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

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Abstract

In this report, updated guidelines for the evaluation, medical, and surgical management of prostate cancer are presented. They are categorized according the stage of the disease using the tumor node metastasis staging system 7th edition. The recommendations are presented with supporting evidence level.

Key Words: Cancer, guidelines, management, prostate, Saudi

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MANUSCRIPT

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. It accounts for 6.1% of all newly diagnosed cases among males in year 2010 with an age-standardized incidence rate of 5.5/100,000 among the male population. Stage at the time of diagnosis is localized in 43.9% of cases with the remainder being either locally advanced, metastatic or unknown.[1]

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1. STAGING EVALUATION

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

- 1.1. Computed tomography (CT) or magnetic resonance imaging (MRI) abdomen and pelvis: Should only be done when the cancer is considered high-risk [Table 1] (EL-2).[2,3]
- 1.2. Bone scan: Should only be done if any of the following (EL-2):[4,5]
  - 1.2.1. Prostate-specific antigen (PSA) level > 20 ng/mL.
  - 1.2.2. Patients with bony pain.
  - 1.2.3. Gleason score >7.
  - 1.2.4. Patient with clinical stage T3 or T4.
  - 1.2.5. Hypercalcemia, high serum alkaline phosphatase.

2. STAGING CLASSIFICATION

The tumor node metastasis staging will be used[6]

Table 1: Partin tables

Prediction of probability of organ-confined disease				
Gleason score	**Clinical stage**			
	T1c	**T2a**	**T2b**	**T2c**
Serum PSA=0.0-2.5 ng/mL				
2-4	95 (89-99)	91 (79-98)	88 (73-97)	86 (71-97)
5-6	90 (88-93)	81 (77-85)	75 (69-81)	73 (63-81)
3+4=7	79 (74-85)	64 (56-71)	54 (46-63)	51 (38-63)
4+3=7	71 (62-79)	53 (43-63)	43 (33-54)	39 (26-54)
8-10	66 (54-76)	47 (35-59)	37 (26-49)	34 (21-48)
Serum PSA=2.6-4.0 ng/mL				
2-4	92 (82-98)	85 (69-96)	80 (61-95)	78 (58-94)
5-6	84 (81-86)	71 (66-75)	63 (57-69)	61 (50-70)
3+4=7	68 (62-74)	50 (43-57)	41 (33-48)	38 (27-50)
4+3=7	58 (48-67)	39 (30-48)	30 (22-39)	27 (18-40)
8-10	52 (41-63)	33 (24-44)	25 (17-34)	23 (14-34)
Serum PSA=4.1-6.0 ng/mL				
2-4	90 (78-98)	81 (63-95)	75 (55-93)	73 (52-93)
5-6	80 (78-83)	66 (62-70)	57 (52-63)	55 (44-64)
3+4=7	63 (58-68)	44 (39-50)	35 (29-40)	31 (23-41)
4+3=7	52 (43-60)	33 (25-41)	25 (18-32)	21 (14-31)
8-10	46 (38-56)	28 (20-37)	21 (14-29)	18 (11-28)
Serum PSA 6.1-10 ng/mL				
2-4	87 (73-97)	76 (56-94)	69 (47-91)	67 (45-91)
5-6	75 (72-77)	58 (54-61)	49 (43-54)	46 (36-56)
3+4=7	54 (49-59)	35 (30-40)	26 (22-31)	24 (17-32)
4+3=7	43 (35-51)	25 (19-32)	19 (14-25)	16 (10-24)
8-10	37 (28-46)	21 (15-28)	15 (10-21)	13 (8-20)
Serum PSA>10 ng/mL				
2-4	80 (61-95)	65 (43-89)	57 (35-86)	54 (32-85)
5-6	62 (58-64)	42 (38-46)	33 (28-38)	30 (21-38)
3+4=7	37 (32-42)	20 (17-24)	14 (11-17)	11 (7-17)
4+3=7	27 (21-34)	14 (10-18)	9 (6-13)	7 (4-12)
8-10	22 (16-30)	11 (7-15)	7 (4-10)	6 (3-10)

PSA: Prostate-specific antigen

Primary tumor (T)
- TX - Tumor cannot be assessed
- T0 - No evidence of the primary tumor
- T1 - Clinically neither palpable nor visible by imaging
  - T1a - Found incidental to other surgery; present in 5% or less of tissue
  - T1b - Found incidental to other surgery; present in 5% or more of tissue
  - T1c - Identified by needle biopsy
- T2 - Tumor confined within prostate
  - T2a - Involving one-half of one lobe or less
  - T2b - Involving more than one-half of one lobe, but not both lobes
  - T2c - Involving both lobes
- T3 - Tumor extends through prostate capsule
  - T3a - Extracapsular extension (unilateral or bilateral)
  - T3b - Tumor invades the seminal vesicle (s)
- T4 - Involves structures other than seminal vesicles
  - T4a - Invades adjacent structure (s) other than seminal vesicles: Bladder, external sphincter, or rectum, lavatory muscle and (or) pelvic side walls
  - T4b - Invades muscles and/or pelvic wall

Regional lymph nodes (N)
- NX - Nodes cannot be assessed
- N0 - No regional node metastasis
- N1 - Metastasis in regional nodes

Distant Metastasis (M)
- M0 - No distant metastasis
- M1 - Distant metastasis
- M1a - Nonregional lymph node (s)
- M1b - Bone (s)
- M1c - Other site (s) with or without bone disease

3. MANAGEMENT OPTIONS

This will depend on the stage (localized vs. metastatic), the risk group and life expectancy.[7]

3.1. Localized disease (cT1–cT2)

3.1.1. Low risk: Options of therapy depend on the following factors:

3.1.1.1. If the patient is asymptomatic with life expectancy <5 years: No further intervention required until he becomes symptomatic or clinical progression[8-10] (EL-2).

3.1.1.2. 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 the cancer progresses)[8-10] (EL-2).

3.1.1.3. If asymptomatic with life expectancy >10 years: Options include active surveillance,[10] radical prostatectomy (RP),[11] external beam radiation therapy (EBRT),[12] or brachytherapy[13] (EL-2).

3.1.1.4. The choice of therapy should depend on the patient's general condition, his preference and side-effect profile.

3.1.1.5. Active surveillance candidates must have all the following criteria: Number of positive cores ≤2, percentage of cancer involvement in any positive core <15%, PSA < 10, PSA density <0.15 and Gleason sum ≤6. Follow-up should entitle history, physical exam and PSA every 3-6 months, and repeated biopsy every 12-18 months; radical therapy should be offered if PSA velocity >0.35 ng/mL/year

or progression in any of the aforementioned criteria.[14,15]

3.1.1.6. All RPs should be done in tertiary care centers by high-volume surgeons[16] (EL-2).

3.1.1.7. Lymphadenectomy can be omitted if the chance of being positive is <5%[17] (EL-2).

3.1.1.8. Intensity-modulated EBRT is the minimal standard of EBRT, in which the only acceptable biological dose is ≥74 Gy[12,18-22] (EL-2).

3.1.2. Intermediate risk: Options of therapy depend on the following factors:

3.1.2.1. If life expectancy is < 5 years: Patient will have no further intervention until he becomes symptomatic or clinical progression[8-10] (EL-2).

3.1.2.2. If life expectancy is between 5 and 10 years: Options include active surveillance,[10] EBRT with 6 months of androgen deprivation therapy (ADT),[12,20,23] or RP[11] (EL-2).

3.1.2.3. If life expectancy is more than 10 years: Options are RP with extended lymphadenectomy[11,24] (EL-1) or EBRT + 6 months of ADT[12,18,19,23] (EL-2).

3.1.3. High-risk: Options include EBRT (to include pelvic lymph nodes) with 18-36 months of ADT.[25-31] (EL-1) or RP with extended lymphadenectomy[32,33] (EL-3). Patients who have advanced local disease and are unfit for the above mentioned two options may be given ADT alone (when PSA level exceeds 10 ng/mL)[34] (EL-1).

3.1.4. Follow-up after curative therapy: Patients should have a disease-specific history, serum PSA and digital rectal examination at 3, 6, and 12 months after therapy, then every 6 months for 3 years and then annually[35] (EL-3).

3.1.2.4. Patients who have pT3 with undetectable PSA, may undergo adjuvant EBRT to the prostatic bed (64-66 Gy)[36-40] (EL-2).

3.1.2.5. Patients who have positive (not focal) surgical margins may undergo adjuvant EBRT to the prostatic bed,[25,26] or intensive expectant follow-up[41,42] (EL-2).

3.1.5. Management of recurrence post RP:

3.1.5.1. Definition: Recurrence post-RP is defined by PSA level >0.2 ng/mL in two consecutive readings.[43,44]

3.1.5.2. Factors helping to differentiate local relapse or distant metastasis are: The timing of PSA increase after surgery, PSA doubling time (PSADT), and the pathological stage and final Gleason score.[45-52]

3.1.5.3. Treatment of local recurrence is salvage EBRT; for treatment of metastatic disease see 3.2.

3.1.5.3.1. Bone scan and CT scan are of no diagnostic value unless PSA value is higher than 20 ng/dl,[53-55] Gleason >7, or clinically indicated (EL-2).

3.1.6. Management of local recurrence after EBRT

3.1.6.1. Definition: A PSA rise 2 ng/mL above the PSA nadir is the most reliable indication for recurrence[56,57] (EL-2). However, local recurrence is defined by the presence of all of the following:[58,59] 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.

3.1.6.2. Options of therapy include: Observation up to PSA of 10 ng/dl, then ADT,[60] or in carefully selected patients, salvage prostatectomy, or brachytherapy may be considered.[61-64]

3.2. Advanced disease (including recurrence and metastasis)

3.2.1. Hormone responsive disease:

3.2.1.1. ADT palliates symptoms and reduces the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, and extraskeletal metastasis)[65-67] (EL-1).

3.2.1.2. Options of ADT include: Orchiectomy, luteinizing hormone releasing hormone (LHRH) antagonist, LHRH agonists, and complete androgen blockade (CAB) continuous or intermittent.[65-67]

3.2.1.3. When treating with LHRH agonists a concomitant anti-androgen during the initial 4 weeks, to counteract the testosterone surge, must be given; also, it should be preceded with 10 days of antiandrogen in patients with significant disease burden.

3.2.1.4. All patients receiving ADT must be prescribed vitamin D and calcium supplements.[68]

3.2.1.5. High-risk patients with short PSADT, high initial PSA and symptomatic patients should preferably receive combined androgen blockade[69-75] (EL-2).

3.2.1.6. Castrate level of testosterone should be <20 ng/dl (0.7 nmol/L).[76,77]

3.2.1.7. In case of intermittent androgen blockade (EL-2), the following should be observed:[78-92]

3.2.1.7.1. LHRH antagonist or CAB (antiandrogen and LHRH) should be used.

3.2.1.7.2. Initial induction cycle should last 6-9 months.

3.2.1.7.3. 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 recurrent disease post local therapy.

3.2.1.7.4 Therapy is re-instituted for 3-6 months cycle if PSA reaches 10-15 ng/dl in metastatic disease or 4 ng/dl in recurrent disease post local therapy.

3.2.1.8. In general, use of steroidal anti-androgens should be discouraged.

3.2.2. Castrate resistant prostate cancer (CRPC):

3.2.2.1. Definition: Two consecutive rises in PSA in the presence of castrate testosterone level.

3.2.2.2. Therapy should depend on the presence or absence of metastases.

3.2.2.2.1. In nonmetastatic CRPC treatment secondary hormonal manipulations may be offered by either adding a nonsteroidal anti-androgen, anti -androgen withdrawal, ketoconazole, steroids, diethylstilbestrol, or other estrogens.[93-98]

3.2.2.2.2. In asymptomatic metastatic CRPC treatment options include abiraterone with prednisone, systemic chemotherapy, or secondary hormonal manipulations (adding a nonsteroidal antiandrogen, or antiandrogen withdrawal).[99-103]

3.2.2.2.3. In symptomatic metastatic CRPC treatment options include abiraterone with prednisone (only in mildly symptomatic patients) or systemic chemotherapy.[99-103]

3.2.2.2.4. Systemic chemotherapy in the form of docetaxel with prednisone should be offered only to patients with performance status 0-2 by Eastern Cooperative Oncology Group scale.[101-103] (EL-1) The decision when to start chemotherapy should depend on factors like PSADT and presence of symptoms.

3.2.2.2.5. Patients who fail abiraterone may receive docetaxel with prednisone.

3.2.2.2.6. Patients who fail docetaxel, have several options of therapy including: Cabazitaxel with prednisone, abiraterone acetate (if not received in chemo-naive setting), and enzalutamide.[104-107]

3.2.2.2.7. Patients who fail docetaxel and have disease limited to the bone can also be offered in addition to (3.2.2.2.6) alpharadin (Radium 223) where available.[108]

3.2.2.2.8. Patients with CRPC who were on LHRH antagonist/agonists should continue on them indefinitely[109-111] (EL-3).

3.2.2.2.9. Patients with bony metastatic CRPC should receive rank-ligand antibodies (Denosumab) therapy every 4 weeks (EL-1), but when not available zoledronic acid can be given (EL-1).[112-117]

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