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Saudi Clinical Management Guidelines for Invasive Epithelial Ovarian Cancer

National Cancer Center

(NCC)

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ABSTRACT

This is Saudi guidelines for the evaluation, medical and surgical management of patients diagnosed with invasive epithelial ovarian cancer. It is categorized according to the 2014 International Federation of Gynecology and Obstetrics (FIGO)/Tumor, Nodes, Metastasis (TNM) classification system. The recommendations are presented with supporting level of evidence. 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 Gynecological Society. Considerations to the local availability of drugs, technology, and expertise have been regarded. These guidelines should serve as a roadmap for the gynecologist, oncologists, general physicians, support groups, and healthcare policy makers in the management of patients diagnosed with invasive epithelial ovarian cancer.

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INTRODUCTION

Ovarian cancer ranked seventh in incidence among Saudi females. There were 194 cases accounting for 3% of all newly diagnosed cases were reported in 2013. The age standardized rate (ASR) was 2.7/100,000 for females [1]. The median age at diagnosis was 51 years.

PURPOSE AND METHODS

This guideline should serve as a roadmap to provide guidance on the most effective therapeutic treatment and management of patients diagnosed with invasive epithelial ovarian cancer to gynecologist, oncologists, general physicians, support groups, and healthcare policy makers. It is categorized according to the stage of the disease using 2014 International Federation of Gynecology and Obstetrics (FIGO)/Tumor, Nodes, Metastasis (TNM) classification system. The recommendations are based on comprehensive MEDLINE and Cochrane library English only literature review, hand-searching journals, several internationally recognized guidelines and the collective expertise of the guidelines committee members (authors) who were selected by the Saudi Oncology Society and Saudi Gynecological Society.

The following evidence levels are adopted for these guidelines: 1) Evidence level-1 (EL-1) (highest level) evidence from phase III randomized trials or meta-analyses; 2) EL-2 (intermediate-level) evidence from good phase II trials or phase III trials with limitations; and 3) EL-3 (low-level) from retrospective or observational data and/or expert opinion. This easy-to-follow grading system is convenient for the reader and allows accurate assessment of the applicability of the guideline in individual patients.

GUIDELINES

All ovarian cancer cases are preferably seen and discussed in a multidisciplinary form.

1. **Initial presentation:**
   - 1.1 Perform history and clinical examination including pelvic assessment
   - 1.2 Full blood count, liver and renal function tests
   - 1.3 CA-125 or other tumor markers as clinically indicated
   - 1.4 Ultrasound of abdomen and pelvis
   - 1.5 Calculate risk of malignancy index

2. **Initial oncology assessment if highly suspicious or confirmed diagnosis:**
   - 2.1 CT scan of the chest, abdomen and pelvis
   - 2.2 Review of outside pathology and imaging
   - 2.3 BRCA mutation test if available

3. **Staging:**
   Use FIGO/TNM staging system 2014 (see table)

4. **Treatment:**
   - 4.1 Surgery
     - 4.1.1 should be performed by gynecologic oncologist
     - 4.1.2 Early stage ovarian cancer (stage I)
       - 4.1.2.1 Staging surgery (laparotomy, laparoscopic or robotic) with the following: unilateral salpingo-oopherectomy or Total hysterectomy and bilateral saplingo-oopherectomy (depending on the fertility desire), pelvic, right and left washings for cytology, infracolic

omentectomy, multiple peritoneal biopsies (right and left paracolic gutters, anterior and posterior cul-de-sac, mesentery of large and small bowel, right and left diaphragm (this could be replaced by diaphragmatic scrapping), pelvic and para-aortic lymph node sampling, +/- appendectomy and consider biopsy of any suspicious lesion in the contralateral ovary

4.1.2.2 Consider unilateral salpingo-oopherectomy (fertility-sparing surgery) with comprehensive staging for stage IA or IC (grade 1+/- grade2) with unilateral involvement and favorable histology if patient desire fertility

4.1.3 Advanced stage ovarian cancer (stage II- IV)

4.1.3.1 Perform optimal debulking / cytoreductive surgery with removal of all visible disease(EL-1)[2]

4.1.3.2 Cytoreductive surgery & HIPEC can be considered if available (EL-2)[3]

4.1.3.3 Consider interval debulking after chemotherapy for patients with bulky stage IIIC/IV who are poor surgical candidates due to location and volume of disease or medical comorbidities(EL-1)[4]

4.1.3.4 Poor surgical candidate includes: diffuse and/or deep infiltration of the small bowel mesentery, diffuse carcinomatosis involving the stomach and/or large parts of the small or large bowel, infiltration of the duodenum and/or parts of the pancreas (not limited to the pancreatic tail), involvement of the large vessels of the hepatoduodenal ligament,

celiac trunk or behind the porta hepatis, bulky high lymph nodes above renal vessels or involvement of the liver parenchyma.

4.2 Chemotherapy

4.2.1 Early stage ovarian cancer (stage I)

4.2.1.1 Observation for stage IA or IB (grade 1) is recommended

4.2.1.2 Adjuvant chemotherapy can be considered for stage IA or IB (grade 2), observation is an acceptable alternative

4.2.1.3 Adjuvant chemotherapy is recommended for stage I grade 3, clear cell by histology, or stage IC to IV[5]

4.2.1.4 Intravenous paclitaxel 175mg/m^2 plus carboplatin AUC 5 or 6 Q3W for 3-6 cycles is recommended (preferably 6 cycles for serous cancer) (EL-1)[6]

4.2.2 Advanced stage ovarian cancer (stage II- IV)

4.2.2.1 For women who undergo optimal cytoreductive surgery, we recommend IV paclitaxel/carboplatin Q3W for 6 cycles (EL-1)

4.2.2.2 Intraperitoneal chemotherapy can be considered for women with optimally debulked stage III ovarian cancer (EL-1)[7]

4.2.2.3 For women who had suboptimal cytoreductive surgery, weekly IV dose dense chemotherapy can be considered as carboplatin AUC 5 or 6 on day 1 plus paclitaxel 80 mg/m^2 on days 1, 8 and 15 of 21 days cycle, particularly if histological subtype is not clear cell or mucinous. However, for patients who refuse weekly treatment or those with clear

cell or mucinous carcinoma, we suggest IV paclitaxel/carboplatin Q3W(EL-1)[8]

4.2.2.4 Paclitaxel/carboplatin with bevacizumab can be considered for suboptimal debulked stage III and stage IV (EL-1)[9, 10]

4.2.2.5 For elderly patient and/or those with comorbidities, we consider single agent carboplatin or weekly carboplatin AUC 2 plus weekly paclitaxel 60mg/m^2 (EL-1)[11]

4.2.2.6 Docetaxel may be substituted for paclitaxel if there is significant neuropathy (EL-1)[12]

4.2.2.7 Liposomal doxorubicin/carboplatin can be considered as an alternative for patients who develop allergy to taxane (EL-1)[13]

5. Follow-up:

Evaluation includes: history and physical examination including pelvic exam, CA-125 or other tumor markers if initially elevated

5.1 Every 3 months for 2 years then every 6 months for 3 years and thereafter annually

5.2 Imaging as clinically indicated (development of new symptoms, signs, or raised tumor markers)

6. Relapse:

6.1 Biochemical relapse: observation is recommended for rising CA 12-5 with no evidence of clinical relapse (EL-1) [14]

6.2 Platinum-sensitive relapse

6.2.1 Patients who respond to initial platinum-based therapy and have relapse ≥ 6 months after completing chemotherapy

6.2.2 Secondary cytoreductive surgery is to be considered if optimal debulking is feasible and the patient is fit (EL-2)[15, 16].

6.2.3 Platinum-based combination therapy is recommended. Acceptable regimens include liposomal doxorubicin /carboplatin, paclitaxel/carboplatin, or gemcitabine/carboplatin (EL-1) [17-19]

6.2.4 Other regimens that may be considered include: paclitaxel/carboplatin, or gemcitabine/carboplatin with bevacizumab (EL-1)[20, 21]

6.2.5 For patients with BRCA mutation, a poly-ADP ribose polymerase (PARP) inhibitor is recommended as maintenance therapy (EL-1) [22-24].

6.3 Platinum-resistant relapse

6.3.1 Patients who don't respond to initial platinum-based therapy or relapse < 6 months after completing chemotherapy

6.3.2 Single agent chemotherapy rather than combination therapy is recommended

6.3.3 Acceptable regimens include: weekly paclitaxel, Liposomal doxorubicin, gemcitabine, oral etoposide, topotecan and docetaxel (EL-1)[25-27]

6.3.4 Bevacizumab in combination with paclitaxel, liposomal doxorubicin or topotecan is recommended in patients meeting the following criteria: if there is no history of bowel obstruction or evidence of malignant bowel involvement, no prior treatment with bevacizumab, and no more than 2 prior lines of chemotherapy (EL-1)[28]

6.3.5 PARP inhibitors are recommended for patients with BRCA mutation who have progressed on multiple prior lines of treatment and not received prior PARP inhibitors (EL-2)[29].

6.3.6 Endocrine therapy can be reasonable option for patients with disease progression but with little or no symptoms (Tamoxifen or Aromatase inhibitors) (EL-2)[30, 31]

6.3.7 Palliative radiation therapy can be considered to alleviate symptoms in patients with recurrent disease.

6.3.8 Best supportive care is recommended for patients who failed multiple lines of therapy or with poor performance status.

Table: FIGO/TNM staging system 2014

FIGO	TNM	
I	**T1**	**Tumor confined to ovaries or Fallopian tube(s)**
IA	T1a	Tumor limited to 1 ovary (capsule intact) or Fallopian tube; no tumor on ovarian or Fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IB	T1b	Tumor limited to both ovaries (capsules intact) or Fallopian tubes; no tumor on ovarian or Fallopian tube surface; no malignant cells in the ascites or peritoneal washings
IC		Tumor limited to 1 or both ovaries or Fallopian tubes, with any of the following:
IC1	T1c1	Surgical spill
IC2	T1c2	Capsule ruptured before surgery or tumor on ovarian or Fallopian tube surface
IC3	T1c3	Malignant cells in the ascites or peritoneal washings
II	**T2**	**Tumor involves 1 or both ovaries or Fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer**
IIA	T2a	Extension and/or implants on uterus and/or Fallopian tubes and/or ovaries
IIB	T2b	Extension to other pelvic intraperitoneal tissues
III	**T1/T2-N1**	**Tumor involves 1 or both ovaries or Fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/ or metastasis to the retroperitoneal lymph nodes**
IIIA1		Positive retroperitoneal lymph nodes only (cytologically or histologically proven):
IIIA1(i)		Metastasis up to 10 mm in greatest dimension
IIIA1(ii)		Metastasis more than 10 mm in greatest dimension
IIIA2	T3a2-N0/N1	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
IIIB	T3b-N0/N1	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
IIIC	T3c-N0/N1	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)
IV	**Any T, any N, M1**	**Distant metastasis excluding peritoneal metastases**
IVA		Pleural effusion with positive cytology
IVB		Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

Reprinted with permission: Prat J, FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, Fallopian tube, and peritoneum. Int J Gynaecol Obstet 2014; 124(1):1-5.

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