 200 newly diagnosed oligometastatic prostate cancer patients, who were randomly divided into ADT combined with local lesion treatment group and ADT alone treatment group. Local treatment included radical prostatectomy or radical radiotherapy. After 48 months of follow-up, the results showed that compared with ADT alone, ADT combined with local treatment could significantly prolong the median rPFS of newly diagnosed oligometastatic prostate cancer patients (NR vs. 40 months, HR = 0.43, 95% CI: 0.27–0.70, $P = 0.001$). In addition, the 3-year overall survival rate of the combined treatment group was 88%, significantly higher than 70% of the ADT alone treatment group (HR = 0.44, 95% CI: 0.24–0.81, P = 0.008). Therefore, for newly diagnosed oligometastatic patients, ADT combined with radical prostatectomy or radical radiotherapy can significantly improve patient survival. It is worth noting that such clinical diagnosis and treatment are still recommended to be conducted in the form of clinical trials. A long-term

follow-up analysis report of the CHAARTED study found that patients with low tumor burden could benefit from ADT combined with radiotherapy in terms of overall survival time (median time 61 months, HR = 0.64) [100]. Therefore, patients with M1 disease for the first time and diagnosed with low tumor burden according to the CHAARTED criteria can be treated with ADT combined with non-radical prostate radiotherapy (2 Gy/72 Gy).

A single-arm, phase I/II clinical trial in China enrolled 12 oligometastatic prostate cancer patients. All patients received neoadjuvant endocrine therapy and neoadjuvant local radiotherapy after 1 month, followed by robot-assisted radical prostatectomy for all patients. The results showed that the average rPFS was 21.3 months, and the 2-year rPFS was 83.3%. The study concluded that neoadjuvant radiotherapy combined with endocrine therapy is tolerable for oligometastatic patients [101].

f. In asymptomatic M1 stage, intermittent treatment is only provided to patients with high willingness and good PSA response after the induction period. The treatment phase generally does not exceed 9 months to avoid the inability of testosterone to recover. Treatment is stopped if PSA levels are < 4 ng/mL after 6–7 months of treatment. Treatment is resumed when PSA levels reach > 10–20 ng/mL (or return to the initial level < 20 ng/mL).

g. Multiple randomized controlled clinical studies have indicated that docetaxel combined with ADT should be considered the standard treatment for high tumor burden hormone-sensitive metastatic PC (definition of high tumor burden: the presence of ≥ 4 bone metastases, including ≥ 1 bone metastasis located outside the pelvis or spine, or visceral metastasis).

Specific regimen: Docetaxel 75 mg/m2 (administered once every 3 weeks) + dexamethasone 8 mg (given 12 h, 3 h, and 1 h before chemotherapy) ± prednisone 5 mg bid. Continue for 6 cycles. If disease regression is achieved at the end, discontinue treatment. If disease progresses, adjust the treatment plan according to mCRPC treatment. The main toxic side effects of combination chemotherapy are hematological, with approximately 12–15% experiencing grade 3–4 neutropenia, and 6–12% experiencing grade 3–4 neutropenia with fever. The use of granulocyte colony-stimulating factor receptor (G-CSF) can reduce febrile neutropenia. Glucocorticoids can also cause cardiovascular complications. Both complications require active follow-up and observation during treatment for timely management.

Clinical Study Summary:

The CHAARTED study enrolled 790 patients with hormone-sensitive metastatic PC. The docetaxel treatment group achieved a 13-month survival benefit compared to the control group, with a 39% increase in survival rate. Among patients with high metastatic burden PC (≥ 4 bone metastases, including one metastasis outside the axial skeleton or visceral metastasis), the combination of docetaxel achieved a 17-month survival benefit (Prednisone was not used in this study).

The STAMPEDE study enrolled 1184 patients with high-risk locally advanced or distant metastatic or lymph node metastatic PC. It was found that M1 stage patients achieved a 15-month survival benefit when combined with docetaxel chemotherapy, while M0 stage patients did not benefit from OS when combined with docetaxel chemotherapy (Prednisone 5 mg bid was used in this study).

A single-center retrospective study in China analyzed the efficacy of docetaxel combined with ADT in 153 patients with high metastatic burden mHSPC. The results showed that compared with ADT alone, the PFS was significantly prolonged in the docetaxel combination group (16.9 months vs. 11.2 months, $P < 0.001$), and the time to reach the lowest PSA level was shorter (6.3 months vs. 7.9 months, $P = 0.018$). During the trial, fewer patients in the combination chemotherapy group died of prostate cancer and related complications compared to the ADT alone group (6 cases, 9.5% vs. 15 cases, 16.7%), and the adverse reactions were controllable [102].

h. It is mainly used for local treatment of clinically symptomatic metastases or for clinical diagnosis and treatment in clinical trials.

i. The ARCHES and ENZAMET studies indicate that the novel anti-androgen drug enzalutamide combined with ADT for mHSPC can effectively prolong overall survival time [103, 104]. In the ARCHES study, compared to the control group, enzalutamide combined with ADT significantly improved the rPFS of HSPC patients (not reached vs. 19.0 months), with an HR of 0.39 (0.3–0.5). In the ENZAMET study, the 3-year OS was 80% and 72% for the enzalutamide group and the control group, respectively (HR = 0.67, $P = 0.002$).

j. The TITAN study showed that apalutamide combined with ADT can effectively prolong the rPFS (HR of 0.48 (0.39–0.6)) and OS of mHSPC patients [105]. The 2-year OS was 82.4% for the apalutamide group and 73.5% for the control group (HR = 0.67, $P = 0.005$). The latest study in Asian populations showed that the efficacy and safety of apalutamide in Asian populations were consistent with the overall population [106].

k. The international multicenter, randomized controlled, open phase III clinical trial CHART showed that in 654 enrolled patients with high tumor burden mHSPC, compared with bicalutamide (50 mg, qd) combined with ADT, the use of revilutamide (240 mg,

qd) combined with ADT can significantly extend the median OS (NR vs. NR, HR = 0.58, 95% CI 0.44–0.77, $P = 0.0001$) and the median rPFS (NR vs. 23.5 months, HR = 0.46, 95% CI 0.360.60, $P < 0.000\ 1$) of patients with high tumor burden mHSPC. The incidence of adverse reactions in the two groups was similar (20.7% vs. 14.5%) [107].

l. PEACE-1 is an international multicenter, randomized controlled, open phase III clinical trial that enrolled 1,173 patients with mHSPC and combined abiraterone/prednisone and/or local radiotherapy on the basis of standard treatment. The results showed that ADT combined with abiraterone (1,000 mg, once daily) and docetaxel (75 mg/m2, once every 3 weeks) could significantly improve the overall survival time (5.7 years vs. 4.7 years, $P = 0.03$) and imaging progression-free survival time (4.5 years vs. 2.2 years, HR = 0.54, $P < 0.000\ 1$) of patients. However, subgroup analysis showed that ADT combined with abiraterone and docetaxel was more significant in improving overall survival for patients with high tumor burden (5.1 years vs. 3.5 years, HR = 0.72, $P = 0.019$), while there was no significant benefit for patients with low tumor burden (NR vs. NR, HR = 0.83, $P = 0.66$) [108]. Therefore, this combination regimen can be considered for patients with high tumor burden mHSPC without contraindications to chemotherapy.

m. An international multicenter phase III clinical trial, ARASENS, enrolled 1,306 patients with mHSPC and showed that ADT combined with darolutamide (600 mg, bid) and docetaxel (75 mg/m2, q3w, 6 cycles) significantly prolonged the overall survival time (NE vs. 48.9 months, HR = 0.68, $P < 0.001$) and the time to progression to mCRPC (NE vs. 19.1 months, HR = 0.36, $P < 0.001$) of patients with mHSPC compared to ADT combined with placebo and docetaxel. The incidence of treatment-related grade 3–4 adverse reactions was similar between the two groups (66.1% vs. 63.5%) [109]. This regimen can be considered for patients without contraindications to chemotherapy.

n. A further analysis of the STAMPEDE clinical trial demonstrated that patients with low tumor burden can benefit from EBRT targeting the primary tumor, while this phenomenon was not observed in the group of patients with high tumor burden mHSPC [110]. Therefore, ADT combined with local radiotherapy can be considered for patients with low tumor burden mHSPC.

o. When starting ADT, for patients with imminent clinical complications such as spinal cord compression or bladder outlet obstruction, the use of LHRH or surgical deprivation, i.e., bilateral orchiectomy, may be considered.

5.1.4 Diagnosis of non-metastatic CRPC (M0CRPC)

Diagnosis
Confirmation of castration status [a]
Serum PSA progression[b]
Radiological non-progression [c]

Note: a. Serum testosterone < 50 ng/mL or 1.7 nmol/L.

b. PSA > 2 ng/ml with a continuous rise in PSA levels over three consecutive measurements taken 1 week apart, with each increase greater than 50% of the lowest value.

c. Traditional imaging examinations including CT, MRI, and bone scans do not reveal distant metastases. If there is no evidence of metastasis, C11 choline PET/CT or PET/MRI, or F18 PET/CT can be used to further exclude soft tissue and bone metastases.

5.1.5 Treatment recommendations for non-metastatic castration-resistant prostate cancer (M0CRPC)

Systematic therapy	Category I	Category II	Category III
PSADT > 10 m[a]	Active surveillance	Other second line ADT[e]	
PSADT ≤ 10 m	apalutamide + ADT[b]		FDG/PSMA PET/CT for metastatic sites [f]
	darolutamide + ADT[c]	Other second line ADT[e]	
	enzaluatmide + ADT[d]		

Note: a. PSADT (PSA doubling time) refers to the time required for the serum PSA level to double. For those with a PSADT greater than 10 months, the tumor is generally considered to be indolent, and ADT treatment can be continued for some time. For those with PSADT ≤ 10 months, ADT can be combined with new endocrine therapy drugs. Not all PSA recurrences are clinically significant, and PSADT may better reflect disease progression. It has been confirmed that PSADT is an independent predictor of prognosis for nmCRPC, and authoritative guidelines define "PSADT ≤ 10 months" as a high risk of metastasis. Patients with nmCRPC with a high risk of metastasis have a faster rate of metastasis and a higher risk of death than other nmCRPC patients [111].

b. The SPARTAN study enrolled 1,207 M0CRPC patients with PSADT ≤ 10 months. The results showed that treatment with ADT + apalutamide (240 mg/day) significantly prolonged the metastasis-free

survival compared to the placebo group (40.5 months vs. 16.2 months, HR = 0.28, 95% CI 0.23–0.35, $P < 0.001$). After a median follow-up time of up to 52 months, the final analysis confirmed a significant overall survival benefit in nmCRPC (73.9 months vs. 59.0 months, HR = 0.78, 95% CI 0.64–0.96, $P = 0.016$). After excluding the impact of crossover enrollment, the 6-year overall survival rate in the apalutamide combined with ADT group was 50%, and 40% in the control group, reducing the risk of death by 31% (HR = 0.69, $P < 0.001$) [112, 113].

c. The ARAMIS study showed that darolutamide + ADT therapy significantly prolonged the metastasis-free survival of nmCRPC patients (40.4 months vs. 18.4 months, HR = 0.41, 95% CI 0.34–0.50, $P < 0.001$). The overall survival in the darolutamide group was significantly better than the placebo group, reducing the risk of death by 31% (median overall survival not yet reached, HR = 0.69). The 3-year OS in the darolutamide group was 83%, and 77% in the control group [114]. It is worth noting that some patients in the placebo group crossed over to the darolutamide group after disease progression (about 170 patients).

d. The PROSPER study showed that enzalutamide + ADT therapy significantly prolonged the metastasis-free survival compared to the placebo group (36.6 months vs. 14.7 months), and enzalutamide + ADT significantly reduced the risk of metastasis or death by 71% [115, 116]. Enzalutamide + ADT therapy significantly prolonged the median survival time compared to the placebo group (67.0 months vs. 56.3 months, HR = 0.73, 95% CI 0.61–0.89, $P < 0.001$). In addition, including the time to pain progression, the time to first antitumor treatment, PSA progression time, and quality of life assessments, enzalutamide demonstrated a therapeutic advantage for nmCRPC.

e. Other second-line endocrine therapies refer to first-generation anti-androgen drugs (bicalutamide, flutamide), ketoconazole, nilutamide, glucocorticoids, etc.

f. A domestic study showed that the use of 68 Ga-PSMA PET/CT combined with 18F-FDG PET/CT can detect lymph node and distant metastases earlier in nmCRPC patients, and about 51% of patients can be enrolled in clinical trials for metastatic lesion treatment [117, 118].

5.2 Diagnosis of metastatic CRPC

Diagnosis	
Confirmation of castration status [a]	
Serum PSA progression[b]	Or
Radiological progression[c]	

Note: a. Serum testosterone < 50 ng/mL or 1.7 nmol/L

b. PSA > 2 ng/ml and PSA continuously increases three times over a 1-week period, with each increase greater than 50% of the lowest value

c. The appearance of clear new lesions; bone scan suggests two or more new bone lesions; CT or MR suggests progression of soft tissue lesions (RECIST 1.1)

5.3 Treatment of metastatic CRPC

Treatment
Multidisciplinary Team(MDT to HIM) for Metastatic Castration-resistant Prostate Cancer (m CRPC)[a]
Select a medication treatment plan based on the patient's physical condition, symptoms, severity of the disease, and patient preferences, while considering the therapeutic effects of previous medications on hormone-sensitive metastatic PCa
Maintain continuous ADT
Consider supportive treatment besides systemic treatment.[b]
Regularly monitor of disease and effective evaluation [c]
Gene text[d]

Note: a. The multidisciplinary integrated diagnosis and treatment team should include urologists, oncologists, radiation oncologists, imaging diagnosticians, pathologists, and nuclear medicine physicians.

b. Metastatic castration-resistant prostate cancer often occurs in elderly and frail males. Supportive treatment includes pain management, nutritional support, traditional Chinese medicine adjustment, psychological comfort, and prevention of bone-related events.

c. Baseline examinations should include medical history, physical examination, and auxiliary examinations (PSA, testosterone, blood routine, liver and kidney function, ALP, bone scan, chest, abdomen, and pelvic CT, etc.). Even if the patient has no clinical symptoms, blood tests should be performed every 2–3 months, and bone scans and CT examinations should be performed at least every 6 months. The evaluation of treatment effectiveness needs to integrate PSA, imaging examination results, and clinical symptoms. At least two types of progression need to be considered before stopping the current treatment.

d. Genetic testing includes the detection of tumor cell dMMR MSI-H and germline or somatic homologous recombination gene (BRCA1, BRCA2, ATM, PALB2, FANCA, etc.) mutations [119]. A positive result for the former suggests the possibility of Lynch syndrome, and PD-1 inhibitors (such as Pembrolizumab) may become one of the optional treatment options in the later stage. A positive result for the latter suggests the possibility of benefiting from platinum-based chemotherapy drugs or PARP inhibitors, and relevant clinical studies can be participated in.

Recent high-level studies from China have shown that there are significant differences in the genetic mutations of prostate cancer patients in China compared with Western populations [6, 120, 121]. A domestic study published in "European Urology" based on a large sample of Chinese prostate cancer patients mapped the germline DNA repair gene mutation spectrum of Chinese prostate cancer patients. The results showed that although the incidence of prostate cancer in the West is much higher than in China, the overall germline pathogenic variations in DNA repair genes are similar (12% vs. 12%), but there are differences in specific genes. Among the germline gene mutations in Chinese patients, 62% are BRCA2 [6]. Another domestic study further identified POLN and POLG, two prostate cancer susceptibility genes unique to the Chinese population, which have not been reported in Western populations [120]. In addition, a domestic study analyzed the mismatch repair gene mutation data of 3,338 Chinese prostate cancer patients and found that the frequency of pathogenic mutations in mismatch repair genes in metastatic prostate cancer in China is much higher than in Western populations (4.8% vs. 2.2%, $P=0.006$), and mutation carriers have poor responsiveness to ADT and abiraterone [121]. Further research found that pathogenic mutations in mismatch repair genes are related to the efficacy of PD-1 treatment, and patients with better PD-1 treatment responsiveness have more CD8+T cell infiltration in their tumors. This study suggests that mismatch repair gene mutations are more common in Chinese prostate cancer patients and are associated with poor response to hormone therapy. The infiltration of CD8+T cells is expected to become a potential predictor of immunotherapy efficacy for such patients [121].

Systematic therapy	Category I	Category II	Category III
First line	abiraterone + Prednisone[a]	Olaparib + abiraterone[e]	Apalutamide[j]
	docetaxel[b]	Talazoparib + enzalutamide[f]	Darolutamide[k]
	enzalutamide[c]		
	Ra-223[d]	Rezvilutamide[h]	
		Sipuleucel-T[i]	Niraparib + abiraterone[g]
1st line new gerenation ARSI failure without chemotherapy	docetaxel	docetaxel[n]	abiraterone + Dexamethasone[q]
	Olaparib[m]	enzalutamide/ abiraterone + Prednisone	Another second generation ARSI without previously used
	Ra-233	enzalutamide + docetaxel[o]	
		Talazoparib + enzalutamide	Clinical trials[t]
		Niraparib + abiraterone	
		Sipuleucel-T	
		Rucaparib[p]	
1st line doxetaxol failture without new generation ARSI	abiraterone + Prednisone	cabazitaxel	
	enzalutamide		Another second generation ARSI without previously used
	Olaparib	Rezvilutamide	
	Ra-233	Talazoparib + enzalutamide	Clinical trials[t]
		Niraparib + abiraterone[g]	
		Sipuleucel-T	
Both ARSI and docetaxel failure	Olaparib(HRRmut)	^{177}Lu-PSMA-617 + SOC[r]	Clinical trials[t]
		Ra-223	Pembrolizumab[u]
		Docetaxel rechallenge[s]	Ra-223 + enzaluatimde[v]
		cabazitaxel	platinum-based chemotherapy[w]
		Rucaparib	etoposide[x]

Note: a. COU-AA-302 Phase III clinical trial results showed that compared with placebo, with the first-line use of abiraterone, the overall survival (34.7 vs. 30.3 months, HR: 0.81, $p=0.0033$, median follow-up of 49.2 months) and radiographic progression-free survival (16.5 vs. 8.2 months, HR: 0.52, $p<0.001$, median follow-up of 22.2 months) were significantly prolonged [122]. Abiraterone was equally effective and well tolerated in patients > 75 years of age. In addition to first-line treatment, the Phase III CUU-AA-301 study suggested a significant increase in survival of abiraterone versus placebo after a failure of docetaxel (15.8 versus 11.2 months, HR: 0.74, $p<0.001$, median follow-up of 20.2 months) [123]. Specific regimen: abiraterone 1000 mg qd + prednisone 5 mg bid. Abiraterone needs to be administered under fasting conditions. Abiraterone treatment requires attention to adverse effects such as edema, hypertension, and hypokalemia.

A retrospective study in China used the result of 68 Ga-PSMA-PET/CT to define the the spatial heterogeneity of PSMA uptake. The study included 153 mCRPC patients and sequenced their ctDNA. The result showed that patients with metastatic PC who had visceral metastases and multiple metastases tended to have higher heterogeneity scores on PSMA-PET/CT imaging (SUVhetero). Meanwhile, heterogeneity scores were significantly correlated with ctDNA%, total tumor burden, and tumor metabolic volume. Furthermore, patients with high heterogeneity scores had a lower PSA response rate after treatment with abiraterone (52% vs. 90%, $P=0.036$). Further independent validation in an external cohort revealed that patients with high heterogeneity scores had a significantly higher probability of progression at 3 months after enzalutamide treatment (50.0% vs 12.5%),

indicating the excellent predictive accuracy of the heterogeneity score for endocrine therapy efficacy [124].

b. Docetaxel plus prednisone significantly increases the median survival by 2 ~ 2.9 months compared to that with mitoxantrone plus prednisone [125]. The standard first-line chemotherapy is docetaxel 75 mg/m2 every 3 weeks combined with prednisone 5 mg bid, with pretreatment of dexamethasone (8 mg each, at 12 h, 3 h, and 1 h before chemotherapy, respectively). Generally, docetaxel is administered for 8 or more cycles during this period. The side effects are mainly bone marrow suppression. Approximately 12 ~ 15% of patients experience grade 3 ~ 4 agranulocytosis, and 6 ~ 12% have fever after grade 3 ~ 4 agranulocytosis. Prophylactic administration of G-CSF may reduce febrile granulocytopenia. Other side effects include neurotoxicity, gastrointestinal reactions such as nausea and vomiting, skin itching with red rash, nail pigmentation, etc. A multicenter, single-arm, prospective, observational study in China included 403 cases of mCRPC treated with docetaxel plus prednisone [126]. In the overall study population, the median overall survival with docetaxel was 22.4 months (95% CI, 20.4–25.8), with a PSA response rate of 70.9%.

ADT plus docetaxel chemotherapy is the standard treatment approach for patients with mCRPC. However, mCRPC patients are mostly weak elderly patients, frequently with complications and poor tolerance to the standard dose of docetaxel chemotherapy. In order to explore the non-inferiority clinical outcomes of modified docetaxel chemotherapy doses, a open-label, multicenter, double-blind non-inferiority clinical trial included 128 mCRPC patients and they were randomly assigned to the ADT plus modified docetaxel dosage group and the ADT plus standard docetaxel dosage group. Compared with the standard docetaxel dose, the docetaxel dose in the modified group was adjusted to 40 mg/m2, D1; 35 mg/m2, D8, and was repeated every 21 days. The primary endpoint was 2-year progression-free survival (PFS), while secondary endpoints included overall survival (OS), PSA response rate, pain relief rate, drug toxicity, and quality of life. Currently, this clinical trial is still ongoing, and the results are yet to be announced [127].

c. Enzalutamide: Phase III clinical trials (PREVAIL) [128] have demonstrated that when used as first-line treatment for mCRPC, enzalutamide significantly prolongs overall survival (35.3 months vs. 31.3 months, HR = 0.77, $P = 0.0002$) compared to placebo, with an extension in radiographic progression-free survival (20.0 months vs. 5.4 months, HR = 0.32, $P < 0.0001$). Subgroup analysis suggests that enzalutamide is effective even in patients older than 75 years, but shows no clinical benefit in those with liver metastasis. The Asian PREVAIL study, conducted in Asia, enrolled chemotherapy-naïve mCRPC patients from Asian countries, with 74% being Chinese patients. Results showed that compared to placebo, enzalutamide reduced the risk of PSA progression by 62% (HR = 0.38, $P < 0.0001$). Enzalutamide treatment benefits were observed across all subgroups. Five-year overall survival analysis revealed that enzalutamide significantly prolonged overall survival compared to placebo (39.06 months vs. 27.10 months, HR = 0.70, $P = 0.0208$) [129, 130]. The AFFIRM study [131] indicated that enzalutamide provides survival benefits as second-line treatment following docetaxel chemotherapy failure. The recommended dose of enzalutamide is 160 mg daily. Common adverse reactions include fatigue, diarrhea, hot flushes, headache, and seizures (with an incidence rate of 0.9%).

d. Radium-223 is a bone metastasis-specific drug that can significantly improve the quality of life and survival outcomes in patients with bone-only metastases. Phase III clinical trials (ALSYMPCA) [132] have shown that radium-223 can extend median overall survival by 3.6 months and significantly delay the time to the occurrence of bone-related events (15.6 months vs. 9.8 months). A single-arm Phase IIIb study of radium-223 in asymptomatic mCRPC patients with bone metastases demonstrated that even asymptomatic patients can benefit from radium-223 treatment; compared to symptomatic patients, asymptomatic patients had longer OS (20.5 months vs. 13.5 months, HR = 0.486, 95% CI 0.325–0.728), later onset of first symptomatic skeletal events (HR = 0.328, 95% CI 0.185–0.580), higher PSA response rates (21% vs. 13%), and lower incidence of grade 3–4 adverse reactions (29% vs. 40%) [133]. The main adverse reactions of radium-223 are hematological toxicities, although grade 3–4 toxicities are not common. Before initial use, neutrophils should be ≥ 1.510^9/L, platelets ≥ 10010^9/L, and hemoglobin ≥ 10 g/dL. Non-hematological adverse reactions are relatively mild, with nausea, vomiting, and diarrhea being common.

e. An international, multicenter, randomized, double-blind, phase III clinical trial, the PROpel study, showed that on the basis of ADT, olaparib (300 mg, twice a day) plus abiraterone (1000 mg, daily) significantly prolonged the rPFS in patients with mCRPC receiving the first-line treatment, compared with the abiraterone monotherapy (24.8 months vs. 16.6 months, HR = 0.66, $p < 0.0001$), regardless of HRR mutation status. And a subgroup analysis revealed that both patients with and without HRR mutations could benefit from the combination therapy (HRR mutations: HR = 0.50, 95% CI 0.34–0.73; non-HRR mutation: HR = 0.76, 95% CI 0.60–0.97). Among the enrolled patients, chemotherapy was allowed during the locally advanced or metastatic hormone-sensitive phase, but no other treatments

were employed during the CRPC stage [134]. The latest result of OS indicated that the median OS of the combination therapy and the abiraterone monotherapy failed to reach statistical significance (42.1 months vs. 34.7 months, HR = 0.81, 95% CI = 0.67–1.00, $p = 0.054$) [135]. The overall incidence of adverse events in the combination therapy group and the abiraterone monotherapy group was 97.7% and 96.0%, respectively, while the incidence of grade 3 or higher adverse events was 55.8% and 43.2%, respectively. Common adverse events (> 20%) included anemia (49.7%), fatigue (38.7%), and nausea (30.7%) [136].

f. The results of an international, multicenter, double-blind, randomized controlled, phase III clinical trial, the TALAPRO-2 study, showed that talazoparib (0.5 mg, daily) combined with enzalutamide (160 mg, daily) significantly prolonged the rPFS of first-line mCRPC patients compared with enzalutamide monotherapy (NR vs. 21.9 months, HR = 0.63, 95% CI 0.51–0.78, $p < 0.001$). Patients who had previously been treated with abiraterone accounted for 5.7% of the study population. Stratification factors such as prior use of abiraterone/docetaxel and HRR mutation status were considered in the randomization process. Regardless of prior use of abiraterone/docetaxel (used: HR = 0.56, 95% CI 0.38 ~ 0.83, $p = 0.004$; not used: HR = 0.68, 95% CI 0.53 ~ 0.88, $p = 0.003$) or HRR status (HRR mutation: HR = 0.48, 95% CI 0.31 ~ 0.74, $p < 0.001$; HRR non-mutant/unknown: HR = 0.69, 95% CI 0.54 ~ 0.89, $p = 0.004$), the superiority in efficacy favored the combination therapy group. The objective response rates in the two groups were 61.7% vs. 43.9% ($p = 0.005$), with a CR rate of 37.5% in the talazoparib plus enzalutamide group. There was an overall trend towards improved OS in the combination therapy group (HR = 0.69, 95% CI 0.46–1.03, $p = 0.07$), but the current data is still immature [137, 138]. In the subgroup analysis, the OS of the HRR mutation subgroup in the combination therapy group and the monotherapy group was 41.9 months vs. 31.1 months (HR = 0.57, 95% CI 0.36–0.91, $p = 0.02$).

g. An international, multicenter, randomized, double-blind, phase III clinical trial, the MAGNITUDE study, verified that on the basis of ADT, niraparib (200 mg, daily) plus abiraterone (1000 mg, daily), compared with the abiraterone monotherapy, could significantly prolong the rPFS of patients with mCRPC harboring germline and/or somatic BRCA gene mutations (19.5 months vs. 10.9 months, HR = 0.55, 95% CI 0.39 ~ 0.78, $P = 0.0007$). Among the overall HRR gene-deficient patients group, the rPFS was also notably prolonged in the combination therapy group compared with the abiraterone monotherapy group (16.5 months vs. 13.7 months, HR = 0.73, 95% CI 0.56–0.96, $p = 0.022$). The OS data is not yet mature, but the combination therapy has shown a trend of benefit (HR = 0.88, 95% CI 0.58–1.34, $p = 0.55$; after excluding the influence of crossover enrollment: HR = 0.68, 95% CI 0.45–1.05, $p = 0.0793$). The overall incidence of adverse events for the niraparib plus abiraterone therapy and the abiraterone monotherapy was 99.1% and 94.3%, respectively. The incidence of grade 3 or higher adverse events was 67.0% and 46.4%, respectively [139, 140].

h. A multicenter, open-label, single- and multiple-dose, dose-escalation, dose-expansion, phase I/II clinical trial in China included 197 mCRPC patients. The result showed that revilutamide exhibited excellent tolerability and good safety. At the end of the 12th week, the PSA response rate was 68.0% (95% CI 61.0% ~ 74.5%), with 75.7% (95% CI 66.8% ~ 83.2%) among patients without a history of prior chemotherapy (114 cases) and 57.3% (95% CI 45.9% ~ 68.2%) among patients with a history of prior chemotherapy (81 cases). The median rPFS was 14.0 months (95% CI 11.1 ~ 19.5 months), with 19.5 months (95% CI 11.1 ~ 27.6 months) and 11.1 months (95% CI 8.3 ~ 19.4 months) among patients without and with a history of prior chemotherapy, respectively. The median OS was 27.5 months (95% CI 24.6 ~ 30.8 months), with 30.8 months (95% CI 27.1 months ~ NR) and 22.9 months (95% CI 16.8 ~ 27.0 months) among patients without and with a history of prior chemotherapy, respectively [141].

i. A double-blind, multicenter, phase III clinical trial demonstrated a significant improvement in the OS rate in the Sipuleucel-T treatment group compared with the placebo group (HR = 0.78, 95% CI 0.61–0.98, $P = 0.03$). Even after adjustment for the treatment factor of docetaxel, a significant benefit was still observed (HR = 0.78, 95% CI 0.62–0.98, $p = 0.03$). Sipuleucel-T was mainly used for mCRPC patients with no symptoms or mild symptoms, no liver metastases, an expected survival of more than 6 months, and an ECOG score of 0–1. For patients with visceral metastasis, as well as small cell carcinoma and neuroendocrine carcinoma, it is not recommended. Common adverse reactions include flu-like symptoms such as headache, fever, and chills [142].

j. An open-label phase II clinical trial (ARN-509) evaluating the efficacy and safety of apalutamide plus ADT in the treatment of patients with mCRPC suggested that the safey of apalutamide is tolerable, and it is reliable for treating patients with mCRPC. In the cohort of patients who had not previously received novel endocrine therapy, the PSA50 response rate at 12 weeks of treatment was 88%, with a maximum PSA decline of 92%. The median treatment duration was 21 months, and the median PSA PFS was 18.2 months. However, in the cohort of patients who had failed in the abiraterone

treatment, the PSA50 response rate at 12 weeks was 22%, with a maximum PSA decline of 28%. The median treatment duration was 4.9 months, and the median PSA PFS was 3.7 months [143].

k. ARADES is a multicenter, open-label, dose-escalation, and dose-expansion, phase I/II clinical study that enrolled a total of 134 patients with mCRPC. Among them, 31% of patients received darolutamide as a first-line treatment for mCRPC (without prior chemotherapy or novel endocrine therapy). In this subgroup, the PSA response rate (PSA decline ≥ 50%) at 12 weeks was as high as 86%. The median time to PSA progression was 72 weeks (95% CI 24 weeks ~ NR), and the median time to radiological progression was not reached (95% CI 36.4 weeks ~ NR) [144].

m. A randomized, open-label, phase III study (PROfound) to assess the efficacy and safety of olaparib versus enzalutamide or abiraterone acetate in mCRPCs failing prior to hormonal therapy and carrying a homologous recombinant repair mutation (HRRm) showed that in patients with BRCA1/2 and ATM mutations (Cohort A), olaparib significantly reduced the radiographic progression and mortality risk by 66%, with a median radiographic progression-free survival (rPFS) of 7.4 months, which was superior to the 3.6 months in the enzalutamide or abiraterone acetate group; in the overall population with HRR-related gene mutations (Cohort A + B), olaparib significantly reduced the radiographic progression and mortality risk by 51%, with a median rPFS of 5.82 months, which was better than the 3.52 months in the enzalutamide or abiraterone acetate group [145]. At the same time, olaparib significantly prolonged the overall survival of patients with BRCA1/2 and ATM gene mutations (Cohort A) by 19.1 months, compared to only 14.7 months for second-generation antiandrogen drugs [146, 147].

Several real-world studies in China found that mCRPC patients with HRR gene mutations achieved a PSA response rate of over 50% after receiving the olaparib therapy. Additionally, among patients with HRR wild-type or variants of uncertain significance (VUS) in HRR genes, as well as other DDR pathway mutations, studies all found that olaparib exhibited antitumor efficacy, with adverse reactions generally safe and controllable.

n. Cabazitaxel has activity against docetaxel-resistant tumors, so it is recommended as a second-line drug after docetaxel failure [148]. The PROSELICA study demonstrated that cabazitaxel at a dose of 20 mg/m2 was not inferior to the dose of 25 mg/m2 in patients treated with docetaxel and was better tolerated [149]. Therefore, the current recommended dose is 20 mg/m2, once every 3 weeks, requiring hormone therapy such as docetaxel. Cabazitaxel mainly leads to hematologic toxicity, followed by neurotoxicity that is milder than that of docetaxel. The side effects require management by an experienced medical oncologist.

o. An international, multicenter, randomized, double-blind, placebo-controlled, phase III clinical trial, the PRESIDE study, showed that for patients with mCRPC who achieved a PSA decline of ≥ 50% at week 13 compared to baseline after previous enzalutamide treatment and later experienced PSA or radiological progression, continuing receiving enzalutamide (160 mg, daily) plus docetaxel (75 mg/m2, once every 3 weeks) resulted in a longer PFS compared with second-line docetaxel chemotherapy alone (9.53 months vs. 8.28 months; HR = 0.72, 95% CI 0.53 ~ 0.96, $p = 0.027$). And the incidence of treatment-related adverse reactions was similar between the two groups, suggesting that the combination therapy did not significantly increase toxicity [150]. Therefore, this combination regimen can be considered for patients who respond to enzalutamide but later experience progression.

p. Rucaparib is another PARP inhibitor that has been approved for use in patients with mCRPC. A open-label, single-arm, phase II clinical trial, the TRITON2 study, showed that in mCRPC patients with BRCA1/2 mutations who have received novel endocrine therapy combined with chemotherapy, the use of rucaparib (600 mg, bid) resulted in an ORR of 43.5% (95% CI 31% ~ 56.7%). The rPFS was 9.0 months (95% CI, 8.3 ~ 13.5) [151, 152]. Immediately after, in the randomized phase III TRITON3 study, mCRPC patients with BRCA1/2 or ATM mutations who had previously received novel endocrine therapy but not chemotherapy were randomly assigned in a 2:1 ratio to receive rucaparib treatment or standard-of-care therapy (abiraterone, enzalutamide, or chemotherapy). The TRITON3 study indicated that the rPFS of the 270 patients receiving rucaparib was significantly longer than that of the 135 patients receiving the control agents (10.2 months vs. 6.4 months, HR = 0.61, 95% CI 0.47 ~ 0.80, $p < 0.001$). The same effect was observed in the 201 and 101 patients with BRCA mutations in each group (11.2 months vs. 6.4 months, HR = 0.50, 95% CI: 0.36 ~ 0.69). For patients with ATM mutations, an exploratory analysis also indicated a possible improvement (8.1 months vs. 6.8 months, HR = 0.95, 95% CI: 0.59 ~ 1.52) [153]. The two studies both suggested that the most common adverse events included fatigue, nausea, and decreased hemoglobin levels [154].

q. A single-arm, open-label, phase II clinical trial, the SWITCH study, indicated that for patients who had failed in the abiraterone therapy, a switch from prednisone to dexamethasone (1 mg, daily) could be considered. Among a population of 26 patients, the proportion of patients achieving a ≥ 30% decline in PSA within 6 weeks was 46.2%. No significant toxicity was observed, and

two cases of radiographic response were noted [155]. In another study, for 48 mCRPC patients who had progressed after the previous treatment with abiraterone plus prednisone, after they received abiraterone plus dexamethasone (0.5 mg, daily) treatment, the median PFS reached 10.35 months and PSA levels declined or remained stable in 56% of the patients [156].

r. Lu-177-PSMA-617 is a radioactive drug through intravenous injection, suitable for PSMA-positive mCRPC patients who have undergone novel endocrine therapy and chemotherapy. Its active component is a radionuclide that releases radiation to PSMA-positive cells and their surrounding cells, causing DNA damage and leading to cell death. An international, multicenter, open-label, phase III clinical trial, the VISION study, showed that among 831 patients who had previously received novel endocrine therapy and failed in second-line chemotherapy or above, with positive PSMA expression demonstrated by 68 Ga-PSMA PET/CT scans, the use of Lu-177-PSMA-617 combined with standard therapy (excluding chemotherapy, immunotherapy, radium-223, and experimental drugs) resulted in a radiographic progression-free survival (8.7 months vs. 3.4 months, $p<0.001$, HR = 0.40) and overall survival (15.3 months vs. 11.3 months, $p<0.001$, HR = 0.62), longer than those in the standard therapy group (abiraterone, enzalutamide, bisphosphonates, radiotherapy, denosumab, and/or glucocorticoids). The incidence of adverse events of grade ≥ 3 (especially anemia, thrombocytopenia, lymphocytopenia, and fatigue) was significantly higher in the Lu-177-PSMA-617 group compared with the control group [157].

Utilizing the reversible binding properties of Evans Blue (EB) with plasma albumin, the combination with the PSMA-617 molecule can improve the pharmacokinetics and pharmacodynamics of the drug. And further binding with 177Lu resulted in the novel radionuclide therapeutic agent 177Lu-EB-PSMA-617. A single-arm, low-dose, phase I clinical trial in China included 30 patients with mCRPC who had failed in the docetaxel chemotherapy and ADT treatment. All patients received a dose of 2.0 GBq of 177Lu-EB-PSMA therapy once every 8 weeks. The results showed that among the 30 subjects, 17 patients (56.7%) had a PSA reduction of at least 50%. The median PSA PFS reached 4.6 months (95% CI 2.7 ~ 6.5 months), and the median OS was 12.6 months (95% CI 8.1 ~ 17.1 months). In addition, there was a significant improvement in patients' health-related quality of life [158].

Besides Lu-177-PSMA-617, in order to increase the retention of 177Lu in tumors and improve its utilization, a second-generation long-circulating PSMA-targeted probe, 177Lu-PSMA-EB-01, also known as [177Lu]Lu-LNC1003, has been developed. A phase I clinical trial in China enrolled 13 patients with mCRPC, all receiving [177Lu]Lu-LNC1003 treatment and using a standard 3 + 3 dose escalation scheme. Each patient received a maximum of two cycles of [177Lu]Lu-LNC1003 treatment, with a 6-week interval between cycles. The final results showed that the maximum tolerated dose of [177Lu]Lu-LNC1003 was 1.85 GBq, delivering high effective tumor doses in bone and lymph node metastases, which established the safety profile of this novel therapeutic approach [159].

s. Docetaxel rechallenge: For patients who have responded well to docetaxel and have not shown definitive progression during previous hormone-sensitive stages, docetaxel retreatment can be considered [160, 161].

t. Clinical research includes studies on novel therapies such as deutenzalutamide (HC-1119), new PARP inhibitors like fuozapalide, and PSMA radionuclide therapy [162]. Deutenzalutamide is a deuterium-substituted derivative of enzalutamide that exhibits different metabolic characteristics from previous drugs and maintains biological activity at lower doses. A multicenter, randomized, double-blind phase III trial in China, the HC-1119-04 study, enrolled mCRPC patients who had failed in the abiraterone treatment or docetaxel treatment, or were ineligible for these treatments. Patients were randomly assigned to receive deutenzalutamide (80 mg, daily) or placebo in a 2:1 ratio. The results showed that deutenzalutamide significantly prolonged rPFS (5.55 months vs. 3.71 months, HR = 0.58, 95% CI 0.439 ~ 0.770, $p=0.001$). There was no significant difference in the overall incidence of treatment-related adverse events of grade 3 or higher between the deutenzalutamide group and the placebo group [163].

u. Pembrolizumab: A treatment targeting 149 cancer patients involving 5 clinical trials included patients with MSI-H or MMR-deficient (dMMR) solid tumors. Among them, 2 patients had mCRPC, with 1 achieving partial remission and the other maintaining stable disease for over 9 months [164]. KEYNOTE-199 was a multicohort, open-label, phase II clinical study that enrolled 258 patients with mCRPC who had previously received chemotherapy and at least one novel endocrine therapy. The aim of the study was to evaluate the efficacy of pembrolizumab in patients regardless of their microsatellite status. Cohort 1 and Cohort 2 included PD-L1-positive (n = 133) and PD-L1-negative (n = 66) mCRPC patients, respectively. Cohort 3 comprised patients with mainly bone metastases regardless of PD-L1 status (n = 59). The results showed that the overall response rate (ORR) was 5% (95% CI, 2% ~ 11%) in Cohort 1 and 3% (95% CI, < 1% ~ 11%) in Cohort 2. However, the anti-cancer effect was durable, ranging from 1.9 to ≥ 21.8 months [165]. Pembrolizumab's most common adverse events

include fatigue, pruritus, diarrhea, anorexia, constipation, nausea, rash, fever, cough, dyspnea, and musculoskeletal pain. Pembrolizumab could also be associated with immune-related adverse reactions, including colitis, hepatitis, endocrinopathies, pneumonitis, or nephritis. The use of pembrolizumab was restricted to mCRPC patients with MSI-H, dMMR, or TMB ≥ 10 mut/Mb who had progressed after prior novel endocrine therapy and chemotherapy.

v. A randomized, controlled Phase II clinical study was conducted to investigate the efficacy of radium-223 in combination with enzalutamide versus enzalutamide alone in the treatment of mCRPC. A total of 47 patients were enrolled in the study, with a median follow-up time of 22 months. The study results demonstrated that compared to enzalutamide monotherapy, the combination of radium-223 and enzalutamide showed better outcomes, with a PSA-PFS2 (defined as the time from the start of study drug treatment until PSA progression or death during subsequent treatment) of 18.7 months versus 8.41 months ($P=0.033$) and a TTNT (time to next treatment) of 15.9 months versus 3.47 months ($P=0.067$). Among the Phase II study participants, 37.8% of patients experienced fractures, with 8.9% occurring during treatment and 28.9% occurring after treatment completion. Subsequent safety data from the PEACE-3 Phase III clinical study (radium-223 + enzalutamide vs. enzalutamide) confirmed that under the use of bone-protecting agents, the combination of radium-223 and enzalutamide did not increase the incidence of fracture events compared to enzalutamide alone (12-month fracture incidence rate of 2.7% vs. 2.6%) [166, 167].

w. A study that enrolled 113 patients with mCRPC demonstrated a median OS of 16 months (95% CI 13.6 ~ 19.0 months) following platinum-based chemotherapy [168]. Another study showed that after using platinum-based chemotherapeutic drugs, 36% of patients with mCRPC achieved a PSA decline of more than 50% [169]. The main adverse reactions associated with platinum-based chemotherapy include bone marrow suppression, renal adverse reactions, gastrointestinal reactions, neurotoxicity, hair loss, liver dysfunction and generalized fatigue.

x. A domestic study involving 39 patients with mCRPC who had progressed after hormone therapy found that after treatment with etoposide, 41% of the patients achieved a PSA decline of more than 50%. The median PFS was 5.9 months (range: 1 ~ 17 months) [170]. The primary adverse reactions associated with etoposide treatment include bone marrow suppression, gastrointestinal reactions, allergic reactions, skin reactions, neurotoxicity, fever, electrocardiogram abnormalities, hypotension and phlebitis.

5.4 Prevention of skeleton-related events

Prevention of skeleton-related events[a]
Drug therapy
Bone-modifying drugs: bisphosphonates[b] (zoledronic acid, incadronate disodium, etc.) denosumab[c]
Analgesics[d]
Radiotherapy [e]
Surgical treatment [f]

Note: a. Skeleton-related complications arise from bone metastasis. These primarily include pathological fractures (especially vertebral compression or deformation), spinal cord compression, post-radiotherapy bone symptoms, progression of bone metastases, and hypercalcemia [171].

b. Zoledronic acid significantly reduces skeleton-related events, especially pathological fractures. However, no clinical studies have found survival benefits. It may also cause a serious adverse event, i.e., mandibular necrosis, so a dental examination should be performed before treatment. A history of trauma, dental surgery, or dental infection increases the risk of jaw necrosis. The recommended dose is 4 mg, injected once every 3–4 weeks. The drug is not recommended for use in patients with renal impairment (creatinine clearance < 30 mL/min).

c. Denosumab is a humanized monoclonal antibody targeting the receptor activator of nuclear factor κB ligand (RANKL). According to phase III clinical trials comparing the efficacy and safety of denosumab and zoledronic acid in the treatment of metastatic castration-resistant PC, denosumab is superior to zoledronic acid in delaying and preventing bone-related complications, with a subcutaneous dose of 60 mg once every 4 weeks [172]. Denosumab is prone to cause hypocalcemia and thus requires supplementation with both calcium and vitamin D.

d. The use of analgesics: Analgesics are one of the main treatment therapies for relieving pain caused by bone metastases in PC. The use of analgesics should follow the basic principles of WHO for cancer pain treatment, with oral and non-invasive administration routes as the preferred options. Administration should be based on the principles of stepped dosing, regular dosing, and individualized dosing. Meanwhile, appropriate comprehensive treatment measures should be taken based on the patient's condition, physical status, location, and characteristics of the pain, to achieve the goal of eliminating pain and improving quality of life. Commonly used analgesics include: ①non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen; ②opioid analgesics; ③bisphosphonates; ④adjunctive analgesic medications, which mainly include anti-convulsants, antidepressants,

corticosteroids, N-methyl-D-aspartate receptor (NMDAR) antagonists, and local anesthetics [171].

e. Bone metastases often cause vertebral collapse, pathological fractures, and spinal cord compression. External beam radiotherapy can significantly reduce bone pain.

f. Spinal cord compression is an emergency condition. Once it is suspected, high-dose hormone treatment must be given as soon as possible, and surgical intervention must be carried out as early as possible after full examinations [171].

6 Traditional Chinese Medicine (TCM) diagnosis and treatment of PC

6.1 TCM diagnosis of PC

TCM diagnosis of PC
Disease diagnosis[a]
Syndrome diagnosis[b]

Note: a. PC is caused by the combined action of various factors, such as external pathogens, internal damage, diet, and viscera dysfunction, resulting in disorders of "yin" and "yang", deficiency of healthy "qi", and obstruction of "qi" and blood to meridians and collaterals, causing local "qi" stagnation, blood stasis, phlegm coagulation, dampness accumulation, and heat toxin. Spleen-kidney deficiency is the primary cause, and pouring down of dampness or heat, phlegm and blood stasis, as well as other factors, accelerate the progression of the disease.

b. Syndrome diagnosis

(1) Before local and systemic treatment

1) Syndrome of liver "qi" depression: chest distress and discomfort, hypochondriac pain, abdominal distension, no appetite for food, or "qi" ascending in a counterflow to the throat, limb fatigue, light red tongue with a thick, white coating, and wiry pulse.

2) Syndrome of "qi" depression transforming into fire: chest distress and discomfort, hypochondriac pain, abdominal distension, no appetite for food, red face and eyes, vexing heat in the chest, dark urine with burning pain, red tongue with a yellow coating, and wiry pulse.

3) Syndrome of malnutrition of the heart spirit: trance, restless mind, suspicious and easily startled, sad and easily crying, temperamental, or always stretching and yawning, having a pale tongue with a thin coating, and having a wiry pulse.

4) Syndrome of heart-spleen deficiency: severe palpitations, insomnia, dreaminess, dizziness and amnesia, sallow complexion, inappetence, abdominal distension and loose stool, fatigue and weakness, pale and tender tongue or tooth-marked tongue with a thin coating, and thready-weak pulse.

5) Syndrome of heart-kidney "yin" deficiency: heartache, palpitations, night sweats, insomnia, soreness and weakness of the waist and knees, dizziness and tinnitus, frequent and urgent urination, frequent nocturnal urination, dry mouth and constipation, red tongue with fluid inadequacy and a thin or peeling coating, thready and rapid pulse, regularly intermittent pulse, and irregular-rapid pulse.

(2) After Local and Systemic Treatment

1) Syndrome of stasis-heat injuring fluid: pain in the surgical wound, no aversion to cold, fever, dry mouth, dark red tongue with a sparse coating, and pulse that is wiry and thready.

2) Syndrome of spleen deficiency and "qi" stagnation: weakness, shortage of "qi", abdominal distension, poor appetite, constipation, light red tongue with thick or yellow and greasing coating, and pulse that is wiry and thready.

3) Syndrome of kidney deficiency with dampness and fever: urinary pain, dribbling, even incontinence, light red tongue with a yellow coating, deep and thready pulse.

4) Syndrome of "qi"-blood deficiency: fatigue, physical deficiency and weak "qi", pale tongue with a thin or sparse coating, and thready pulse.

6.2 TCM treatment of PC

TCM treatment
Before local or systemic treatment[a]
After local or systemic treatment[b]

Note: a. Before local and systemic treatment:

(1) Syndrome of liver "qi" depression

Therapeutic methods: soothing the liver and relieving depression, regulating "qi" and clearing the middle energizer

1) Recommended prescription: modified Bupleurum Liver-Soothing Powder (Dried Tangerine Peel, Bupleurum, Sichuan Lovage Rhizome, Nutgrass Galingale Rhizome, Orange Fruit, Peony, Licorice Root, etc.) or Chinese patent medicines (including TCM injections) with the same effect.

2) TCM soaking and washing techniques: Select traditional Chinese medicines for regulating "qi" and activating blood, wash and press the feet with the decoction obtained therefrom, once daily, for 15 ~ 30 min each time. The water temperature should be 37 ~ 40 °C. After soaking the feet for a few minutes, water is gradually added to reach a level above the ankle joint. The water temperature should not be too high to avoid scalding the skin.

(2) Syndrome of "qi" depression transforming into fire

Therapeutic methods: soothing the liver and relieving depression, clearing the liver and draining fire

1) Recommended prescription: modified Danzhi Xiaoyao Pill (Tree Peony Root Bark, Cape Jasmine Fruit (stir-fried to brown), Bupleurum (processed with liquor), Debark Peony Root (stir-fried with liquor), Chinese Angelica, White Atractylodes Rhizome (stir-fried with earth), Poria, Peppermint, processed Licorice Root, etc.) or Chinese patent medicines (including TCM injections) with the same effect.

2) TCM soaking and washing techniques: Traditional Chinese medicines are selected for regulating "qi" and heat clearing, washing and pressing the feet with the decoction once daily for 15 ~ 30 min each time. The water temperature should be 37 ~ 40 °C. After soaking the feet for a few minutes, water is gradually added to reach a level above the ankle joint. The water temperature should not be too high to avoid scalding the skin.

(3) Syndrome of malnutrition of the heart spirit

Therapeutic methods: moistening with sweet and relaxing spasms, nourishing the heart and tranquilizing the mind

1) Recommended prescription: modified licorice, wheat and jujube decoction (licorice root, wheat, Chinese date, etc.) or Chinese patent medicines (including TCM injections) with the same effect.

2) TCM soaking and washing techniques: Traditional Chinese medicines are selected for nourishing the heart and tranquilizing the mind, washing and pressing the feet with the decoction obtained therefrom, once daily, for 15 ~ 30 min each time. The water temperature should be 37 ~ 40 °C. After soaking the feet for a few minutes, water is gradually added to reach a level above the ankle joint. The water temperature should not be too high to avoid scalding the skin.

(4) Syndrome of heart-spleen deficiency

Therapeutic methods: invigorating the spleen and nourishing the heart, tonifying "qi" and blood

1) Recommended prescription: modified Returning to Spleen Decoction (Largehead Atractylodes Rhizome, Ginseng, Milkvetch Root, Chinese Angelica, Licorice Root, Poria, Milkwort Root, Spine Date Seed, Common Aucklandia Root, Longan Aril, Ginger, Chinese Date, etc.) or Chinese patent medicines (including TCM injections) with the same effect.

2) TCM soaking and washing techniques: Traditional Chinese medicines are selected for invigorating the spleen, nourishing the heart and tonifying "qi", washing and pressing the feet with the decoction obtained therefrom once daily for 15 ~ 30 min each time. The water temperature should be 37 ~ 40 °C. After soaking the feet for a few minutes, water is gradually added to reach a level above the ankle joint. The water temperature should not be too high to avoid scalding the skin.

(5) Syndrome of heart-kidney "yin" deficiency

Therapeutic methods: nourishing the heart and kidney

1) Recommended prescription: modified Celestial Emperor Heart-Tonifying Pill (Ginseng, Poria, Figwort Root, Salvia Root, Platycodon Root, Milkwort Root, Chinese Angelica, Chinese Magnolia Vine Fruit, Ophiopogon, Cochinchinese Asparagus Root, Chinese Arborvitae Kernel, Spine Date Seed, Unprocessed Rehmannia Root, etc.) or Chinese patent medicines (including TCM injections) with the same effect.

2) TCM soaking and washing techniques: Traditional Chinese medicines are selected for nourishing the heart and tonifying the kidney, washing and pressing feet with the decoction obtained therefrom, once daily, for 15 ~ 30 min each time. The water temperature should be 37 ~ 40 °C. After soaking the feet for a few minutes, water is gradually added to reach a level above the ankle joint. The water temperature should not be too high to avoid scalding the skin.

[b]After local and systemic treatment:

(1) Syndrome of stasis-heat injuring fluid

Therapeutic methods: dispelling stasis, clearing heat, and promoting fluid production

Recommended prescription: modified Five-Ingredient Toxin-Eliminating Decoction + Stomach-benefiting Decoction (Honeysuckle Flower, Wild Chrysanthemum Flower, Dandelion, Coastal Glehnia Root, Fragrant Solomonseal Rhizome, Unprocessed Rehmannia Root, Ophiopogon, Licorice Root, Villous Amomum Fruit, Dried Tangerine Peel, etc.), or Chinese patent medicines (including Chinese medicine injections) with the same effect.

(2) Syndrome of spleen deficiency and "qi" stagnation

Therapeutic methods: replenishing "qi" and invigorating the spleen, moving "qi" and dredging fu-organs

Recommended prescription: modified four milled ingredient decoction (combined Spicebush Root, Ginseng, Chinese Eaglewood Wood, Acao Seed, etc.), or Chinese patent medicines (including Chinese medicine injection) with the same effect.

(3) Syndrome of kidney deficiency and dampness heat

Therapeutic methods: Replenishing the kidney, relieving stranguria, and applying both warming and clearing therapies

Recommended prescription: modified gate-freeing pill + two wonderful herbal powders (Amur Cork-Tree, Common Anemarrhena Rhizome, Cassia Bark, Atractylodes Rhizome, etc.) or Chinese patent medicines (including TCM injections) with the same effect.

(4) Syndrome of "qi"-blood deficiency

Therapeutic methods: tonifying and replenishing "qi" and blood

Recommended prescription: modified Eight Precious Ingredients Decoction (Ginseng, Largehead Atractylodes Rhizome, white Poria, Chinese Angelica, Sichuan Lovage Rhizome, Debark Peony Root, Prepared Rehmannia Root, Licorice Root, etc.) or Chinese patent medicines (including TCM injections) with the same effect.

6.3 Other therapies of PC with TCM characteristics

TCM can promote body function recovery from PC surgery, reduce adverse reactions to ADT and chemotherapy, improve self-immunity, and improve quality of life. It can be used alone or in combination with other antitumor drugs. With its dialectical principle similar to the individualized treatment principle of Western medicine, TCM can provide specific therapy for individuals. Chinese medicine is unique in its promotion of functional recovery after PC surgery, with evidence from multiple published articles that acupuncture can effectively improve sexual function and urinary continence.

(1) Acupuncture and moxibustion: 1) moxibustion: Select Qihai, Guanyuan and other acupoints as per specific symptoms (moxibustion box may be used), 20 min each time, twice a day. 2) Drug acupoint application: Shenque, Shenyu, Yaoyangguan, Zusanli, Yongquan and other acupoints are selected to apply medicines such as Kanli Coarse Powder, Four Seeds Powder and Medicinal Evodia Fruit for 4 ~ 6 h each time. 3) Acupuncture: Select acupoints such as Sanyinjiao, Zusanli, Guanyuanyu, Weizhong, Pangguangyu, Zhongji, Chengshan, Yinlingquan and Guanyuan twice a week, with 1 treatment course lasting 3 months.
(2) Dietary recuperation: Patients should have a light diet and avoid spicy food, alcohol, coffee, strong tea and so on; it is good to eat some cancer-fighting fruits such as the strawberry, orange, apple, cantaloupe, kiwifruit, lemon, grape, and pineapple. Patients should eat more cruciferous vegetables, such as peas, turnips, carrots, broccoli and cauliflower; consume less meat and dairy products, especially red meats such as beef, dog meat and mutton; supplement their diets with more vitamin E, or ingest more nuts, olive oil, soybean oil, corn oil, sesame oil and so on.
(3) Emotional regulation: 1) Pay attention to emotional care to avoid emotional stimulation. 2) Strengthen publicity and education regarding common aspects of the disease to help patients correctly understand their illness; learn self-psychoregulation; avoid adverse emotions such as anxiety, tension, depression and fear; and maintain a comfortable mood.

7 Rehabilitation from PC

Rehabilitation Therapy
7.1 Psychotherapy[a]
7.2 Cancer pain management[b]
7.3 Physical rehabilitation[c]

Note: a. Psychotherapy: 1) At the first diagnosis of the disease: analyze and correct the patients' incorrect understanding of malignant tumors so that they can correctly understand and treat the disease and quickly enter the adaptation period after passing through the psychological shock period and conflict period. Meanwhile, mobilize their family members and friends to cooperate with medical personnel to eliminate patients' concerns, solve practical difficulties and achieve psychological recovery. 2) During the treatment: Before the treatment, inform the patients of the purpose and method of treatment, the possible side effects, functional disorders, and disabilities as well as the management and rehabilitation therapy thereof so that the patients can quickly adapt to and deal with such situations correctly after treatment. For patients with severe dysfunction and recurrence, psychological rehabilitation should be strengthened to enable them to pass through the period of psychological shock and conflict as soon as possible. In addition, it may be helpful to invite other patients with the same disease to share their experience, if necessary. 3) End stage of the disease: Provide the maximum help and support to patients who can correctly deal with the disease and try one's best to fulfill their last wishes. Pessimistic and desperate patients should be provided with a quiet and comfortable environment, careful and considerate care and consolation, along with relaxation techniques and necessary drugs. Patients with severe cancer pain should be given analgesia and spiritual support to alleviate physical and mental suffering until their death.

b. Cancer pain management: 1) Drug therapy is the most commonly used analgesic measure. The WHO's "three-step analgesic ladder for cancer pain relief" should be followed. Mild to moderate pain: Nonopioid analgesics can be used, first with antipyretic analgesics such as aspirin and acetaminophen, then followed by nonsteroidal anti-inflammatory drugs such as ibuprofen and indomethacin if without an obvious effect of the former category. Moderate to severe pain: Weak opioid analgesics can be used, such as codeine and fentanyl. Severe pain: Strong opioid analgesics can be used, such as morphine, pethidine and methadone. During the abovementioned steps of administration, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, antihistamines, antispasticity agents, muscle relaxants,

nerve-damaging drugs and hormones may be added as appropriate. This combination can enhance the analgesic effect, reduce the classification level of narcotic analgesics, and reduce the total dosage. 2) Radiotherapy has a good relief effect, relieving pain within several days and controlling cancer. For patients with a few metastases and confirmed pain sites, radiation oncologists may be consulted to formulate the plan. 3) TCM treatment: Acupuncture of related remote acupoints has a certain analgesic effect, but it is prohibited in the tumor area. 4) Injection therapy includes peripheral nerve block, nerve root block, sympathetic nerve block, subarachnoid block, epidural block, etc. Local anesthetics, 6% phenol (carbolic acid), 10% phenol glycerol, anhydrous alcohol, etc., can be selected as blocking agents. Cryotherapy or radiofrequency ablation of the spinal dorsal root may also be applied. 5) Surgical treatment: For stubborn severe pain, neurolysis, neurotomy, etc., can be performed.

c. Physical rehabilitation: 1) Urinary continence recovery: Conservative therapy is usually adopted, such as pelvic floor muscle training, electrical stimulation, acupuncture, extracorporeal magnetic innervation, and penile clamping. Pelvic floor muscle training, also known as Kegel exercises, is applied to contract the perianal muscles and actively drive the contraction of the external urethral sphincter and thus help actively control urine. Pelvic floor muscle training should be carried out daily, 200 to 500 times, until the recovery of urinary continence gradually occurs. 2) Sexual function rehabilitation: Erectile dysfunction after radical prostatectomy is the most common sexual dysfunction. For patients with sexual requirements, the nerve-sparing technique can be selected during radical surgery. Certain drugs, such as PDE5 inhibitors (e.g., sildenafil, vardenafil and tadalafil), can be given to treat erectile dysfunction after surgery. Instruments, such as penile rehabilitation devices and penile prostheses, may also be implanted.

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