Review Article

Saudi Oncology Society and Saudi Urology Association combined clinical management guidelines for prostate cancer 2017

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Abstract

This is an update to the previously published Saudi guidelines for the evaluation and medical and surgical management of patients diagnosed with prostate cancer. Prostate cancer is categorized according to the stage of the disease using the tumor node metastasis staging system 7th edition. The guidelines are presented with supporting evidence levels based on a comprehensive literature review, several internationally recognized guidelines, and the collective expertise of the guidelines committee members (authors) who were selected by the Saudi Oncology Society and Saudi Urological Association. Local factors, such as availability, logistic feasibility, and familiarity of various treatment modalities, have been taken into consideration. These guidelines should serve as a roadmap for the urologists, oncologists, general physicians, support groups, and health-care policymakers in the management of patients diagnosed with adenocarcinoma of the prostate.

Keywords: Guidelines, management, prostate cancer, Saudi Oncology Society, Saudi Urological Association

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INTRODUCTION

In Saudi Arabia, prostate cancer is the sixth most common cancer among men of all ages. There were 310 cases of prostate cancer in 2001, accounting for 6.8% of all cancer cases among adult males in that year. The age-standardized rate (ASR) was 6.0/100,000. The five regions with the highest ASR were the Eastern region at 11.3/100,000, the Riyadh region at 8.0/100,000, the Makkah region at

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5.9/100,000, the Northern region at 5.1/100,000, and the Asir region at 4.9/100,000. The median age at diagnosis was 72 years (range 6–101 years). The cancer stage at the time of diagnosis is localized in 46.9% of cases, with the remaining 53.1% being locally advanced (7.1%), metastatic (30.2%), or unknown (15.8%).[1] Notably, there has been a steady increase in the number of reported cases in the Saudi Cancer Registry for the last two decades, which could be secondary to wider prostate-specific antigen (PSA) utilization, improved documentation, and reporting.

The present guidelines are an update to the previously published Saudi Oncology Society guidelines for the evaluation, medical, and surgical management of prostate cancer.[2-4] More than 95% of primary prostate cancers are adenocarcinomas, so these guidelines are focused on this category of prostate tumors. This cancer is categorized according to the stage of the disease using the tumor node metastasis staging system 7th edition. The guidelines are presented with supporting evidence level according to an article accompanying the guidelines 1st edition, as well as the scope, purpose, and methods of these guidelines.[5]

DIAGNOSIS AND STAGING EVALUATION

When a biopsy is indicated, systematic transrectal ultrasound-guided core biopsies (10–12) should be performed. A multi-parametric magnetic resonance imaging (MRI)/ultrasound fusion-targeted biopsy may also be used, if available. Once the diagnosis is confirmed, the following staging evaluations should be done:

1. Computed tomography (CT) or MRI (abdomen and pelvis) should only be done when cancer is considered high risk according to D'Amico risk groups (EL-2) [Table 1][6,7]
2. Bone scan should only be done if any of the following (EL-2):[8-11]
    i. PSA level >20 ng/mL
    ii. Patients with bone pain
    iii. Gleason score ≥8
    iv. Patient with clinical stage T3 or T4
    v. Hypercalcemia or high serum alkaline phosphatase.

STAGING CLASSIFICATION

The tumor node metastasis AJCC staging 7th edition should be used [Table 2].

Table 1: D'Amico risk groups for prostate cancer

Low-risk	Intermediate-risk	High-risk
T1–T2a and GS ≤6 and PSA ≤10	T2b and/or GS=7 and/or PSA >10–20	≥ T2c or GS 8-10 or PSA >20

PSA: Prostate-specific antigen, GS: Gleason score

MANAGEMENT

The management options for prostate adenocarcinoma depend on the stage (localized vs. metastatic), risk group, and life expectancy.[12] The approach to treatment is influenced by patient's age, general condition, and coexisting medical problems, as well as his preferences. Side effects of various forms of treatment should be considered in selecting appropriate management.

1. Localized disease (cT1-2 N0): Any benefits of definitive local therapy with curative intent may take years to emerge. Therefore, therapy with curative intent is usually reserved for men with a sufficiently long life expectancy
    i. Low-risk – Therapy options depend on the following factors:
        - If a patient is asymptomatic with life expectancy <5 years: No further intervention required until symptoms or clinical progression develops (EL-2)[13-15]
        - If asymptomatic with life expectancy between 5 and 10 years: Active surveillance: involves active monitoring of the course of disease with the expectation to intervene with curative intent if cancer progresses (EL-2)[13,15,16]
        - If asymptomatic with life expectancy >10 years: Options include active surveillance, radical prostatectomy (RP), external-beam radiation therapy (EBRT), or brachytherapy (EL-2)[16-19]
        - The strategy behind active surveillance is to defer therapy for the clinically localized disease but regularly follow the patient and initiate local therapy with curative intent if there are any signs of local tumor progression. Active surveillance candidates must have all the following criteria: PSA <10 ng/ml, Gleason sum ≤6, number of positive cores ≤2, percentage of cancer involvement in any positive core <50%, and PSA density <0.15. Follow-up should entitle history, physical examination, and PSA every 3–6 months and repeated biopsy every 12–18 months (at least once); radical therapy should be offered if PSA velocity >0.35 ng/ml/year or progression in any of the aforementioned criteria[20-24]
        - All RPs should be done in tertiary care centers by high-volume surgeons (EL-2); surgeon experience has been associated with improved recovery of postoperative continence and erectile function, with a very low surgical mortality[25,26]
        - Lymph node dissection (LND) can be omitted if the chance of being positive is <5% according to nomograms (EL-2)[27,28]

Table 2: Tumor node metastasis stage definitions for prostate cancer

Primary tumor (T)	Regional lymph nodes (N)	Distant metastasis (M)[§]
TX: Primary tumor cannot be assessed	NX: Regional lymph node (s) were not assessed	M0: No distant metastasis
T0: No evidence of primary tumor	N0: No regional lymph node metastasis	M1: Distant metastasis or positive peritoneal cytology
T1: Clinically inapparent tumor neither palpable nor visible by imaging	N1: Metastasis in regional lymph node (s)	M1a: Nonregional lymph node (s)
T1a: Tumor incidental histological finding in 5% or less of tissue resected		M1b: Bone (s)
T1b: Tumor incidental histological finding in more than 5% of tissue resected		M1c: Other site (s) with or without bone disease
T1c: Tumor identified by needle biopsy (e.g., because of elevated PSA)		
T2: Tumor confined within prostate*		
T2a: Tumor involves one-half of one lobe or less		
T2b: Tumor involves more than one-half of one lobe but not both lobes		
T2c: Tumor involves both lobes		
T3: Tumor extends through the prostate capsule[#]		
T3a: Extracapsular extension (unilateral or bilateral)		
T3b: Tumor invades seminal vesicle (s)		
T4: Tumor is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall		

*Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c, [#]Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2, [§]When more than one site of metastasis is present, the most advanced category is used. M1c is most advanced

- Intensity-modulated EBRT is the minimal standard of EBRT, in which the only acceptable biological dose is ≥74 Gy (EL-2).[29-31]

ii. Intermediate risk – Therapy options depend on the following:
- If life expectancy is <5 years, a patient will have no further intervention until he becomes symptomatic or develops clinical progression (EL-2)[13,16]
- If life expectancy is between 5 and 10 years, options include active surveillance,[9] RP with LND as per nomograms,[32] or EBRT with 6 months of androgen deprivation therapy (ADT) (EL-2)[33,34]
- If life expectancy is >10 years, options are RP with LND (EL-1)[35] or EBRT with 6 months of ADT (EL-2)[33,34]

iii. High risk – Therapy options include EBRT (including pelvic lymph nodes and with or without brachytherapy boost) with ADT for 18 months[36-43] or RP with LND[44,45]

2. Locally advanced disease (cT3-4 or N1)
   i. EBRT (including pelvic lymph nodes and with or without brachytherapy boost) with ADT for 2–3 years (EL-1)[46-49]
   ii. RP with LND only if no clinical evidence of lymph node involvement and no tumor fixation (EL-3)[44,45]
   iii. Patients who are unfit for the above-mentioned two options may be candidates for deferred castration when PSA level exceeds 10–15 ng/ml (EL-2)[50]
3. Management after local therapy
   i. RP patients who have pT3 (extraprostatic extension or seminal vesicle invasion), or positive margin with undetectable postoperative PSA, may undergo adjuvant EBRT to the prostatic bed (64–66 Gy) (EL-2)[50-56]
   ii. Follow-up after curative therapy: Patients should have a disease-specific history, PSA at 3, 6, and 12 months after therapy, every 6 months for 3 years, and then annually (EL-3)[57]
4. Management of local recurrence after RP
   i. Recurrence post-RP is defined by PSA level >0.2 ng/ml in two consecutive readings[58-62]
   ii. After excluding metastases, treatment of local recurrence is early salvage EBRT, preferably with ADT for 6 months, to be started as early as possible when PSA value (<0.5 ng/ml)[63-73]
5. Management of local recurrence after EBRT
   i. A PSA rise of 2 ng/mL above PSA nadir is the most reliable indication for recurrence (EL-2).[74,75] However, local recurrence is defined by the presence of all of the following: A positive prostatic biopsy 18 months or longer after EBRT associated with rise in PSA and no evidence of distant metastasis documented by CT scan or MRI and bone scan[76,77]

ii. Options of therapy include ADT, which can be delayed up until a PSA result of 10 ng/ml or in carefully selected patients,[78] salvage prostatectomy or brachytherapy may be considered[79,80]
iii. Intermittent ADT for nonmetastatic relapse after EBRT is recommended (EL-1).[81] See item 6 below for intermittent ADT

6. Management of metastatic disease [Figure 1]
   i. Castration-sensitive prostate cancer
      - Chemohormonal therapy with six cycles of docetaxel and ADT is the standard of care (EL-1),[82,83] with the following considerations:
        - Good performance status ECOG PS (0–1)
        - Newly diagnosed cases (<120 days of preexisting ADT therapy)
        - Prednisone 10 mg PO once daily is optional

   ADT options include bilateral orchiectomy (including subcapsular), luteinizing hormone-releasing hormone (LHRH) agonist, LHRH antagonists, and complete androgen blockade (CAB).[84-87] Intermittent or continuous ADT are appropriate options (EL-1)[88-91]

      - In case of intermittent androgen blockade, the following should be observed:
        - CAB (anti-androgen and LHRH) or LHRH antagonist should be used
        - Initial induction cycle should last for 6–9 months
        - Treatment is usually stopped only if the patient is compliant, showing good PSA response (PSA <4 ng/ml) in patients with metastatic disease and <0.5 ng/ml in biochemical relapse postlocal therapy, otherwise, should be on continuous ADT. PSA monitoring every 2–3 months is essential
        - Therapy is re-instituted in cycles of 3–6 months if PSA reaches 10–15 ng/ml in metastatic disease or 4 ng/ml if biochemical relapse occurs after local therapy
      - When treating with LHRH agonists, a concomitant anti-androgen must be given during the initial 4 weeks to counteract the testosterone surge. Furthermore, this treatment should be preceded with 7–10 days of anti-androgen, in patients with impending cord compression or impending urinary outflow obstruction
      - Preventive measures for metabolic, cardiovascular, and bone complications should be considered for patients on ADT.[92,93] See item 7 for bone health in prostate cancer
      - In general, use of steroidal anti-androgens should be discouraged
      - The care of patients should be coordinated through or taking place in hospitals with specialized oncology service

   ii. Castration-resistant prostate cancer
      - Defined as two consecutive rises in PSA in the testosterone level postcastration, which is <20 ng/dL (0.7 nmol/L), using early-morning samples[94]
      - Treatment options for those who did not receive chemohormonal therapy include docetaxel with prednisone, abiraterone with prednisone, enzalutamide, and radium-223 (EL-1)[95-98]
      - The treatment choice may depend on the following factors:
        - For symptomatic patients and rapidly progressing disease: Docetaxel with prednisone
        - For patients with no or mild symptoms and no visceral metastases: Abiraterone and prednisone

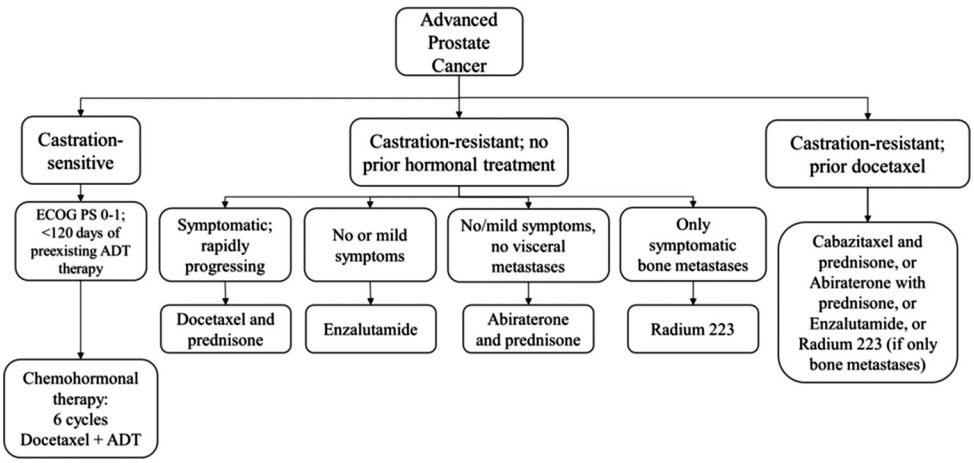

Figure 1: Algorithm for the management of advanced prostate cancer

- For patients with no or mild symptoms: Enzalutamide
- For patients with only symptomatic bone metastases: Radium-223

- Treatment options for those who have progressed on or after docetaxel include cabazitaxel with prednisone, abiraterone with prednisone, enzalutamide, and radium-223[97,99-101]
- Cabazitaxel (20 mg every 3 weeks) with prednisone (10 mg OD) is an appropriate option for patients with rapidly progressing or symptomatic disease and still in good performance status (EL-1)[102]
- Patients with CRPC should continue ADT indefinitely.

7. Bone health in prostate cancer patients
   i. All patients receiving any form of ADT should be prescribed Vitamin D (800 IU/day) and calcium supplements (1200 mg/day). Initial and periodic assessment of bone density and fracture risk may be beneficial in these patients. For patients at risk, (T-score <−1.5), treatment with either denosumab (60 mg every 6 months) or bisphosphonates can prevent bone loss associated with ADT[92]
   ii. Patients with CRPC with bone metastases should receive rank-ligand antibodies (denosumab) therapy 120 mg every 4 weeks to reduce skeletal-related events (pathological fractures, bone radiation or surgery, and spinal cord compression) (EL-1).[103] However, when not available zoledronic acid can be given (EL-1).[104]

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Conflicts of interest

There are no conflicts of interest.

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