Review Article

Saudi oncology society and Saudi urology association combined clinical management guidelines for prostate cancer

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Abstract

This is an update to the previously published Saudi guidelines for the evaluation, medical, and surgical management of patients diagnosed with prostate cancer. It 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, they are based on 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. Considerations to the local availability of drugs, technology, and expertise have been regarded. These guidelines should serve as a roadmap for the urologists, oncologists, general physicians, support groups, and health care policy makers in the management of patients diagnosed with adenocarcinoma of the prostate to.

Key Words: Guidelines, management, prostate cancer, Saudi oncology society, Saudi urological association

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INTRODUCTION

In Saudi Arabia, prostate cancer is the 6th most common cancer among men of all ages and the most common cancer among men over the age of 75. There were 280 cases of prostate cancer accounting for 6.1% of all newly diagnosed cases among males

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in 2010 with an age-standardized incidence rate of 5.5/100,000 among the male population, the median age at diagnosis was 73 years (range 2–105 years). Stage at the time of diagnosis is localized in 17.5% of cases with the remainder being either locally advanced (9.6%), metastatic (28.9%), or unknown (43.9%).[1]

Notably, there had 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. More than 95% of primary prostate cancers are adenocarcinomas, so these guidelines are focused on this category of prostate tumors.

PURPOSE AND METHODS

This is an update to the previously published Saudi guidelines for the evaluation, medical, and surgical management of prostate cancer.[2,3] It 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.[4] They are based on comprehensive MEDLINE and Cochrane Library English only literature review (1966 to December 2014), hand-searching journals, reviewing conference proceedings, and the collective expertise of the guidelines committee members [Table 1] who were appointed by the Saudi urological association and Saudi oncology society (comprised uro-oncologists, radiation oncologists [genitourinary focused interest and practice], and medical/clinical oncologists [genitourinary focused interest and practice]). The first version of these guidelines committee included an additional general urologists, general radiation oncologists, and general medical oncologists. Considerations to the local availability of drugs, technology, and expertise have been regarded, as well as, considerations of both benefits and harms, side effects, and risks. To formulate the recommendations, final decisions were taken by a voting system. External review of the guidelines was done before submission for publication.

GUIDELINES

These guidelines should serve as a roadmap to provide guidance on the most effective therapeutic treatment and management of patients diagnosed with adenocarcinoma of the prostate to urologists, oncologists, general physicians, support groups, and healthcare policy makers.

Diagnosis and staging evaluation

When a biopsy is indicated, then a systematic transrectal ultrasound guided 10–12 core biopsies should be performed or a multi-parametric magnetic resonance imaging (MRI)/ultrasound fusion targeted biopsy if available.

Once diagnosis is confirmed, the following staging evaluation should be done:

Computed tomography (CT) or MRI abdomen and pelvis:
- Should only be done when the cancer is considered high-risk according to D'Amico risk groups (EL-2)[5,6]
- Bone scan: Should only be done if any of the following (EL-2):[7-10]
  - PSA level >20 ng/mL
  - Patients with bony pain
  - Gleason score ≥8
  - Patient with clinical stage T3 or T4
  - Hypercalcemia or high serum alkaline phosphatase.

Staging classification

The tumor node metastasis AJCC staging 7th edition should be used.[11]

Management options

The management options depend on the stage (localized vs. metastatic), the 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.

Localized disease (cT1–cT2)

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.

Low-risk

Options of therapy depend on the following factors:
- If the patient is asymptomatic with life expectancy <5 years: No further intervention required until symptomatic or clinical progression (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]
- If asymptomatic with life expectancy >10 years: Options include active surveillance, radical prostatectomy (RP), external-beam radiation therapy (EBRT), or brachytherapy (EL-2)[15-18]

Table 1: D'Amico risk groups

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

- 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, 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[19-24]
- 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]
- Lymphadenectomy can be omitted if the chance of being positive is <5% according to nomograms (EL-2)[27]
- Intensity-modulated EBRT is the minimal standard of EBRT, in which the only acceptable biological dose is ≥74 Gy (EL-2).[28-31]

Intermediate risk

Options of therapy depend on the following:

- If life expectancy is <5 years: Patient will have no further intervention until he becomes symptomatic or clinical progression (EL-2)[13,15]
- If life expectancy is between 5 and 10 years: Options include active surveillance, RP, or EBRT with 6 months of androgen deprivation therapy (ADT) (EL-2)[15-17,32-35]
- If life expectancy is more than 10 years: Options are RP with lymphadenectomy (lymph node dissection [LND])[36] (EL-1) or EBRT + 6 months of ADT (EL-2).[32-35]

High-risk

Options include EBRT (may include pelvic lymph nodes) with 18 months of ADT,[37-48] (EL-1) or RP with LND[49,50] (EL-3). Patients who have the advanced local disease and are unfit for the above mentioned two options may be candidates for castration or high-dose bicalutamide, when PSA level exceeds 10–15 ng/mL (EL-1).[51-53]

- RP patients who have pT3 (extraprostatic extension, or seminal vesicle invasion), final Gleason score ≥8, or positive margin with undetectable postoperative PSA, may undergo adjuvant EBRT to the prostatic bed (64–66 Gy) (EL-2)[54-60]
- Follow-up after curative therapy: Patients should have a disease-specific history, serum PSA at 3, 6, and 12 months after therapy, and then every 6 months for 3 years and then annually (EL-3).[61]

Management of recurrence postradical prostatectomy

- Definition: Recurrence post-RP is defined by PSA level >0.2 ng/mL in two consecutive readings[61-65]
- Factors helping to differentiate local relapse or distant metastasis are: The timing of PSA recurrence, PSA doubling time (PSADT), pathological stage, and final Gleason score[66,67]
- Treatment of local recurrence is early salvage EBRT preferably with ADT, which results are improved if given with lower PSA value (<0.5)[68-78]
- In biochemical recurrence, bone scan and CT are of no diagnostic value unless PSA value is higher than 20 ng/dL,[79-81] Gleason >7, or clinically indicated (EL-2).

Management of local recurrence after external beam radiation therapy

- Definition: A PSA rise 2 ng/mL above PSA nadir is the most reliable indication for recurrence (EL-2).[82,83] However, local recurrence is defined by the presence of all of the following: A prostatic biopsy showing malignant cells 18 months or longer after EBRT, associated rise in PSA, and no evidence of distant metastasis documented by CT scan or MRI, and bone scan[84,85]
- Options of therapy include: Observation up to PSA of 10 ng/dL then ADT,[86] or in carefully selected patients, salvage prostatectomy or brachytherapy may be considered.[87-89]

Advanced disease (including recurrence and metastasis)

Hormone naive disease

- ADT palliates symptoms and reduces the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, and extraskeletal metastasis) and may improve survival (EL-1)[90-92]
- Options of ADT include: Bilateral orchiectomy (including subcapsular), luteinizing hormone releasing hormone (LHRH) antagonist, LHRH agonists, and complete androgen blockade (CAB) continuous or intermittent[93-95]
- When treating with LHRH agonists, a concomitant anti-androgen during the initial 4 weeks must be given, to counteract the testosterone surge; also, it should be preceded with 7–10 days of anti-androgen, in patients with significant disease burden, to prevent flare of symptoms
- Metabolic, cardiovascular, and bone complications preventive measures for patients on ADT should be considered Check 4.[96,97] Bone health in prostate cancer patients
- Patients with high initial PSA, short PSADT (<12 months), pain at diagnosis, locally advanced

disease, or Gleason score ≥8 should preferably receive CAB (EL-2)[98-103]
- Castrate level of testosterone should be <20 ng/dL (0.7 nmol/L), early morning sample[104-107]
- In case of intermittent androgen blockade (EL-2), the following should be observed:[108-121]
  - CAB (anti-androgen and LHRH) or LHRH antagonist should be used
  - Initial induction cycle should last 6–9 months
  - Treatment is usually stopped only if the patient is compliant, showing good PSA response with PSA <4 ng/dL in patients with metastatic disease and <0.5 ng/dL in biochemical relapse postlocal therapy, otherwise, should be on continuous ADT. PSA monitoring every 2–3 months is essential
  - Therapy is re-instituted for 3–6 months cycle if PSA reaches 10–15 ng/dL in metastatic disease or 4 ng/dL in biochemical relapse postlocal therapy.
- In general, use of steroidal anti-androgens should be discouraged
- In high-risk hormone sensitive patients (defined as patients with visceral metastases or ≥4 bone metastases [at least one nonaxial]), ADT plus 6 cycles of docetaxel have shown an excellent survival advantage over ADT alone (EL-1).[122]

Castrate resistant prostate cancer
- Definition: Two consecutive rises in PSA in the presence of castrate testosterone level
- The care of castrate-resistant prostate cancer (CRPC) patients should be coordinated through or taking place in a hospital with specialized oncology service. Therapy options depend on the presence or absence of metastases
- In non-metastatic CRPC (mCRPC), observation is preferred, but treatment with secondary hormonal manipulations may be offered by either adding or switching an anti-androgen, anti-androgen withdrawal, ketoconazole, steroids, diethylstilbestrol, or other estrogens[123-127]
- In asymptomatic or minimally symptomatic mCRPC (not needing opiates), treatment options include abiraterone with prednisone, enzalutamide, systemic chemotherapy (docetaxel with prednisone) (EL-1)[128-134]
- In highly symptomatic patients with good performance, systemic chemotherapy (docetaxel with prednisone) is the treatment of choice.[128-135] Systemic chemotherapy should be offered only to patients with performance status 0–2 by Eastern Cooperative Oncology Group scale. The decision when to start chemotherapy should depend on factors like PSADT and severity of symptoms (EL-1). For highly symptomatic patients with poor performance status, they may be offered abiraterone with prednisone or enzalutamide (EL-3)
- Patients who fail docetaxel (prior docetaxel), have several options of therapy including: Cabazitaxel with prednisone, abiraterone acetate with prednisone, or enzalutamide (if not received in chemo-naive setting); in addition, may also be offered alpharadin (radium 223) where available, if metastasis are limited to bone[136-140]
- Clinicians should offer palliative care to patients with mCRPC with poor performance status who received prior docetaxel chemotherapy. Alternatively, for selected patients, clinicians may offer treatment with abiraterone + prednisone, enzalutamide, or radionuclide therapy (EL-3)
- Clinical progression (symptoms, imaging) should be considered primarily in deciding success/failure of CRPC treatment options
- Patients with CRPC who were receiving LHRH antagonist/agonists should continue them indefinitely (EL-3).[141-143]

Bone health in prostate cancer patients

- All patients receiving any form of ADT should be prescribed Vitamin D (800 IU) and calcium supplements (1200 mg). Initial and periodic assessment of bone density and fracture risk may be beneficial in these patients. At risk patients (T score <-1.5) treatment with either denosumab (60 mg every 6 months) or bisphosphonates can prevent bone loss associated with ADT[97]
- Patients with bony mCRPC should receive rank-ligand antibodies (denosumab) therapy 120 mg every 4 weeks to reduce skeletal-related events (bone pain, pathological fractures, bone radiation or surgery, and spinal cord compression) (EL-1), however, when not available zoledronic acid can be given (EL-1).[144-149]

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Conflicts of interest

There are no conflicts of interest.

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