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The Saudi Clinical Management Guidelines for Testicular Germ Cell Tumors

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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 testicular germ cell tumors. 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 upon the request and the support of the National Cancer Center (NCC). 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 testicular germ cell tumors.

Introduction

Testicular cancer is a rare disease. A total of 78 cases have been diagnosed in 2010, with an age standardized rate of 0.8 cases/100,000 representing 1.7% of all diagnosed cancer in Saudi males (www.scr.org.sa). Owing to the rarity of the This is an open access article distributed under the terms of the Creative Commons disease and the multidisciplinary approach in managing testis cancer, the group recommended that all testicular cancer cases should be managed in tertiary care centers.

1. Staging

- TheAmericanJointCommitteeonCancertumor-node-metastasis staging for testis cancer (7^{th} edition 2010) was used. [1]

2. Evaluation of testicular tumors

4.2 Ultrasound of the scrotum is recommended to diagnose the tumor.

4.2 Serum tumor markers includes alpha fetoprotein (AFP), beta human chorionic gonadotropin (beta-hCG),andlactatedehydrogenaseshould prior to orchiectomy.

4.2 Computed tomography (CT) chest, abdomen, and pelvis should performed for confirmed testicular cancer.

3. Risk stratification

- TheInternationalGermCellCancerCollaborativeGroupriskclassification.

4 Treatment of testicular germ cell cancer

General considerations:

- Patients at all stages should undergo urgent inguinal orchiectomy unless the clinical situation requires immediate chemotherapy in patients with a testicular mass and clear germ cell malignancy based on elevated tumor markers.
- Trans-scrotal biopsy or orchiectomy for any intra-testicular lesion is absolutely contra-indicated.
- All patients who will undergo treatment with chemotherapy, retroperitoneal lymph node dissection (RPLND), or radiotherapy should be offered sperm banking. To maintain treatment intensity, chemotherapy cycles should be repeated every 3 weeks, independent of leukocyte count.
- Tumor markers are to be determined immediately before the start of each new chemotherapy cycle. The treatment will depend on the histological subtype as follow:

4.1 Seminoma

Further treatment will depend on the stage:

4.1.1 Stage I

4.1.1.1 S urveillance: Is considered the preferred strategy, except in patients with expected poo compliance or with primary tumor size ≥ 4cm and ≥pT2 (evidence level [el-1])[2]

4.1.1.2 C hemotherapy: Single agent carboplatin: 1–2 doses at area under the curve 7 (EL-1)[3]

4.1.1.3 R adiotherapy: Infradiaphragmatic para-aortic strip only and in patient with prior scrotal surgery, ipsilateral iliac nodes should be included (EL-1).[4,5]

4.1.2 Stage IS

4.1.2.1 Infradiaphragmatic radiotherapy to para-aortic strip only and in patient with prior scrotal surgery, ipsilateral iliac nodes should be included (EL-3).[6]

4.1.3 Stage IIA and IIB

All of thefollowing options are acceptable: -

4.1.3.1 Radiotherapy to infradiaphragmatic para-aortic and ipsilateral Iliac nodes, preferred forstageIIAandforstageIIBwhoare not fit for chemotherapy (EL-2). [7]

4.1.3.2 Three cycles of bleomycin, etoposide, and cisplatin(BEP)chemotherapyorfourcycles ofetoposide and cisplatin (EP), if there are concerns about bleomycin toxicity as in patients with reduction in lung capacity, emphysema, heavy smoking (including former smokers) (EL-2).

4.1.4 Stage IIC and III

Treatment will depend on the risk classification: -

4.1.4.1 Goodrisk:ThreecyclesofBEPchemotherapyor four cycles of EP, if there are concerns about bleomycin lung toxicity (EL-1) [8]

4.1.4.2 I intermediate risk: Chemotherapy with fourcyclesofBEPorfour cycles ofVIP chemotherapy (etoposide, ifosfamide, and cisplatin) (EL-1).[9]

4.1.5 Management of post chemotherapy residual nodes/ masses seen on computed tomography scan

This depend on the size andthe level of tumor markers (hCG):

4.1.5.1 If size <3 cm and normal markers: Surveillance.

4.1.5.2 I f more than 3 cm and normal markers: Do positron emission tomography: [10]

4.1.5.3 If negative: Surveillance (EL-2).

4.1.5.4 I f positive consider one of the following options:

4.2.5.4.1 Surgical resection

2.3.5.4.2. Second-line chemotherapy if positive for residual disease (see item 4.2.1.6.3.2).

4.2.5.4.3 Radiotherapy.

4.1.5.5 I f the residual mass is enlarging or markers increasing: Second-line chemotherapy (EL-2) - (see item 4.2.1.6.3.2).

4.1.6 Management of patients failing 1st line chemotherapy

Patients will receive second-line chemotherapy; options are:

4.1.6.1 F our cycles of vinblastine, ifosfamide, and cisplatin (VeIP) regimen[11] (EL-2) or

4.1.6.2 F our cycles of paclitaxel, ifosfamide, and cisplatin (TIP) regimen (EL-2).[12]

4.1.7 Management of patients failing second-line chemotherapy

Patients will be treated with monotherapy or combination of paclitaxel and gemcitabine (for those who did not receive paclitaxel before), gemcitabine and Oxaliplatin, or oral etoposide. [13]

4.2 Nonseminoma

Treatment will depend on the stage as follow:

4.2.1 Stage I

Treatment will depend on the presence of any the following risk factors: Lymph vascular invasion, presence of embryonal histology (50% or more), absence of yolk sac histology, and tumor stage >T1. [14,15]

4.2.1.1 Stage I with no risk factors, options are:

4.2.1.1.1 Surveillance: Should be reserved in compliant patients (EL-2). [16,17]

4.2.1.1.2 T w oc y c l e so fB E Pregimen (EL-1), [16-18] also one cycleofBEP chemotherapycanbeconsidered in such cases. [18]

4.2.1.1.3 Open nerve sparing RPLND to be done only in high volume tertiary care centers (EL-2),[18] further therapy will depend on the pathological result as follow:

4.2.1.1.4 pN0: Surveillance.

4.2.1.1.5 p N1: Surveillance in compliant patients or two cycles of chemotherapy with BEPinnoncompliantpatients (EL-3).

4.2.1.1.6 pN2-3: Three cycles of chemotherapywithBEPregimen (EL-3).

4.2.1.2 Stage I with any risk factor of above, options are:

4.2.1.2.1 T wo cycles of adjuvant chemotherapy withBEPmregimen. [16]

4.2.1.2.2 Open nerve sparing RPLND: To be done only in case of contraindication for chemotherapy and in high volume tertiary care centers (EL-2): [19] Further therapy will depend on the pathological stage as in item 4.2.1.1.3.1-3.

4.2.1.3 Stage IS:

Patient should receive three cycles of systemic chemotherapy withthe BEP regimen (EL-3).

4.2.1.4 StageIIAandIIB:

Optionsoftherapywilldependifmarkers(AFP andhCG)arenormal or elevated:

4.2.1.4.1 Normal markers, options are:

4.2.1.4.1.1 Primary chemotherapy with three cyclesofBEP.[8]

4.2.1.4.1.2 Open nerve sparing RPLND, [20,21] only if the nodal metastases is in the primary landing zone and in selected patients, it should be done only in high volume center by experienced uro-oncologist. Further therapy will depend on the pathological stage as in item 4.2.1.1.3.1-3.

4.2.1.4.2 Elevated markers: Systemic chemotherapy depending on the international risk classification group:

4.2.1.4.2.1 Lowrisk:ThreecyclesofBEP

Chemotherapy. [7, 8]

4.2.1.4.2.2. Intermediate and high risk: Four cycles of BEP chemotherapy. [9]

4.2.1.5. Stage IIC and III:

Treatment will be with chemotherapy depending on the International risk classification

4.2.1.5.1. Low risk: Three cycles of BEP chemotherapy. [7,8]

4.2.1.5.2. Intermediate and high risk: Four cycles ofBEPchemotherapy. [9]

4.2.1.6. Management of post chemotherapy:

Tumor markers and imaging with CT scan should be done 4–8 weeks after the last cycle of chemotherapy.

4.2.1.6.1. No residual disease and normal markers: Surveillance is recommended. [22]

4.2.1.6.2. No residual disease and elevated markers: Second-line chemotherapy. See item 4.2.1.6.3.2

4.2.1.6.3. Residual disease byCT scan (>1cm):This depends on the level of serum markers:

4.2.1.6.3.1. Normal markers: RPLND and resection of all residual disease, if technically feasible: [23,24] Further therapy will depend on pathology result:

4.2.1.6.3.1.1. Mature teratoma, necrosis, or fibrosis: No further therapy

4.2.1.6.3.1.2. R esidual germ cell tumor: Two cycles of chemo therapy [25] with E P, VIP or TIP (see below) (EL-2).

4.2.1.6.3.2. Elevated markers: Second-line chemotherapy options include

4.2.1.6.3.2.1. F our cycles of VeIP regimen. [11]

4.2.1.6.3.2.2. Four cycles of TIP regimen. [12]

4.2.1.6.3.2.3. High-dose chemotherapy with autologous stem-cell transplant. [26]

5.0 Salvage treatment for seminoma and nonseminoma

5.1. Conclusive recommendations cannot be made at present.

5.2. Prognosis is variable with 2 years survival rate ranging between 75% and 6% based on prognostic score.

5.3. Options includes TIP × 4 or VeIP × 4 or high-dose chemotherapy with TI-CE mainly for patients at second-line setting.

5.4. Carboplatin based high-dose chemotherapy as third line or later is an option, despite absence of randomized trials in this area.

5.5. Desperation surgery should be part of the strategy whenever possible, particularly in patients with localized disease and with poor response to chemotherapy. [27]

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