

INTRODUCTION



GUIDELINES FOR MANAGEMENT OF OVARIAN CANCER

in the State of Qatar

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This document is a best practice guide intended to assist in the diagnosis, management, treatment and care of ovarian cancer in the State of Qatar compiled by members of the Gynae-Oncology Tumour Board and Supreme Council of Health and based on guidelines from Hamad Medical Corporation, the National Comprehensive Cancer Network (NCCN), London Cancer Alliance (LCA) Clinical Network, Scottish Intercollegiate Guideline Network (SIGN) and National Institute for Health and Care Excellence (NICE).

This guideline is subject to ongoing review on a 12 monthly basis.

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INTRODUCTION

1. Introduction

In 2014, 21 new cases of ovarian cancer (including fallopian tube and primary peritoneal of gynaecological origin) were diagnosed in the State of Qatar¹. It is the second most common gynaecological cancer and the fifth most common malignancy in women in the world². The incidence of ovarian cancer increases with age and is most prevalent in the sixth and seventh decades of life. The outcomes are usually poor because the majority of cases present with advanced disease with little prospect of cure³.

Ovarian cancers consist of several histopathologic entities and treatment depends on the specific tumour type. Epithelial ovarian cancer comprises about 90% of malignant ovarian neoplasms³ and is recognized as a heterogeneous disease consisting of several histological sub-types with distinct clinical behaviour and molecular pathways⁴.

For the majority of women with ovarian cancer, standard therapy consists of a combination of surgery and chemotherapy. Survival is largely dependent on the stage of cancer at initial presentation. Treatment is usually curative in the early stages and in certain histological types. Typically, a patient with advanced epithelial cancer can develop relapsed disease requiring repeated courses of chemotherapy. Relapsed disease is invariably fatal and its diagnosis has a huge impact on patients and their carers. The prospects for improving survival lie with earlier diagnosis and optimal management after initial presentation. The goal for healthcare professionals must be to ensure that where a cure is not possible a woman can have a good quality of life with judicious use of surgery, chemotherapy and palliative care.

1.1 Purpose of the Guideline

This guideline is intended to articulate the agreed standards of care for the treatment of ovarian cancer within the State of Qatar and to assist clinical staff to provide appropriate care and treatment for patients with ovarian cancer.

1.2 End Users of the Guideline – Professional and Patient Groups

This guideline is relevant to all healthcare professionals (physicians, nurses, allied health professionals, others) who come into contact with ovarian cancer patients, as well as to the patient themselves and their carers.

It is also expected that this guideline will be of value to those involved in clinical governance in both primary, secondary, tertiary care and private healthcare to help ensure that arrangements are in place to deliver appropriate care to this group of patients.

1.3 Target Areas

This guideline is intended as a reference for the following departments: gynaecology, gynae-oncology, medical oncology, radiation oncology, surgery, diagnostic radiology, pathology/laboratory, nursing, pharmacy, medical genetics, palliative care.

GENERAL PRINCIPLES OF CARE

2. General Principles of Care

The main recommendations are that:

- Patients should be managed by a multidisciplinary team which discusses ideally a minimum number of 20 new ovarian cancer cases per year.
- Patients should be informed of the different treatment options (including no treatment) and should be involved in the decision making process to the extent that they wish.
- All patients should be offered access to an advanced clinical nurse specialist to support them through their cancer experience.
- Patients should be offered prompt access to specialist psychological support and, if appropriate psychiatric services.
- Patients should be made aware of, and have the choice to enter clinical trials if available.
- Following the MDT discussion, the decision is validated and 'signed off' by members present. The MDT outcome proforma is then uploaded onto the patient's records. This ensures that those involved in the patients care can access the decision; this includes the patient's primary health care physician. The recommended decision for patients from the private sector is fed back to the referring clinician.

THE SPECIALIST MULTI-DISCIPLINARY TEAM (MDT)

3. The Specialist Multi-Disciplinary Team (MDT)

The MDT is the group of people from different health care disciplines, who meet regularly to discuss an agreed cohort of patients. This forum allows each specialist to independently contribute to the diagnosis and treatment decisions about patients who meet the criteria for the MDT discussion. This forum also recommends treatment regimens for individual patients.

Referrals for discussion at the MDT are managed by the MDT coordinator and these referrals are accepted in line with the guidelines for the referral pathway (see chapter 4). A list of patients for discussion is generated from the referrals made and this list is circulated to the MDT members for review prior to the meeting. A deadline is set for referrals for discussion in order to enable the members to prepare for the MDT discussion.

3.1 Criteria for Discussion at MDT

Patients who meet the following criteria should be referred for discussion by the MDT:

- All new patients with a diagnosis of ovarian cancer prior to commencing treatment. Optimally, patients with newly diagnosed cancer should be referred once the primary assessment is complete (clinical review, imaging and biopsy), enabling a diagnosis to be made and initial treatment plan agreed.
- Patients with suspected cancer.
- Patients presenting post operatively for pathology review and further management decision making.
- Patients presenting with relapsed or progressive disease whilst on or after treatment.
- Patients who may require palliative surgery, radiotherapy, systemic treatment or other treatment for metastatic or recurrent disease.
- Patients who may require palliative therapy due to poor general condition that precludes curative intent.
- Patients that have initiated or completed their management abroad and require further management or follow up recommendations from the MDT.

3.2 Individual Patient Treatment Plans

The core function of the MDT is to agree and record individual patient's treatment plans. During the MDT meeting, a record is made of the case discussion, and the agreed management plan including plans for further investigation, clinical review and treatment. The MDT individualized treatment plan includes the following information:

- The patient identity (patient name and medical number).
- Summary of clinical presentation.
- Summary of investigations completed and summary of results.
- The MDT agreed treatment planning decision.

The MDT discussion and decision is validated and 'signed off' by members present. The MDT outcome proforma is then uploaded onto the patient's records. This ensures that those involved in the patient's care can access the decision including the patient's primary health care physician. The recommended decision for patients from the private sector is fed back to the referring clinician.

Referrals for patients requiring chemotherapy or radiotherapy treatment are completed after the MDT. An appointment is made by the patient pathway coordinator with the patient who is then informed of the MDT decision by the clinician. Patients requiring radiotherapy are first referred to the medical oncology for initial assessment and planning of eventual or concomitant systemic therapy. Consequently, the patients are referred to the radiation oncology by the medical oncologist.

3.3 Arrangements for Decision Making Outside of the Regular MDT Forum

Decisions in the management of ovarian cancer are rarely made urgently (without due consideration), and therefore every effort should be made for the patient to be discussed by the MDT prior to commencing treatment. In the event that an urgent decision is required, discussion should occur between at least 2 core members of the MDT of different disciplines and the patient should be listed for discussion at the next available MDT meeting. Such urgent discussions and resulting recommendations should be adequately documented in the patient's record.

3.4 The MDT Relationship with the Tumour Board

The lead clinician of the gynae-oncological MDT must be a member of the Qatar gynae-oncological Tumour Board. The lead clinician must attend the meetings of these forums or must nominate another core member of the MDT to attend. The attendance at the tumour board will be recorded and demonstrated in the team's annual report.

REFERRAL GUIDELINES AND PATIENT PATHWAY

4. Referral Guidelines and Patient Pathway

Patients are referred to the gynaecological cancer specialist team through the following routes:

- Primary Healthcare Centres (PHC) by using the Urgent Suspected Cancer (USC) form or through routine referral.
- Internal HMC referrals from other consultants within Hamad Medical Corporation, Women's hospital, emergency department.
- Other cancer MDTs.
- Referrals from private providers.
- Referrals from clinicians whose patients are returning to Qatar following treatment overseas.

Patients referred to the gynaecological cancer service should be seen in a specialist clinic by a clinician who has been designated as privileged for this specialty.

Patients should be seen in the following clinics prior to returning to the gynaecology specialist MDT if they have had aspects of their treatment and care delivered elsewhere:

- Patients without a confirmed diagnosis should be seen in the gynae-oncologic clinics.
- Patients on systemic treatment or radiotherapy should be seen in the medical oncology clinics.

4.1 Criteria for using the USC Form in Ovarian Cancer Referral

- Ovarian mass with risk of malignancy index (RMI) > 250.
- Adnexal/ovarian mass with suspicious features on imaging:
 - Solid area.
 - Thickened septae.
 - With extra ovarian spread.
 - With ascites or pleural effusion.
- Ovarian mass in post menopausal women with elevated Ca 125.
- Ovarian mass with family history of breast and ovarian cancer.

Other criteria which should be referred to the gynaecology clinic for further evaluation include:

- Persistent abdominal distension/bloating.
- Abdominal/pelvic pain.
- Feeling full quickly or having difficulty eating..
- Post-menopausal bleeding.
- Rectal bleeding.
- Urinary symptoms (such as increased urinary urgency and/or frequency).
- Weight loss.

4.2 Management of Referrals in HMC

- i. Referrals of all new tertiary cancer patient using the USC form and internal referrals within HMC are managed by the Referral Management Office (RMO).

Any provider who wishes to refer a patient to cancer services at HMC using an urgent suspicion of cancer referral form should complete the USC form and phone the request through to the RMO and then send the USC form to the RMO.

The **RMO** contact details are as follows:

Telephone: +974 40250116

Fax: +974 44398975

Email: suspectedcancer@hamad.qa

- ii. Referral of patients from all providers for discussion and/or opinion at the MDT on confirmed or uncertain/difficult diagnosis of cancer are managed by the MDT coordinator. Other referrals managed by the MDT coordinator include
 - Re-referrals of those patients already discussed at the MDT meeting but who have had a change or cessation in agreed treatment plan.
 - Referrals between teams are communicated by the MDT coordinators to each other by specific tumour type.

The **MDT coordinator** can be contacted on:

Telephone: +974 55825053

Fax: +974 40151082

Email: rpadilla@hamad.qa

The referral should be made by a faxed referral letter or copy of HMC's completed MDT referral proforma. Any relevant imaging and pathology (both report and blocks where possible) should be made available for review as part of the MDT discussion.

The MDT will agree the next steps for the patient and the appropriate appointment will be made. The patient pathway coordinator will take responsibility for facilitating access to the required service.

4.3 The Patient Referral Pathway in Qatar

The following diagram (Figure 1) presents an overview of a cancer patient referral pathway in the State of Qatar.

Significant Timelines in the Patient Referral Pathway

I. Referral to Specialist Clinic:

- Those referred using the USC form should be **seen within 48 hours of referral.**

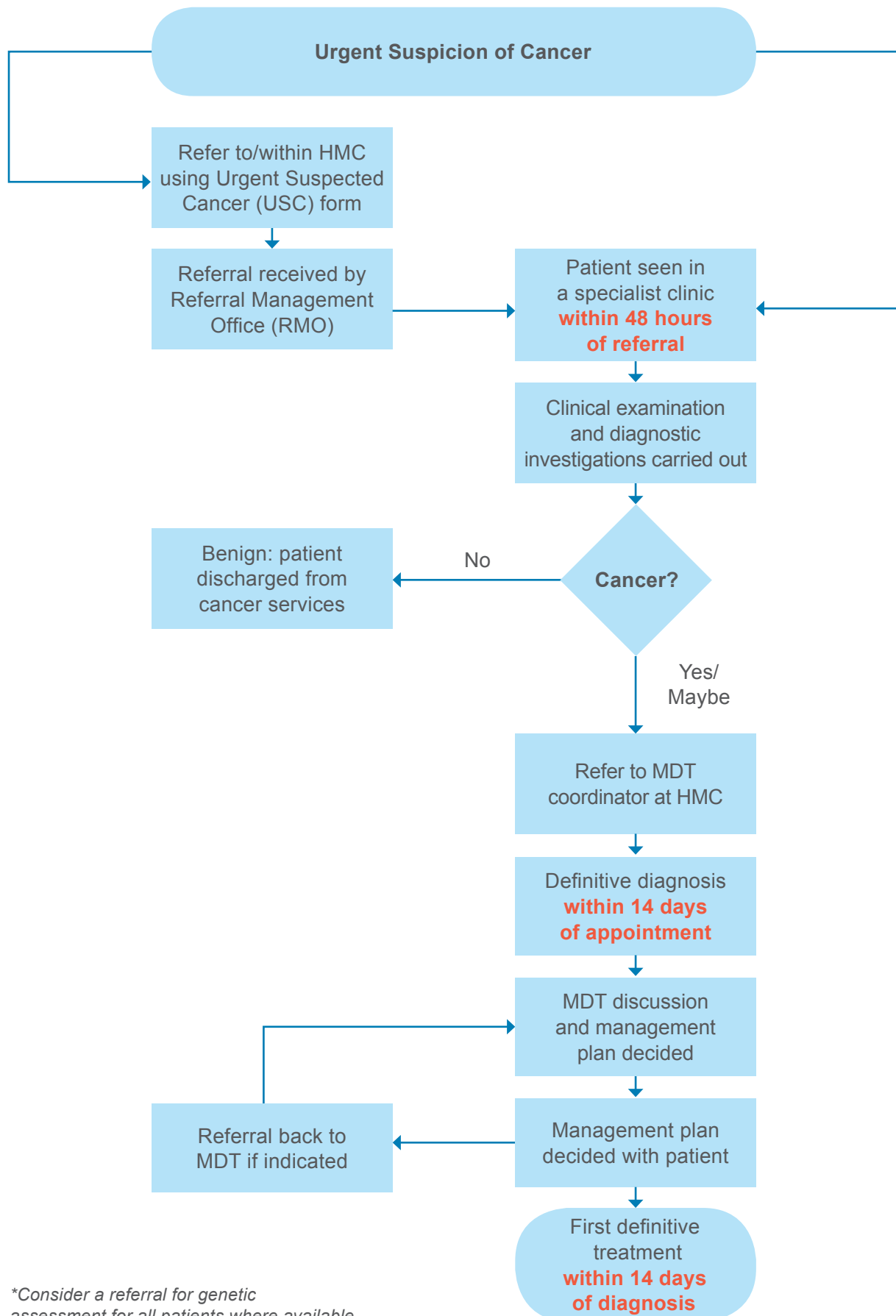
II. Time to Definitive Diagnosis:

- Once a patient is seen, **a definitive diagnosis should be reached in 14 days** using a combination of imaging, pathology and physical examinations. This applies to any patient referred to a specialist clinic and found to have a diagnosis of cancer, regardless of the referral route.

III. Time to Treatment:

- There must be no more than **14 days between the date of confirmed diagnosis at MDT and the date of first definitive treatment.** This applies to any patient, with a confirmed diagnosis of cancer, regardless of the referral route.

Patient Referral Pathway in Qatar



INVESTIGATIONS AND DIAGNOSIS – PRE-OPERATIVE ASSESSMENT

5. Investigations and Diagnosis – Pre-operative Assessment

Ovarian cancer comprises a heterogeneous group of tumours of three major types: epithelial, germ cell and sex cord stromal³.

Epithelial tumours arise from the coelomic mesothelium, which is capable of differentiating into both benign and malignant tumours. Epithelial malignancies represent the majority of all ovarian cancers. The predominant cell types are: serous, mucinous and endometrioid³.

The malignant germ cell tumours are believed to arise from primitive germ cells in the ovary. These tumours represent about 5% of all ovarian malignancies. They include dysgerminoma, embryonal carcinoma, endodermal sinus tumour, choriocarcinoma and malignant teratomas³.

The sex cord stromal neoplasms are derived from mesenchymal stem cells in the ovarian cortex and represent about 10% of all ovarian tumours. They include granulosa–theca cell tumours, granulosa cell tumours (GCTs) and Sertoli–Leydig cell tumours³. Sex cord-stromal tumours are a heterogeneous group of very rare tumours ranging from benign to aggressive, and each histology has a range of often well differentiated to undifferentiated. Therefore, it should be determined whether a patient has a malignant or benign sex cord-stromal tumour.

5.1 The Primary Investigations

- History including past and present medical history and family history of cancer (if any).
- General physical examination including vaginal and rectal examination.
- Serum biochemistry, including renal & liver function tests and electrolyte tests.
- Complete blood count and differential.
- Serology – HIV, Hepatitis B and C.
- Tumour markers based on the type of cancer suspected:
 - Epithelial tumours – CA-125, CEA.
 - Stromal Anti-Mullerian hormone (AMH and/or Inhibin).
 - Germ cell tumours – alpha fetoprotein (AFP), beta human chorionic gonadotropin (hCG) and lactose dehydrogenase (LDH).
- Computed Tomography (CT) of abdomen and chest.
- Dynamic contrast enhanced (DCE) Magnetic Resonance Imaging (MRI) scan of the pelvis in order to characterise indeterminate adnexal masses.
- Mammography if age is greater than 40 years.
- Ultrasound scan – a transvaginal ultrasound scan should be undertaken by an accredited radiographer, radiologist or gynaecologist.

- Upper and lower gastrointestinal endoscopy (if clinically indicated).
- Cytology of ascitic or pleural fluid if present.

5.2 Calculating the risk of malignancy index (RMI)

Table 1

Feature	RMI 1 score
Ultrasound features: • multilocular cyst • solid areas • bilateral lesions • ascites • intra-abdominal • metastases	0 = none 1 = one abnormality 3 = two or more abnormalities
Menopause score	1 = pre-menopausal 3 = post-menopausal
CA-125 level	U/ml
RMI score = ultrasound score x menopausal score x CA-125 level in U/ml	

The RMI is useful as a triaging tool for referrals. It is a product of three features: serum CA-125, menopausal status (M) and ultrasound score.

- Patients with RMI of 250 or greater are considered at high risk of ovarian cancer and should be referred for further management.
- If the imaging is suggestive of ovarian cancer but the RMI score is less than 250, then the patient should also be discussed at the MDT meeting.
- If investigations indicate a probable benign lesion, then further management (observation only) should be undertaken in the cancer unit.

5.3 Genetics

- Ovarian cancer patients with high-grade serous or endometrioid histological subtypes should be considered for BRCA testing regardless of family history⁴.
- If there is a significant family history of cancer (e.g. suspected Lynch syndrome, BRCA), then patient must be discussed with the medical/cancer genetics services⁴.
- Approximately 10–15% of all epithelial ovarian cancer is associated with germline BRCA1 or BRCA2 mutations. It is reported that over 40% of all women identified as having BRCA1/2 mutations do not have a significant family cancer history. Women with high-grade serous and endometrioid histological sub-types are associated with higher rates of BRCA1 or BRCA2 germline mutations⁴.
- Consider a referral for genetic assessment for all patients where available.

5.4 Imaging

Patients with a high clinical suspicion of ovarian cancer based on the initial ultrasound, CA-125 level and menopausal status should be imaged using CT to assess degree of peritoneal involvement, particularly if chemotherapy is planned as a primary treatment⁷.

Patients presenting with peritoneal carcinomatosis should be imaged to assess the extent of disease, plan biopsy, and assess other possible primary pathologies.

- CT is routinely used to monitor response to therapy and to detect recurrent disease.
- MRI is used to characterize indeterminate ovarian cysts or masses found on ultrasound, particularly in young patients or when CA-125 is normal or only slightly elevated.

5.4.1 Staging Objectives

- To determine if optimal surgical cytoreduction is feasible (the definition of optimal cytoreduction is no residual disease >1 cm). This assessment requires the identification of peritoneal involvement in the omentum, subphrenic spaces, falciform ligament, gastro-splenic and gastro-colic ligaments, serosal surfaces of small and large bowel, small bowel mesentery and ascites. Disease over 1 cm in diameter in these areas that are surgically difficult to resect must be clearly indicated.
- To determine involvement of pleural surfaces.
- To detect lymph node enlargement, particularly in the retroperitoneum, superior diaphragmatic and pre-cardiac regions.
- To identify deposits on the liver and splenic surfaces and intra-parenchymal metastases within the liver (<1%) and spleen.
- To identify urinary tract obstruction.

5.4.2 CT

CT of the abdomen and pelvis should be performed to stage the primary tumour. CT of the chest may be performed in suspected advanced disease. CT is the most frequently used technique for staging ovarian cancer, but MRI is useful for characterizing indeterminate ovarian pathology⁷.

- Oral administration of 1 litre of water as a contrast agent, of which 400ml to be drunk immediately prior to going onto the scanner (see Tips).
- 100-150 ml of intravenous iodinated contrast medium injected at 3-4 ml/sec.
- MDCT is commenced at 70-80 seconds post injection.
- Using MDCT, slice thickness will depend on scanner capability. In general, images are reconstructed from one acquisition. Image slice thickness ranges from 1-5 mm. Thin sections are needed for multi-planar reformats, for viewing in the coronal or sagittal planes⁷.

5.4.3 MRI

MRI should be used to characterize indeterminate adnexal mass lesions particularly in young or asymptomatic female patients in who the CA-125 is normal or only mildly elevated, and ultrasound is indeterminate or suspicious for malignancy. MRI may be used in selected patients for problems in staging. Sequences can then be tailored to the clinical question. With MRI of the pelvis, a bowel relaxant (buscopan or glucagon) is strongly recommended⁷.

Table 2: MRI Protocol for Characterising Adnexal Masses⁷

Coils	Sequence	Plane	Slice thickness	Field of view	Principle observations
Abdomino-pelvic surface coil	T1W	Axial	5 ± 1 mm		
	T2W	Axial	5 ± 1 mm		
	T2W	Sagittal	5 ± 1 mm		
	T2W*	Oblique axial	5 ± 1 mm	Parallel to uterus (ovarian plane)	Relationship to uterus and ovary
	DWI (b 0, 1000)	Axial	5 ± 1 mm	To cover the entire mass	To determine presence of restricted diffusion
	T1W + fat sat	Axial	5 ± 1 mm	To cover the entire mass	To distinguish fat and blood
	T1W + fat sat +gad as dynamic acquisition	Axial	5 ± 1 mm	To cover the entire mass	To identify enhancing soft tissue nodules

**Optional – but is particularly useful in characterising relatively small adnexal masses.*

5.4.4 PET-CT

¹⁸FDG PET-CT may be useful on occasion to define disease extent, particularly when follow-up surgery is being considered or detection of recurrence when CA-125 is increasing but CT is negative in cases where further treatment is being considered⁷.

5.4.5 Imaging Monitoring

Monitoring is conducted:

- To assess response to chemotherapy and is therefore performed at a frequency to correspond with the chemotherapy regimens.
- To assess the need for and extent of interval debulking surgery.
- When there is marked evidence of recurrent disease (that is, elevation of CA-125) and it is performed to provide a baseline prior to chemotherapy.
- Prior to salvage surgery for isolated recurrences.

5.4.6 Tips

- Coronal or sagittal reformatted CT images may be very useful to distinguish between intrinsic liver and splenic lesions and peritoneal deposits in the subphrenic spaces.
- Water-filled bowel may allow better detection of serosal involvement than when filled with positive contrast agent on CT.
- Peritoneal deposits are better demonstrated on contrast-enhanced GRE T1W sequences with fat suppression or high b value DWI and are of value when ovarian pathology is characterized as malignant on MRI⁷.

PATHOLOGY ASSESSMENT AND STAGING

6. Pathology Assessment and Staging

The College of American Pathologists (CAP) protocol for ovarian cancer is a useful guide and can be accessed at http://www.cap.org/apps/docs/committees/cancercancerprotocols/2013/0vary_13protocol3200.pdf

The 2013 protocols from the College of American Pathologists (CAP) do not include the new FIGO staging system (see Protocol for the Examination of Specimens from Patients with Carcinoma of the Ovary on the CAP website)⁸.

6.1 Histopathology Assessment of the Surgical Specimen

All tissue specimens removed at laparotomy are submitted for histopathological examination. Specimens are handled according to the standard operating procedures of the pathology department, which cover fixation, dissection, block taking and reporting, and conform to national guidelines and minimum datasets (where available).

Histopathology reports on ovarian cancer cases will include the following:

- summary of clinical history.
- macroscopic description of all specimens including dimensions of ovarian tumours, status of capsule, cyst contents.
- microscopic description (synoptic report available) including:
 - Histological tumour type (WHO classification).
 - Grade.
 - Status of capsule.
 - FIGO stage.

All cases are to be reviewed by consultant pathologists with a special interest in gynaecological pathology, and presented at the MDT meeting prior to decision making about post-surgical management.

6.2 Staging

The two major international systems of classification of gynaecological cancers by their anatomic extent are respectively the FIGO (Federation Internationale de Gynecologie et d'Obstetrique) system, specific for gynaecological malignancies, and the TNM (Tumour, Node, Metastasis) system applicable to all sites and adopted by the UICC (International Union Against Cancer, now the Union for International Cancer Control) and the AJCC (American Joint Committee on Cancer). Both classifications may be utilized in the same patient as long as the general principles of staging are understood and strictly adhered to. The revised FIGO staging system was introduced in January 2014¹¹.

The staging should be based on careful clinical examination before any definitive therapy. It is desirable that the examination under anaesthesia is performed by an experienced gynaecology oncologist jointly with a clinical oncologist. The clinical staging must under no circumstance be changed on the basis of subsequent findings.

Primary peritoneal adenocarcinoma is staged using the ovarian cancer staging system. Fallopian tube carcinomas are staged using a separate FIGO and AJCC staging system. FIGO recently updated the staging for ovarian, fallopian tube, and peritoneal cancer; their new staging system has been approved by the AJCC. However, these changes will be included in the next edition of the AJCC Cancer Staging Manual (8th edition) which will be published in mid-2016 and will be effective for all cancer cases recorded on or after January 1, 2017.

Table 3 - AJCC TNM and International Federation of Gynaecology and Obstetrics (FIGO) 2013

FIGO Guidelines: Staging Classification for Cancer of the Ovary, Fallopian Tube and Peritoneum¹¹

TNM Categories	FIGO Stages	Surgical-Pathologic Findings
T1	I	Tumour confined to ovaries or fallopian tube(s)
T1a	IA	Tumour limited to 1 ovary (capsule intact) or fallopian tube; no tumour on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
T1b	IB	Tumour limited to both ovaries (capsules intact) or fallopian tubes; no tumour on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
	IC	Tumour limited to 1 or both ovaries or fallopian tubes, with any of the following:
T1c1	IC1	Surgical spill
T1c2	IC2	Capsule ruptured before surgery or tumour on ovarian or fallopian tube surface
T1c3	IC3	Malignant cells in the ascites or peritoneal washings.
T2	II	Tumour involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer
T2a	IIA	Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
T2b	IIB	Extension to other pelvic intraperitoneal tissues.
T1/T2-N1	III	Tumour 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):
	IIIA(i)	Metastasis up to 10 mm in greatest dimension
	IIIA(ii)	Metastasis more than 10 mm in greatest dimension
T3a2-N0/N1	IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
T3b2-N0/N1	IIIB	Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
T3c2-N0/N1	IIIC	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 tumour to capsule of liver and spleen without parenchymal involvement of either organ)
Any T, any N, M1	IV	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).

Other major recommendations are as follows:

- Histologic type including grading should be designated at staging.
- Primary site (ovary, Fallopian tube or peritoneum) should be designated where possible.
- Tumours that may otherwise qualify for stage I but involved with dense adhesions justify upgrading to stage II if tumour cells are histologically proven to be present in the adhesions.

Table 4 Anatomic Stage Grouping for Ovarian and Primary Peritoneal Cancer (AJCC 7th ed., 2010)

The staging system for ovarian and primary peritoneal cancer is also used for malignant germ cell tumours, malignant sex cord-stromal tumours, and carcinosarcoma (malignant mixed Mullerian tumours).

Primary peritoneal adenocarcinoma is staged using the ovarian cancer staging system. Fallopian tube carcinomas are staged using a separate FIGO and AJCC staging system. FIGO recently updated the staging for ovarian, fallopian tube, and peritoneal cancer; their new staging system has been approved by the AJCC. However, these changes will be included in the next edition of the AJCC Cancer Staging Manual (8th edition) which will be published in mid-2016 and will be effective for all cancer cases recorded on or after January 1, 2017.

Stage	T	N	M
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC	T1c	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIC	T2c	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T3c	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

Table 5 Anatomic Stage Grouping for Fallopian Cancer (AJCC 7th ed., 2010)

Stage	T	N	M
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC	T1c	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIC	T2c	N0	M0
Stage III	T3	N0	M0
Stage IIIA	T3a	N0	M0
Stage IIIB	T3b	N0	M0
Stage IIIC	T3c	N0	M0
	Any T	N1	M0
Stage IV	Any T	Any N	M1

7. Management of Ovarian Cancer

Primary treatment for presumed ovarian cancer consists of appropriate surgical staging and cytoreduction followed in most but not all patients by systemic chemotherapy³. Initial treatment may be surgical or medical, based on individual circumstances following discussion at the MDT meeting. It is recommended that a gynaecologic oncologist perform the primary surgery.

- In women without a diagnosis of malignancy and having a suspicious mass confined to the ovary, resection of the mass and frozen section should be done.
- If malignancy is confirmed, then surgery should proceed accordingly.

For optimal management of ovarian cancer, the treatment modalities include:

- Surgery (covered in detail in chapter 8)
- Radiotherapy (covered in detail in chapter 9)
- Chemotherapy (covered in detail in chapter 10)

There remains a significant risk of recurrence and resistance to therapy. Systemic therapy options for relapsed ovarian cancer are guided by the platinum-free interval.

Management of fallopian tube and primary peritoneal tumours are currently the same as for ovarian cancer.

7.1 Epithelial Ovarian Cancer

For a young patient who wishes to maintain fertility, a unilateral salpingo-oophorectomy (USO), preserving the uterus and contralateral ovary may be adequate for select stage I tumours (stage 1A and 1C, but not stage 1B) and/or low-risk ovarian tumours (i.e. early-stage, low-grade invasive tumours, ovarian LMP tumours).

7.1.1 Surgery

Based upon the type of tumour, extent of disease, age of the patient and desire for fertility the procedures performed will be either:

- **Standard (Cytoreductive) surgery:** Total abdominal hysterectomy + bilateral salpingo oophorectomy + omentectomy + resection of peritoneal disease ± pelvic/para aortic lymph node dissection.
- **Conservative (Fertility-sparing) surgery:** Unilateral salpingo oophorectomy ± omentectomy ± pelvic/para aortic lymph node dissection.

7.1.2 Chemotherapy

- **Neoadjuvant chemotherapy:** Carboplatin + Paclitaxel.
- **Adjuvant chemotherapy:** Carboplatin + Paclitaxel ± Bevacizumab.
- **Salvage chemotherapy:** Single or combination depending upon performance status and preference for oral or parenteral therapy.
 - **Parenteral:** Gemcitabine, Topotecan, Pegylated doxorubicin, Ifosfamide, Bevacizumab.
 - **Oral:** Etoposide, Hexamethylmelamine (HMM), Tamoxifen.

7.1.3 Radiotherapy

The role of adjuvant and definitive radiotherapy in ovarian cancer is limited. There is a role for palliative radiotherapy in the treatment of relapse.

7.1.4 Treatment Outline

Based upon clinical assessment and radiological imaging, management of patients with epithelial ovarian cancer can be divided into 2 groups:

- I. Patients **not suitable** for primary surgical cytoreduction are should be treated by neoadjuvant chemotherapy followed by surgery after confirmation of diagnosis by laparoscopic biopsy where possible, otherwise by cytology/fine needle aspiration biopsy (FNAB). These will include cases with:
 - significant pleural effusion or other extra abdominal metastasis.
 - rapidly accumulating ascites.
 - gross upper abdominal disease.
 - extensive bowel and mesentery involvement.
 - significant pelvic soft tissue infiltration.
 - CT scan evidence of widespread peritoneal metastasis or retroperitoneal lymphadenopathy.
 - poor performance status (ECOG 3 or more).

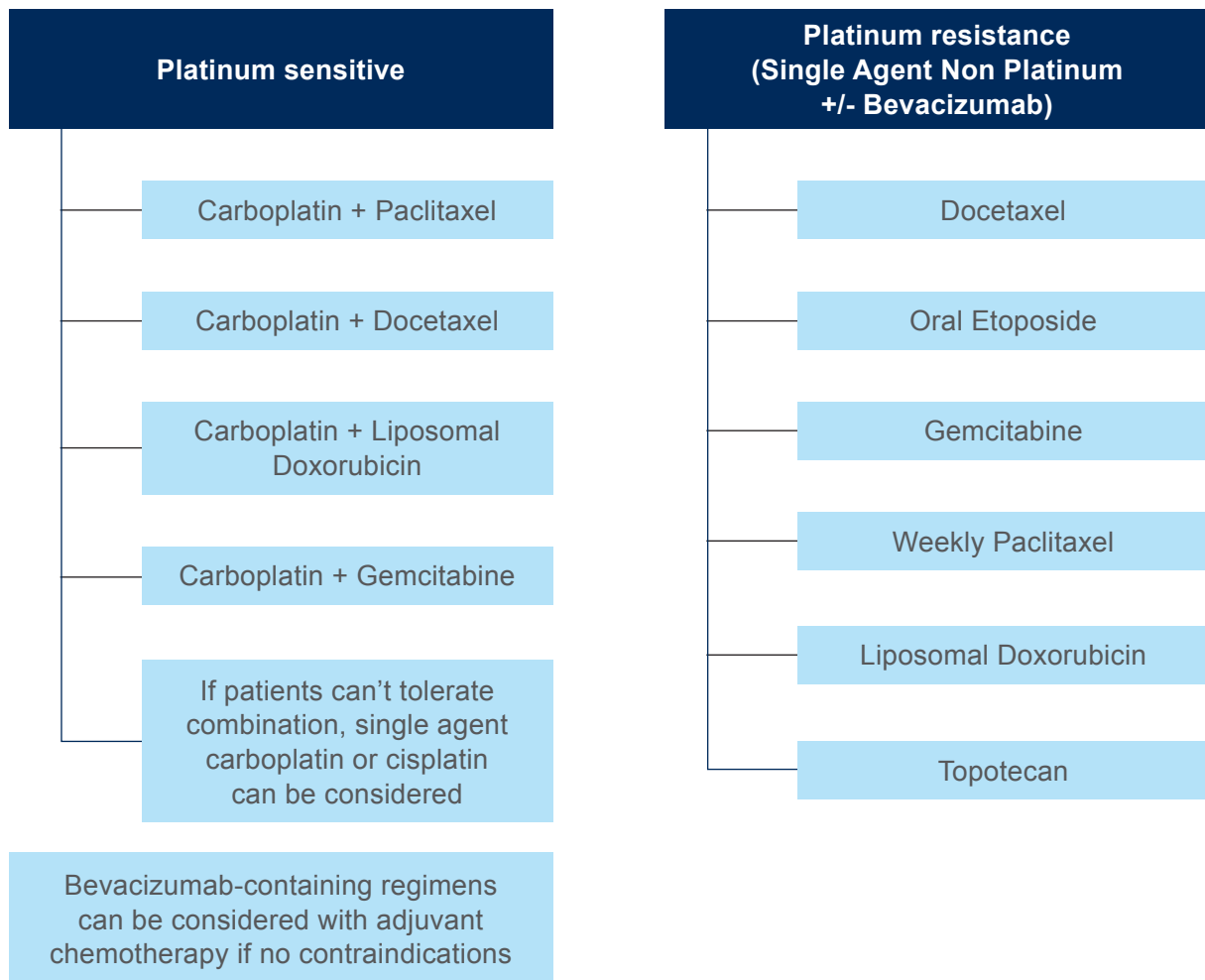
Neoadjuvant chemotherapy + surgery: Up to 3 cycles of chemotherapy followed by standard surgery in responders followed by 3-5 cycles of postoperative chemotherapy.

- II. Patients suitable for primary cytoreduction surgery should be treated by surgery followed by adjuvant chemotherapy based upon final histopathology and stage.

Surgery and adjuvant chemotherapy: After standard surgery adjuvant chemotherapy for 6 cycles will be offered to all patients except those with Stage I A/B grade 1 disease and borderline tumours.

7.1.5 Management of Relapse

1. **Surgery:** The criteria for secondary cytoreduction includes relapse of more than 12 months after chemotherapy, tumour responsive to primary chemotherapy, high performance status (PS), limited disease sites without excessive ascites and the potential for complete resection.
2. **Chemotherapy:**
 - If platinum sensitive: Platinum-based regimens.
 - If platinum resistant: Single therapy depending on performance status and preference for oral or parenteral therapy.



3. **Radiotherapy:** Palliative treatment with or without chemotherapy.
4. **Palliative care and symptom control.**

7.2 Non-epithelial Ovarian Cancers

7.2.1 Sex Cord-Stromal: Granulosa cell tumours, Sertoli-Leydig cell tumours

The standard management is the same as for the epithelial ovarian cancer in section 7.1.

- Cases suitable for surgery based upon disease extent and performance status could be offered primary surgery.
- Patients not suitable for primary surgical cytoreduction should be offered neoadjuvant chemotherapy followed by interval debulking surgery in responders.
- Conservative surgery can be performed if favourable conditions are met.
- Chemotherapy is indicated in Stage IC onwards.

Relapsed disease:

- Consider further surgery for relapsed disease (secondary cytoreduction).
- Platinum-based chemotherapy for selected recurrent unresectable cases.
- Bevacizumab can be considered for granulosa cell tumours.
- Consider anti-oestrogen therapy (e.g. aromatase inhibitors, tamoxifen).
- Palliative radiotherapy.

Pre-menopausal women	Post-menopausal women
Aromatase inhibitors • Anastrozole 1 mg PO daily, until evidence of progression OR • Exemestane 25 mg PO daily, until evidence of progression OR • Letrozole 2.5 mg PO daily, until evidence of progression.	Tamoxifen 20mg PO daily

7.2.2 Germ Cell Tumours

Conservative surgery should always be considered irrespective of stage in young patients if the contralateral ovary and uterus are not grossly involved by the tumour. However complete debulking of tumour elsewhere in the abdomen and pelvis should be done, if feasible in the advanced stages. In older patients not not concerned with maintaining fertility, standard surgery as described for epithelial ovarian cancer should be performed. Principles of surgical staging as for epithelial tumours should be adhered to.

I. **Recommended primary chemotherapy regimens** include:

- BEP: Bleomycin + Etoposide + Cisplatin (high emetogenicity).
- Etoposide + Cisplatin.

II. Recommended chemotherapy regimens for recurrent disease include:

- Etoposide + Cisplatin (high emetogenicity).
- VIP: Etoposide/Ifosfamide/Cisplatin (high emetogenicity).
- Paclitaxel + Gemcitabine.
- Other therapies to be considered include TIP (Paclitaxel +Ifosfamide + Cisplatin), VeIP (Vinblastine + Ifosfamide + Cisplatin).

Nephrotoxic chemotherapies may need to be accompanied by an appropriate hydration regimen.

Adjuvant chemotherapy: 2 to 3 cycles should be given after normalization of tumour markers. In marker negative cases, up to 4 cycles can be given.

7.3 Follow up for Epithelial and Non-epithelial Ovarian Cancers

The follow up schedule depends on the risk of recurrence, clinical symptoms and whether tumour markers were initially elevated. The schedule includes history and exam, CBC and serum chemistry, tumour marker (if elevated initially), ultrasound of abdomen and pelvis (CT scan if indicated), and chest x-ray annually.

Patients will receive a follow-up appointment at the treatment centre.

Stage I disease: Review at

- 3 monthly intervals for the first and second years.
- 4-6 monthly intervals from the third to fifth years.
- Consider discharge at 5 years.

Stage II+ disease (high risk or recurrent disease): Review at

- 3 monthly intervals for the first and second years.
- 4-6 monthly intervals from the third to fifth years
- Annually for life.

7.4 Borderline Ovarian Tumours

The mean age of presentation is typically 10 years younger than invasive ovarian cancer and therefore fertility preservation is an important consideration. The main sub-types are serous and mucinous borderline tumours. Diagnosis is made on the surgical specimen. There is no reliable method with either imaging or tumour markers for differentiating benign from malignant tumours. Staging is as per the ovarian cancer FIGO staging.

7.4.1 Management of Borderline Ovarian Tumours

The management of borderline ovarian disease very much depends on the age and fertility status of the patient. All patients with this disease should undergo staging surgery consisting of:

- thorough exploration of the entire abdominal cavity
- peritoneal washings
- infracolic omentectomy
- removal of all macroscopic suspicious peritoneal lesions
- multiple peritoneal biopsies
- appendicectomy (for mucinous tumours).

Total abdominal hysterectomy/bilateral salpingo-oophorectomy is recommended for women who have completed their family. For women with apparent stage I disease and a desire to preserve fertility, the uterus and part of one ovary may be preserved. The patient should be counselled pre-operatively as to the higher chance of recurrence after conservative surgery.

If there is bilateral ovarian disease or a history of previous unilateral salpingo-oophorectomy, it is reasonable to perform a cystectomy if this is feasible. However, in the presence of gross bilateral disease this may not be possible.

If the disease involves only one ovary and the other appears normal, then the only diseased ovary should be removed. There is no need to perform systematic biopsies from the contralateral normal-looking ovary.

In advanced borderline tumours, complete resection of the disease is necessary. If borderline ovarian disease is diagnosed as an incidental finding during surgery for benign disease, then restaging should be performed if there is no description in the operation note of the abdominal cavity or peritoneal surfaces. Most borderline tumours are stage I at presentation and have an excellent prognosis.

7.4.2 Follow up

The risk of recurrence for borderline ovarian tumours is low for most women. The follow-up schedule depends on stage, histology and whether fertility-preserving surgery was undertaken. Stage I patients should be followed for at least 10 years with transvaginal ultrasound to examine the remaining ovary if they have had fertility-sparing surgery.

Patients with non-invasive peritoneal implants require careful follow-up at the centre. Following treatment, there is no contraindication to pregnancy in stage I patients. Stage III patients should be counselled appropriately if they wish to have a family. Patients should be counselled to consider removal of the remaining ovary after completion of family and/or menopause.

SURGICAL MANAGEMENT OF OVARIAN CANCER

8. Surgical Management of Ovarian Cancer

In all cases where ovarian cancer is suspected, surgery irrespective of stage, should take place in a treatment centre by a designated gynaecological oncologist. If performing surgery for women with ovarian cancer, whether before chemotherapy or after neo-adjuvant chemotherapy, the objective should be complete resection of all macroscopic disease⁴.

Initial surgery should be a comprehensive staging laparotomy, including a total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO).

For select patients, a minimally invasive surgical approach may be employed by an experienced surgeon to achieve the surgical staging in those patients who have undergone the removal of tumours without staging. Minimally invasive surgical approaches may be useful when evaluating whether maximum cytoreduction can be achieved in patients with newly diagnosed or recurrent ovarian cancer. If clinical judgment indicates that maximum cytoreduction cannot be achieved, neoadjuvant chemotherapy should be considered.

8.1 Staging Laparotomy

Diagnosis is made at staging laparotomy with adequate exposure through a midline incision or with minimal access surgery. An open laparotomy including a vertical midline abdominal incision should be used in patients with a suspected malignant ovarian/fallopian tube/primary peritoneal neoplasm in whom a surgical staging procedure, a primary debulking procedure, an interval debulking procedure, or secondary cytoreduction is planned.

Intraoperative pathologic evaluation with frozen sections may assist in guiding surgical management. At operation, malignant disease may be obvious from the appearance and pattern of spread of disease. However, the diagnosis may not be evident where pre-operative investigations have revealed a complex ovarian cyst with no macroscopic metastatic disease or where a suspicious-looking lesion is identified and the nature of this may alter the type of surgery performed (e.g. fertility-sparing surgery). The use of intra-operative frozen section analysis may be used to identify malignant disease and reduce the need for a second staging procedure.

Surgery should include the following:

- peritoneal washings or collection of ascitic fluid for cytology
- palpation of pelvic and abdominal contents including liver, diaphragm, paracolic gutters, intestine and para-aortic and pelvic nodes
- inspection and biopsy where appropriate of peritoneal surfaces, including atypical and 'normal' peritoneum; biopsy any suspicious lesions or adhesions
- infracolic omentectomy
- biopsy of palpable lymph nodes

- extirpative surgery is of prime importance in epithelial ovarian cancers. Removal of both adnexae (bilateral salpingo-oophorectomy) with total abdominal hysterectomy and omentectomy is indicated in stage I epithelial ovarian cancer, and, wherever possible, in stages II to IV.
- appendicectomy for mucinous tumours.

Surgeons should describe the following in the operative reports:

- Extent of initial disease before debulking pelvis, mid abdomen, or upper abdomen (cutoffs: pelvic brim to lower ribs).
- Amount of residual disease in the same areas after debulking.
- Complete or incomplete resection. If incomplete, indicate the size of the major lesion and total number of lesions. Indicate if miliary or small lesions.

8.2 Cytoreductive surgery

Staging surgery is undertaken as above. Cytoreductive surgery is the initial treatment recommendation for patients with clinical stage II, III, or IV disease. Surgical cytoreduction is optimal if the residual tumour nodules are less than 1 cm in maximum diameter or thickness (i.e. residual disease <1 cm). Extensive resection of upper abdominal ovarian metastases is recommended for patients who can tolerate this surgery. Maximal effort should be made to remove all gross disease since this offers superior survival outcomes.

Primary surgery ('debulking') improves chemotherapy response rates as well as increasing survival. The aim of surgery is to remove all visible disease. A careful recording of sites and size of residual disease at the end of surgery is imperative. Patients for surgery should not routinely undergo bowel preparation unless the history, clinical findings or imaging reveal advanced disease where bowel involvement is present.

8.2.1 Ultra-radical (Extended) Surgery for Advanced Epithelial Ovarian Cancer

Ovarian cancer spreads throughout the peritoneal cavity and is frequently very advanced at presentation. The aim of ultra-radical surgery for advanced ovarian cancer is to remove all visible disease, with a view to improving survival compared with standard, less radical surgery.

Procedures that may be considered for optimal surgical cytoreduction (in all stages) include: radical pelvic dissection, bowel resection, diaphragm or other peritoneal surface stripping, splenectomy, partial hepatectomy, cholecystectomy, partial gastrectomy or cystectomy, ureteroneocystostomy, distal pancreatectomy, or appendectomy.

This extended surgery should be undertaken only if it is anticipated that complete debulking of macroscopic disease can be achieved.

Clinicians wishing to undertake ultra-radical surgery for advanced ovarian cancer should ensure that:

- Selection of patients must be done by a specialist gynaecological cancer multidisciplinary team (MDT).
- Patients are clearly informed about alternative treatment options and about their benefits and risks compared with extended surgery for advanced ovarian cancer.
- Ultra-radical surgery for advanced ovarian cancer should be done in collaboration between surgeons with appropriate expertise (such as specialists in gastrointestinal and hepatobiliary surgery) and/or by specialists in gynaecological cancer surgery with specific training in such extensive surgery.
- The procedure should only be done in specialized units with a regular practice in this type of surgery.

8.2.2 Lymphadenectomy

The role of lymphadenectomy in ovarian cancer is unclear. Whereas it does not in itself influence survival, there may be groups of patients who can be spared chemotherapy if they are node negative after optimal surgical staging. Furthermore, knowledge of nodal status may influence which type of chemotherapy should be given.

Pelvic and para-aortic lymphadenectomy are part of complete staging for serous, endometrioid and clear cell histological sub-types. For mucinous tumours, the incidence of lymph node metastasis in tumours otherwise confined to the ovary is extremely small. Retroperitoneal lymph node assessment should be undertaken as part of optimal surgical staging in women who appear to have stage I ovarian cancer. If nodes are enlarged, they should be removed as part of the aim of removing all macroscopic disease.

8.3 Fertility-preserving Surgery

Some young patients with epithelial ovarian cancer wish to retain their fertility. Unilateral salpingo oophorectomy (USO) surgery will involve full staging to assess the extent of disease but without removing the uterus and the contralateral ovary if it looks macroscopically normal. In these circumstances, the recurrence rate for patients is higher than with conventional radical surgery and this risk needs to be carefully communicated to the patient.

Fertility-sparing surgery is more suitable for patients with germ cell tumours or borderline disease. The criteria for considering conservative surgery in epithelial ovarian cancer includes:

- young age desirous of pregnancy.
- apparent stage IA following optimal surgical staging procedures.
- no family history of ovarian cancer.

- favourable histopathologic sub-type. This will not be known until pathology is reviewed.
- negative peritoneal washings.
- no invasion through the tumour capsule.
- no lymph node involvement.

In selected cases of stage 1C and if the patient accepts the risk, conservative surgery plus adjuvant chemotherapy can be considered.

Fertility-sparing surgery is possible in the majority of patients with a suspected germ cell tumour. The involved ovary should be sent for frozen section analysis, and standard surgical staging should be performed. Consider completion surgery after completion of child bearing in epithelial cancers.

8.4 Interval Debulking Surgery or Delayed Primary Debulking Surgery

This surgery is defined as a surgical procedure performed in women whose tumour mass has decreased following three to four courses of chemotherapy and in those who have had no surgery or in those who have previously undergone surgery that was unsuccessful at optimally cytoreducing the disease. These women should show evidence of a response to chemotherapy as determined by CA 125 and imaging.

Interval debulking surgery should be performed only where it was not possible to optimally debulk the disease at initial surgery but where, following a good response to chemotherapy, complete debulking of disease is deemed possible by the specialist multidisciplinary team.

8.5 Secondary Cytoreductive Surgery

A secondary cytoreduction procedure can be considered in patients with recurrent ovarian cancer who recur more than 6-12 months since completion of initial chemotherapy (platinum-free interval), have an isolated focus or limited foci of disease amenable to complete resection and do not have ascites.

Factors to consider include number of sites of recurrent disease, response to prior chemotherapy and volume of residual disease following primary surgery. CT-positron emission tomography (PET) should be considered to determine if any other sites of disease can be identified prior to surgery or radical radiotherapy. Patients are encouraged to participate in ongoing clinical trials evaluating the true benefit of secondary cytoreduction if available.

RADIOTHERAPY MANAGEMENT OF OVARIAN CANCER

9. Radiotherapy Management of Ovarian Cancer

9.1 General Considerations

All patients are seen by a clinical oncologist and a radiation oncologist. A signed and informed consent is gained before they are booked in for radiotherapy.

Patients with pacemakers or implantable cardioverter/defibrillator should be referred to cardiologist prior to referral to radiotherapy. Premenopausal patients with surgically preserved ovaries should be counselled on infertility risks and psychosexual consequences of treatment.

The role of adjuvant and definitive radiotherapy in ovarian cancer is limited.

9.2 Palliative Radiotherapy

Palliative radiotherapy is indicated for relieving symptoms or preventing threatening complications from locally advanced disease or metastatic disease. Examples include treatment of primary tumour to control bleeding or pain or treatment of sites of painful metastasis e.g. bone, para aortic or supra-clavicular lymph nodes. A special indication for urgent palliative radiotherapy is the presence of spinal cord compression due to metastasis.

- Patients with painful bone metastases should be considered for palliative treatment with Magnetic Resonance Guided Focused Ultrasound (MRgFUS).
- Target volume in palliative setting is determined individually.

There are several effective palliative conventional radiotherapy regimens, including

- 30 Gy in 10 fractions.
- 20 Gy in 5 fractions.
- 8 Gy in 1 fraction.

The selection of an appropriate fractionation schedule and treatment technique should take into consideration several factors, including the patient's general condition, site and extent of metastatic disease, symptoms, threatening symptoms, past treatment, prognosis and remaining treatment options.

9.2.1 Stereotactic Radiotherapy or Radiosurgery

Stereotactic radiotherapy or radiosurgery is an alternative to neurosurgery in patients with limited-volume metastatic disease in the brain. Patients who are candidates for stereotactic irradiation techniques should be discussed at the neuro-oncology MDT. Whole brain irradiation should be considered in patients with multiple brain metastases.

9.3 Radiotherapy Treatment Planning

Treatment planning is done on the treatment planning system and is reviewed and approved by the planner, medical physicist, and the radiation oncologist.

The plan review includes but is not limited to analysis of dose volume histogram, isodose distribution, radiation beam parameters and suggestions for plan improvement.

The proposed treatment plan and dose prescription should be documented. Any modification to treatment design will need to be clearly documented. Prior to the beginning of treatment, each plan is subject to intra-departmental peer review by the radiation oncology team, including radiation oncologists, medical physicists, and radiation therapists.

In certain situations all the planning demands cannot be met. In such cases, documented deviations from the recommended values may have to be accepted at the discretion of the radiation oncologist and documented.

9.4 Treatment Delivery

Patients are treated according to the standard treatment instructions. The radiation oncologist is present for the first fraction of radiation. Imaging is performed according to the imaging protocol and typically includes daily cone-beam computed tomography (CT) with on-line review by the radiation therapist and off-line review by the radiation oncologist.

Patients will be reviewed once a week by the radiation oncologist for assessing treatment progress and toxicity. Referrals for evaluations or assessments should be made for any patients developing any toxicity for appropriate treatment.

SYSTEMIC MANAGEMENT OF OVARIAN CANCER – CHEMOTHERAPY

10. Systemic Management of Ovarian Cancer – Chemotherapy

10.1 General Pre-chemotherapy Investigations

- Record residual disease.
- Post-operative baseline CT chest, abdomen, pelvis.
- Baseline tumour markers CA-125 (others, e.g. CA 19-9, if elevated at diagnosis).
- Full blood count (FBC), urea and electrolytes (U&E), liver function tests (LFTs), albumin.
- Calculate glomerular filtration rate (GFR) for patients receiving platinum-based chemotherapy: either EDTA or calculated GFR (Cockcroft and Gault formula).
- Calculate body surface area (BSA).
- Document performance status.

All patients require baseline imaging (CT chest/abdomen/pelvis) within 4 weeks of commencing systemic therapy.

Tumour markers (CA-125) should be performed prior to commencing cycle 1 (baseline) and at every cycle. Repeat imaging is performed following cycles 3 and 6. For patients receiving adjuvant chemotherapy, imaging can be repeated after 6 cycles (i.e. omit after 3 cycles) if there is no measurable disease on the baseline scan.

Performance status (PS) must be documented at the start of each cycle of systemic treatment. Patients receiving chemotherapy should have a PS of 0–2; all patients with a PS >3 receiving chemotherapy should have reasons for this decision documented.

ECOG (Eastern Cooperative Oncology Group) Performance Status Scale

ECOG	Description
0	Fully active, able to carry on all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry out any self-care; totally confined to bed or chair.

Toxicities must be documented at each visit with assessment of severity.

Toxicity Grading

0 = No adverse event or within normal limits
1 = Mild adverse event
2 = Moderate adverse event
3 = Severe and undesirable adverse event
4 = Life-threatening or disabling adverse event
5 = Death related to adverse event

The rationale, aims and possible toxicities of chemotherapy are to be discussed with all patients. Information leaflets on chemotherapy should be provided and patients need to have the opportunity to discuss any questions prior to written informed consent with their oncology team/key worker. It is expected that the treatment centre has local guidelines and/or protocols for:

- dose modifications.
- management of hypersensitivity.
- management of common toxicities.

10.2 Systemic Anti Cancer Treatment

10.2.1 Early Stage (Stage I)

Treatment for early-stage ovarian cancer is potentially curative. Observation, however, is recommended for patients with stage IA or IB grade 1 tumours, because survival is greater than 90% for this group with surgical treatment alone.

The rationale for no adjuvant chemotherapy should be discussed with all patients. Patients who present with one or more of the following are considered to have a worse prognosis and should be offered adjuvant chemotherapy:

- stage IC or above.
- histology: high grade of any sub-type, clear cell or poorly differentiated carcinoma.
- incomplete surgical staging.

Combination chemotherapy is the standard treatment in international trials and is the treatment of choice.

- Platinum (Carboplatin) + Taxane (Paclitaxel).

10.2.2 Advanced Stage (Stages II-IV)

Neo-adjuvant Chemotherapy

- Neoadjuvant chemotherapy refers to treatment that is given to reduce the tumour burden before cancer surgery.
- Treatment options (intravenous) include:
 - Platinum (Carboplatin) + Paclitaxel.
 - Carboplatin + weekly Paclitaxel.
 - Weekly Carboplatin + Paclitaxel.
 - Platinum (Carboplatin) + Docetaxel.

Adjuvant Chemotherapy

- Most patients with epithelial ovarian cancer receive postoperative systemic chemotherapy, which is also referred to as adjuvant therapy.
- All intravenous options mentioned above.
- Bevacizumab-containing regimens.

10.2.3 Recurrent Disease

Approximately 80% of patients diagnosed with ovarian epithelial cancer eventually relapse after first-line platinum/taxane-based combination chemotherapy and may benefit from further treatment. Systemic treatment options for patients with recurrent disease depend on the platinum-free interval:

- **Platinum-sensitive:** disease recurs/progresses more than 6 months after the last dose of platinum-based chemotherapy.
- **Platinum-resistant:** disease recurs/progresses less than 6 months after the last dose of platinum-based chemotherapy.
- **Platinum-refractory:** disease recurs/progresses during platinum-based chemotherapy.
- **Partially platinum-sensitive:** relapse/progression 6–12 months following the last dose of platinum-based chemotherapy.

The timing of commencing systemic therapy for relapsed/persistent disease depends on clinical symptoms, rate, distribution and degree of progression. It is recommended that patients with a rising CA 125 alone (non-measurable/low-volume disease) should be closely monitored (clinical review, imaging) and not routinely commence standard systemic therapy unless in the context of a clinical trial.

Consider adding Bevacizumab to all platinum-sensitive and platinum resistant regimens.

I. Platinum-sensitive (>6 months since last platinum)

Platinum-based combination chemotherapy options include:

- Consider clinical trial.
- Carboplatin + Paclitaxel
- Carboplatin + Liposomal Doxorubicin
- Carboplatin + Docetaxel
- Carboplatin + Gemcitabine
- Bevacizumab + Carboplatin + Gemcitabine for first platinum-sensitive relapse (i.e. second-line treatment)
- Single agent Carboplatin to be considered for patients who cannot tolerate combination therapy.

II. Partially platinum-sensitive (6-12 months since last platinum)

- Consider Carboplatin + Liposomal Doxorubicin ± Trabectedin

III. Platinum-resistant (<6 months since last platinum) and platinum-refractory (during platinum chemotherapy)**Non-Platinum single agents**

- Consider clinical trial.
- Paclitaxel
- Docetaxel
- Liposomal Doxorubicin
- Etoposide
- Gemcitabine
- Topotecan
- For BRCA positive patients, consider Poly ADP ribose polymerase (PARP) inhibitors as maintenance therapy after Carboplatin based regimens or as fourth line of palliative chemotherapy, if available.

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THE GUIDELINE DEVELOPMENT GROUP (GDG)

12 The Guideline Development Group (GDG)

The ovarian cancer clinical guidelines have been produced with the assistance of a multidisciplinary group of clinicians to provide a comprehensive overview of the ovarian cancer patient's journey from referral to treatment and support.

The guideline development process was supported by staff from Hamad Medical Corporation (HMC) and Supreme Council of Health (SCH). The draft of the guideline was prepared by HMC and SCH staff in partnership with the gynae-oncology tumour board chair and lead clinicians. This draft was then discussed and agreed with the tumour board and subsequently forwarded to the stakeholders for consultation.

Following the consultation period, staff from HMC and SCH finalized the recommendations and the final document was sent to the National Cancer Committee (NCC) for approval. On receipt of the NCC approval, publication and dissemination occurred in the state of Qatar.

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Updating the Guideline

One year after publication of the guideline, the gynae-oncology tumour board will review the guideline to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update.

Disclaimer

The GDG assumes that healthcare professionals will use clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply these guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient and clinical expertise.

The SCH disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.