Management of epithelial ovarian cancers

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1. Scope and background

The purpose of this guideline is to describe the management of suspected ovarian cancer and provide currently available best evidence to health care professionals to provide optimal care for these patients. This guideline also reviews their management options depending on the resources available in the local setting.

Ultimate goal of treating a cancer patient is to cure the disease where possible and to have control of primary disease and delay the recurrences in patients in whom complete cure is not possible. Patients beyond above levels should receive appropriate symptom relieving treatment. Pre-operative staging, individualized treatment planning and appropriate adjuvant treatment and risk based follow up are corner stones in managing these patients.

2. Summary of key recommendations

2.1 Patient assessment:

Detailed history including comorbidities and performance status is mandatory. Thorough general, abdominal, pelvic examination should be done in every patient. Per rectal examination should be performed in clinically indicated patients.

All pelvic masses should be assessed for risk of malignancy.

Risk of Malignancy Index (RMI) and/or International Ovarian Tumour Analysis (IOTA) group ultrasound rules can be used for this purpose (See Appendix).

RMI index is more suitable when an epithelial neoplasm is suspected.

IOTA rules can be used in all patient categories.

All the patients with high-risk adnexal masses should have Contrast Enhanced CT scan of chest, abdomen and pelvis (CECT CAP).

Full blood count, Renal functions, Liver functions etc. should be performed to assess the fitness for surgery.

2.2 Treatment of primary ovarian cancer

2.2a Choosing the correct approach:

There are 2 equally effective approaches in epithelial ovarian cancer, which are,

1. Primary surgery
2. Upfront/Neo adjuvant chemotherapy (3 to 4 cycles) followed by interval debulking surgery.

Both approaches have shown similar survival outcomes in randomized controlled trials[7].

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When interval debulking approach is chosen, histological confirmation should be done before starting chemotherapy in all patients except in extreme circumstances.

Following upfront chemo therapy, CECT CAP and tumour markers should be done to assess response and to plan interval debulking surgery.

2.2b Surgical technical details:

When possible, multi-disciplinary inputs should be obtained before planning surgery for suspected ovarian cancer. It is recommended to involve clinicians with oncological background in the decision-making process.

All the patients with high-risk ovarian masses should undergo midline laparotomy (Suprapubic transverse incisions should not be used in suspected or confirmed ovarian cancer).

Thorough abdominal survey should be done including pelvis, paracolic gutters, diaphragm, liver, omentum, spleen, small bowel, large bowel, bowel mesentry and para-aortic lymph nodes.

Surgical approach would be dependent on the results of the abdominal survey.

Patients with apparently early ovarian cancer should undergo complete excision of all macroscopic tumour (optimal cytology reduction) and staging of the disease when the patient is fit enough to undergo extensive surgery.

Patients with advanced ovarian cancer should undergo multi visceral surgery to achieve optimal cyto reduction when the patient is fit enough to undergo extensive surgery. When optimal cyto reduction cannot be achieved, near optimal (residual tumour at a single point < 1cm) cyto reduction should be aimed.

These procedures should be performed in a setting with adequate facilities, staff and surgical expertise. In absence of facilities and expertise, these patients should be referred to a center with such facilities. Surgical team should be led by a Consultant Gynaecologist / Gynaecologgcial Oncologist. Extensive debulking with multi visceral surgery often require advanced anaesthetic and post-operative intensive care support as well.

2.3 Managing patients with fertility wishes:

Systematic individualized approach should be used in young patients with high-risk ovarian tumours to avoid unnecessary interventions that would affect fertility.

Single step approach – Extent of the surgery is decided by the results of intra operative frozen section of the tumour.

2 step approach – A biopsy procedure is done in the initial surgery. Further interventions are planned according to the histology results of the first surgery.

2.4 Adjuvant treatment:

Post-operative histology review should be done in every patient to decide on adjuvant treatment.

Tumour grading and stage of the disease would determine the need for adjuvant treatment.

All the patients who had neo-adjuvant chemotherapy should complete the remaining cycles in the post-operative period. (Should be initiated in the 3rd or 4th post-operative week to achieve best outcome).

2.5 Management of recurrent ovarian cancer

Patients suspected of having recurrent disease should undergo CECT CAP and tumour marker assay.

Patients with recurrent ovarian cancer should be referred to a cancer centre with multi-disciplinary expertise.

Secondary debulking has shown significant survival advantages in patients who fulfill following criteria

- Single focus disease
- No or minimal Ascites (less than 500 ml)
- Disease free interval of more than 6 months from primary chemotherapy
- Optimal debulking at initial surgery
- Good performance status

2.6 Follow up

A follow up based on appropriate history, examination and tumour markers is recommended.

Routine ultrasound scans are recommended in patients who had fertility sparing treatment.

Asymptomatic patients with rising tumour markers without radiological evidence of recurrence should not undergo routine exploratory surgery.

3. Introduction

Ovarian cancer is the second most common gynaecological cancer in Sri Lanka, second only to cervical cancer[3]. In 2020, 1132 new cases of ovarian cancers were diagnosed in Sri Lanka[3]. Due to lack of a reliable screening method more than 70% of ovarian cancers are diagnosed at stage 3 or beyond.

However due to advances in surgery, chemotherapy and immunological therapies, 5 year net survival in ovarian cancer has doubled over last 40 years[4]. Deep understanding of biological behaviour of different subtypes of ovarian cancer was a contributing factor for these advances. Principles of treatment, including meticulous patient selection, proper staging, radical debulking of tumour and timely adjuvant treatment should be followed up in every instance to provide these survival advantages to patients.

4. Recommendations and discussion

4.1 Patient assessment:

Detailed history including comorbidities and performance status is mandatory. Thorough general, abdominal, pelvic examination should be done in every patient. Per rectal examination should be performed in clinically indicated patients:

All pelvic masses should be assessed for risk of malignancy.

Risk of Malignancy Index (RMI)[5] and/or International Ovarian Tumour Analysis (IOTA) group ultrasound rules[6] can be used for this purpose (See Appendix).

RMI index is more suitable when an epithelial neoplasm is suspected.

IOTA rules can be used in all patient categories.

All the patients with high-risk adnexal masses should have Contrast Enhanced CT scan of chest, abdomen and pelvis (CECT CAP).

Full blood count, Renal functions, Liver functions etc. should be performed to assess the fitness for surgery All patients with pelvic masses should undergo Ultrasound scan of abdomen and pelvis and serum assay for tumour markers. Aim of this assessment is to triage the risk of malignancy.

– Tumour markers:

	For all patients	If bowel cancer suspected	If upper gastrointestinal malignancy is suspected
< 40 years	CA 125, LDH, AFP, HCG	CEA*	Ca 19.9
> 40 years	CA 125	CEA*	Ca 19.9

*Where both CA 125 and CEA are elevated, CA125: CEA ratio < 25 is suggestive of primary gastro intestinal malignancy.

With above investigators, patients are triaged as below

Low risk of cancer	Indeterminate/ Intermediate risk	High risk of cancer
RMI of < 20 Or Presence of at least 1 Benign feature without any Malignant features of the IOTA criteria	RMI between 20 to 250 Or Presence of **both** Malignancy and Benign features of the IOTA criteria Or Absence of **both** Malignancy and Benign features of the IOTA criteria	RMI of > 250 Or Presence of at least 1 Malignancy features without any Benign features of the IOTA criteria
To be managed as a benign adnexal mass	Further imaging by MRI or excision (cystectomy or oophorectomy without spillage) **	To be managed as a malignant mass. Need further staging

**Type of surgery and incision should be individualized according to size and other tumour characteristics (size of solid parts, thick septa, etc). Intra-abdominal spillage of tumour should be avoided as this could upstage an early ovarian cancer.

CECT CAP is performed to assess local infiltration and distant metastasis. When CT scan is not available, Chest X-ray and ultrasound of the abdomen should be done.

4.2 Treatment of primary ovarian cancer

4.2a Choosing the correct approach:

There are 2 equally effective approaches in epithelial ovarian cancer, which are,

3. Primary surgery
4. Upfront/Neo adjuvant chemotherapy (3 to 4 cycles) followed by interval debulking surgery.

Both approaches have shown similar survival outcomes in randomized controlled trials[7].

When interval debulking approach is chosen, histological confirmation should be done before starting chemotherapy in all patients except in extreme circumstances.

Following upfront chemo therapy, CECT CAP and tumour markers should be done to assess response and to plan interval debulking surgery.

Where possible primary surgery is recommended in preference to interval debulking, especially in cases of low-grade cancers, due to poor response to chemotherapy (around 4%). Interval debulking surgery is the choice where optimal or near optimal debulking is unlikely due to extensive disease or poor performance status of the patient.

Image guidance (Ultrasound or CT), laparoscopy or mini laparotomy can be used to obtain biopsies before up front chemo therapy. Where biopsy is difficult to obtain, cytology from ascites or pleural fluid can be used. However, cytology is associated with false

positive and false negative results. Preparation of cell blocks and immune-histochemical staining has shown to improve accuracy of diagnosis.

Following 3 to 4 cycles of chemotherapy, response is assessed by CT CAP and tumour markers. Patients who respond to chemotherapy are offered with interval debulking while non responders are referred for further oncological management. (Even with very good response to chemo therapy, surgical debulking is indicated since there can be residual microscopically active tumour cells).

4.2b Surgical technical details:

When possible, multi-disciplinary inputs should be obtained before planning surgery for suspected ovarian cancer. It is recommended to involve clinicians with oncological background in the decision-making process.

All the patients with high-risk ovarian masses should undergo midline laparotomy (Suprapubic transverse incisions should not be used in suspected or confirmed ovarian cancer).

Thorough abdominal survey should be done including pelvis, paracolic gutters, diaphragm, liver, omentum, spleen, small bowel, large bowel, bowel mesentry and para-aortic lymph nodes.

Surgical approach would be dependent on the results of the abdominal survey.

Patients with apparently early ovarian cancer should undergo complete excision of all macroscopic tumour (optimal cytology reduction) and staging of the disease when the patient is fit enough to undergo extensive surgery.

Patients with advanced ovarian cancer should undergo multi visceral surgery to achieve optimal cyto reduction when the patient is fit enough to undergo extensive surgery. When optimal cyto reduction cannot be achieved, near optimal (residual tumour at a single point < 1cm) cyto reduction should be aimed.

These procedures should be performed in a setting with adequate facilities, staff and surgical expertise. In absence of facilities and expertise, these patients should be referred to a center with such facilities. Surgical team should be led by a Consultant Gynaecologist / Gynaecologcial Oncologist. Extensive debulking with multi visceral surgery often require advanced anaesthetic and post-operative intensive care support as well.

Apparently early ovarian cancer in a primary surgery (Disease confined to pelvis)	Peritoneal washings or ascitic fluid sampling, TAH BSO with division of the ovarian vessels at least 2cm lateral to the ovaries, multiple peritoneal biopsies from the para-colic sub-diaphragmatic spaces bilaterally, omentectomy, and pelvic and bilateral para-aortic lymph node assessment up to the level of the insertion of the ovarian vessels. Appendicectomy should be done in mucinous tumours	Aim is for complete excision of all macroscopic tumour (optimal cytology reduction) and staging of the disease when the patient is fit enough to undergo extensive surgical staging. Staging is required to assess the prognosis of disease as well as to identify patients who require adjuvant treatment. (Stage lc or beyond) Up to 30% of apparently early-stage epithelial ovarian cancers are up staged following comprehensive staging[8]

Advanced ovarian cancer or interval debulking surgery	Multi visceral surgery to achieve optimal or near optimal cyto reduction. TAH BSO /Omentectomy (Supracolic where necessary) should be combined with peritoneal stripping, removal of bulky pelvic/para-aortic lymph nodes, splenectomy, diaphragmatic resection and bowel resection to achieve optimal or near optimal debulking. The extent of surgery would depend on the extent of disease spread.	Aim is for complete excision of all macroscopic tumour (optimal cytology reduction) when patient is fit enough to undergo extensive surgery. When this is not possible near optimal cyto reduction (residual tumor at a single point < 1cm) should be attempted. When optimal or nea optimal debulking is not anticipated in the initial survey, biopsy should be taken and surgery should be planned as a interval debulking procedure after 3 to 4 cycles of chemotherapy. Partial debulking followed by second look laparotomy after chemotherapy is not recommended since it is associated with increased morbidity without survival advantage.

4.3 Managing patients with fertility wishes:

Systematic individualized approach should be used in young patients with high-risk ovarian tumours to avoid unnecessary interventions that would affect fertility.

Single step approach – Extent of the surgery is decided by the results of intra operative frozen section of the tumour.

2 step approach: A biopsy procedure is done in the initial surgery. Further interventions are planned according to the histology results of the first surgery. Even though commonest in the elderly, epithelial ovarian cancer also occurs in young patients. Germ cell cancer as well as borderline tumours of the ovaries are commoner in young females. In this patient group, non-neoplastic pathologies such as Tuberculosis, Actinomycosis can mimic ovarian cancer. While germ cell cancers are extremely sensitive for chemotherapy, properly staged early borderline ovarian tumours can be managed with fertility preservation.

Single step approach: Intra operative frozen section can be used following biopsy of peritoneal deposits or ovarian cystectomy or oophorectomy. If there are bilateral ovarian masses, bilateral cystectomy is preferred over oophorectomy.

Further staging procedures such as omentectomy, appendicectomy, lymph node assessment etc should be done at the same surgery according to frozen section outcome. Biopsy of a macroscopically normal contra lateral ovary should not be performed. In young patients with epithelial ovarian cancers confined to one ovary, preservation of uterus and contra lateral ovary should be considered. However, in instances where the disease is upstaged following pathological assessment, completion surgery is recommended. (Uterine preservation is possible even in advanced cases of germ cell malignancies of the ovaries due to extremely high chemo sensitivity)

2 step approach: Biopsy of peritoneal deposits or ovarian cystectomy or oophorectomy is done during the 1st surgery. Once the histological diagnosis is known, further interventions are planned. During this procedure, all the precautions should be taken to avoid spillage of cyst contents to avert upstaging of an early-

stage ovarian cancer. Therefore, if suspicion for malignancy is strong, open surgery is highly recommended.

4.4 Adjuvant treatment:

Post-operative histology review should be done in every patient to decide on adjuvant treatment.

Tumour grading and stage of the disease would determine the need for adjuvant treatment.

All the patients who had neo-adjuvant chemotherapy should complete the remaining cycles in the post-operative period. (Should be initiated in the 3rd or 4th post-operative week to achieve best outcome)

Patients are categorized as below to decide on adjuvant treatment[9,10].

Stage IA/I B Low risk histology (Grade 1 and 2) – No need of adjuvant treatment.

Stage IA/I B High risk histology (Grade 3/poor differentiation) – patient should be referred to an oncologist to consider adjuvant chemotherapy.

Stage l C to Stage IV – patient should be referred to an oncologist for adjuvant chemotherapy.

4.5 Management of recurrent ovarian cancer

Patients suspected of having recurrent disease should undergo CECT CAP and tumour marker assay.

Patients with recurrent ovarian cancer should be referred to a cancer centre with multi-disciplinary expertise.

Secondary debulking has shown significant survival advantages in patients who fulfill following criteria[11].

- Single focus disease
- No or minimal ascites (less than 500 ml)
- Disease free interval of more than 6 months from primary chemotherapy
- Optimal debulking at initial surgery
- Good performance status

Extensive surgery should be done only when patient fulfill the evidenced based selection criteria for secondary debulking. Other patients should undergo surgery only for palliative purposes (Eg – to relieve bowel obstruction). These patients should be managed in a multi-disciplinary setting.

4.6 Follow up

A follow up based on appropriate history, examination and tumour markers is recommended.

Routine ultrasound scans are recommended in patients who had fertility sparing treatment.

Asymptomatic patients with rising tumour markers without radiological evidence of recurrence should not undergo routine exploratory surgery.

Clinical follow up with symptoms (change of bowel habits, dyspeptic symptoms, change of urinary habits, vaginal bleeding/ discharge, loss of appetite), abdominal/ pelvic examination and tumour markers should be done in all patients. Patients with positive clinical findings or rising tumour markers should undergo CECT CAP for further assessment.

Follow up frequency

Up to 2nd year	3 to 4 monthly
2nd year to 5th year	6 monthly
After 5 years	Annual

5. Clinical governance

All female patients above 50 years presenting with new onset dyspeptic symptoms should undergo pelvic ultrasound scanning and CA 125 assay.

Patient presenting with symptom suggestive of ovarian cancer should undergo testing for tumour markers and pelvic/abdominal ultrasound scan within 14 days of presenting to medical care.

The definitive treatment of a high-risk ovarian mass should be aimed to occur within 6 weeks from the date of presentation to medical services. Patients should be promptly referred to specialist centers to achieve this target.

Above time frames are guidance to ensure patient safety and not to be considered as strict rules. Clinical audits on these time frames are highly recommended.

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Appendix

1. Tumour markers elevated in ovarian malignancies

Tumour marker	Malignancy
CA 125	Epithelial ovarian cancer (Mainly serous type)
LDH	Dysgerminoma
Alfa fetoprotein	Yolk sack tumour
HCG	Ovarian choriocarcinoma, Dysgerminoma
Carcino Embryonic Antigen	Gastrointestinal cancer
CA 19.9	Pancreatic cancer
CA 153	Breast cancer

2. RMI index

RMI score = CA 125 level *menopause score *ultrasound score

Menopause score
3 if post-menopausal
1 if pre-menopausal

Ultrasound score
0 if no high-risk features
1 if one high risk feature
3 if 2 or more features

High risk ultrasound scan features
1. Bilateral tumour
2. Solid areas within the tumour
3. Multi locular cyst
4. Ascitis
5. Distant metastasis

3. IOTA Ultrasound rules

Benign rules	Malignant rules
Unilocular cyst	Irregular solid tumour
Presence of solid component with largest part < 7mm	Presence of ascitis
Presence of acoustic shadow	At least 4 papillary structures
Smooth multi locular tumour with largest diameter < 100mm	Irregular multi locular solid tumour with largest diameter > 100mm
No blood flow (colour score 1)	Very strong blood flow (colour score 4)

Presence of at least 1 Benign rule without any Malignant rules	Benign mass
Presence of both Benign rules and Malignant rules Or Absence of any Benign rule and Malignant rule	Indeterminate mass
Presence of at least 1 Malignant rule without any Benign rules	Malignant mass