

Management of histologically confirmed endometrial cancer

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1. Scope and background

The purpose of this guideline is to describe the management of histologically proven endometrial 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

All patients should undergo speculum and per vaginal examination to assess for involvement of cervix, vagina and gross invasion of parametria.

As a minimum, chest X ray should be performed in all patients to assess for lung metastasis. An ultrasound of the abdomen/pelvis (when a cross

sectional imaging is not available) should be performed in all patients to assess for distant solid organ involvement.

If available, an MRI scan can provide more details about myometrial invasion, cervical stromal/parametrial involvement and pelvic lymph node enlargement.

CECT scan of the chest, abdomen and pelvis (CECT CAP) should be performed in patients with possible stage III and IV disease before planning treatment. If available, CT scanning should be considered in patients with poorly differentiated histology subtypes. (Clear cell, serous cells, malignant mixed mullerian tumors, grade 3 endometrioid cancer).

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

All the patients who are diagnosed to have endometrial cancers are better to be discussed in a multi-disciplinary setting before the surgical intervention if the facilities are available.

2.2 Treatment of Stage I endometrial cancer

Both open and laparoscopic routes are acceptable in endometrial cancer. Vaginal hysterectomy with bilateral salpingo-oophorectomy can be considered in patients

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not fit enough to have general anaesthesia or abdominal surgery. However, this is not recommended if the patient can undergo an abdominal or laparoscopic surgery.

A MRI assessment of the pelvis is a pre requisite, prior to a laparoscopic surgery for endometrial cancer. Patients for laparoscopic surgery should be selected meticulously and laparoscopic surgery is recommended only when there is both clinical and radiological evidence of disease confined to the uterus.

Laparoscopic route should only be used when uterine specimen is small enough to be retrieved intact vaginally without excessive manipulation/ sectioning/ morcellation. When uterus is large, where non traumatic retrieval is difficult or there are features of local invasion (stage III or IV disease), laparoscopic surgery should be converted to open or the surgery should be abandoned.

Surgery should be tailored according to risk factors for advanced staged disease. Histology subtypes, cellular differentiation (Grade) and depth of myometrial invasion in the MRI scan (if available) should be considered before planning surgery.

All patients should undergo total hysterectomy (TH) with bilateral salpingo-oophorectomy (BSO).

Further staging by pelvic/para-aortic lymphadenectomy and omentectomy is recommend in high-risk patients. 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. Surgery should be done by a Gynecological Oncologist or a Consultant Gynecologist with experience in performing these procedures.

A total pelvic nodal count more than 10 is recommended.

2.3 Treatment of Stage II endometrial cancer

Simple TH + BSO + Bilateral (B/L) Pelvic lymphadenectomy +/- Para aortic lymphadenectomy followed by adjuvant treatment or radical hysterectomy + B/L Pelvic lymphadenectomy +/- Para aortic lymphadenectomy without adjuvant therapy (if no additional risk factors in the post-operative histology).

2.4 Adjuvant treatment for early endometrial cancer

Post-operative risk assessment should be done in every patient.

All the patients with stage II, III or IV disease on histology should be referred to the clinical oncologist for adjuvant treatment.

Stage I disease is further re classified according to risk of recurrence and patients with intermediate and high risk should be referred to a clinical oncologist for adjuvant treatment.

2.5 Fertility sparing treatment

All the patients who are offered with fertility sparing treatment should be selected carefully and discussed in a multi-disciplinary setting.

Histology should be assessed by a consultant pathologist with good experience in gynae-oncological disease.

All the patients should undergo MRI of the pelvis to exclude overt myometrial invasion and pelvic lymph node involvement.

Patients with Grade 1 endometrioid type tumour without myometrial invasion who are willing to undergo assisted reproduction could be offered with conservative treatment.

Medroxy progesterone acetate (MPA) 400-600 mg per day is the treatment of choice.

All the patients should be assessed with endometrial biopsy at 3 monthly interval and repeat MRI scan at 6 months from initiation of treatment. If remission is achieved, these patients should be referred to reproductive medicine specialist for assisted reproduction.

Those patients who do not respond by 6 months should be offered with standard surgical management.

2.6 HRT in treated endometrial cancer patients (After TAH BSO)

HRT can be considered in patients with grade 1/2 endometrioid adenocarcinoma, stage IA disease, without LVSI.

2.7 Endometrial cancer diagnosed in a post hysterectomy specimen

When endometrial cancer is diagnosed incidentally in a post hysterectomy specimen, they should be considered for repeat staging surgery (Eg: Salpingo oophorectomy, lymph node assessment, omentectomy).

2.8 Advanced endometrial cancer (Stage IIIA, IIIB and IV in the pre-operative assessment)

Clinical pelvic assessment to assess local invasion by an experienced clinician is required in all patients. CECT scan of chest, abdomen and pelvis should be performed to assess for distant disease.

Debulking surgery: Should be performed only when disease is completely resectable. All the patients should be referred to the oncologist for adjuvant treatment.

Primary oncological management: Radiotherapy with or without chemotherapy is the preferred treatment for patients with inoperable disease confined to pelvis. Patients with stage IV disease are usually managed with chemotherapy.

Palliative surgery: Should be reserved for symptomatic control in situation such as severe genital tract bleeding not responding to radiotherapy, chemotherapy or intestinal obstruction.

Hormone therapy: Can be used in patients with advanced disease not fit enough for surgery, radiotherapy or chemotherapy. Medroxy progesterone acetate 200mg/d can be given for grade 1 and grade 2 endometrioid endometrial cancer patients.

2.9 Recurrent endometrial cancer

All patients should receive clinical pelvic assessment by an experienced clinician (Senior Registrar or Consultant) and histological confirmation should be done when the lesion is accessible.

CECT scan of the chest, abdomen and pelvis should be performed in all patients before planning invasive treatment.

Recurrence within 1 year of primary treatment or multi focal disease is not suitable for radical surgery or radiotherapy. For those patients surgery, radiotherapy

or chemotherapy should be given only in palliative intent. Medroxy progesterone acetate 200mg/d can be considered for symptom control.

Single recurrent lesion in a medically fit patient. Those who have no previous radical radiotherapy with a disease-free interval of more than one year can be managed by radical radiotherapy. Need for surgical debulking should be individually assessed in case-based manner.

Central, isolated pelvic recurrence who had previous radiotherapy can be radically excised by pelvic exenteration as these patients are not suitable for further radiotherapy. CT scan or Positron Emission Tomography (PET) scan to exclude any distant metastasis should be done in all patients before selecting for pelvic exenterative procedure.

2.10 Follow up

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

Follow up frequency should be dictated by risk of recurrence of the cancer.

3. Introduction

Endometrial cancer is a completely curable condition in majority of the patients with an overall 5 year survival around 75%¹. Adherence to adequate staging, radical treatment of the cancer and adjuvant treatment for patients with risk factors for recurrence would provide maximum survival benefit for these patients.

4. Recommendations and discussion

4.1 Patient assessment

All patients should undergo speculum and per vaginal examination to assess for involvement of cervix, vagina and gross invasion of parametria.

As a minimum, chest X ray should be performed in all patients to assess for lung metastasis. An ultrasound of the abdomen/pelvis (when a cross sectional imaging is not available) should be performed in all patients to assess for distant solid organ involvement.

If available, an MRI scan can provide more details about myometrial invasion, cervical stromal/parametrial involvement and pelvic lymph node enlargement.

CECT scan of the chest, abdomen and pelvis should be performed in patients with possible stage III and IV disease before planning treatment. If available, CECT scanning should be considered in patients with poorly differentiated histology subtypes. (Clear cell, serous cells, malignant mixed mullerian tumors, grade 3 endometrioid cancer².) Therefore, histology should be known prior to definitive treatment in all patients with suspected endometrial cancer.

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

All the patients who are diagnosed to have endometrial cancers are better to be discussed in a multi-disciplinary setting before the surgical intervention if the facilities are available.

Clinical examination is an essential part of patient evaluation. Clinical pelvic assessment should be done by an experienced clinician. MRI scanning of pelvis and CECT CAP in high-risk patients is the current gold standard^{2,3}. Rationale behind pre-treatment imaging is to risk stratify the patients before surgery in order to plan tailor made treatment/surgery.

Table 1 illustrates the pre-operative assessment in an ideal setting.

4.2 Treatment of Stage I endometrial cancer

Both open and laparoscopic routes are acceptable in endometrial cancer^{2,3,4}. Vaginal hysterectomy with bilateral salpingo-oophorectomy can be considered in patients not fit enough to have general anaesthesia/abdominal surgery. However, this is not recommended

if the patient can undergo an abdominal or laparoscopic surgery.

An MRI assessment of the pelvis is a pre requisite, prior to a laparoscopic surgery for endometrial cancer. Patients for laparoscopic surgery should be selected meticulously and laparoscopic surgery is recommended only when there is both clinical and radiological evidence of disease confined to the uterus.

Laparoscopic route should only be used when uterine specimen is small enough to be retrieved intact vaginally without excessive manipulation/sectioning/morcellation. When uterus is large, where non traumatic retrieval is difficult or there are features of local invasion (Stage III or IV disease), laparoscopic surgery should be converted to open or the surgery should be abandoned.

Surgery should be tailored according to risk factors for advanced staged disease. Histology subtypes, cellular differentiation (Grade) and depth of myometrial invasion in the MRI scan (if available) should be considered before planning surgery.

All patients should undergo total hysterectomy (TH) with bilateral salpingo-oophorectomy(BSO).

Further staging by pelvic/para-aortic lymphadenectomy and omentectomy is recommend in high-risk patients. 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. Surgery should be done by a Gynaecological Oncologist or a Consultant Gynaecologist with experience in performing these procedures.

Table 1. Pre-operative imaging in endometrial cancer

Grade 1/2 endometrioid	Chest X ray, MRI of the pelvis	If stage III or more in MRI, CT scan of chest, abdomen, pelvis should be done
Grade 3 endometrioid/ Type 2 histology	MRI of the pelvis CT scan of chest, abdomen, pelvis	

Even though accurate staging is only known after surgery and pathological examination, pre-operative staging by clinical assessment and medical imaging is helpful to plan treatment. According to the risk and patterns of metastasis, tailor made surgery is recommended as below. It should be noted that, tumor grading and depth of myometrial invasion are

independent risk factors for lymphatic metastasis⁵. Patients for laparoscopic surgery should be selected meticulously and laparoscopic surgery is recommended only when there is both clinical and radiological evidence of disease confined to the uterus. This recommendation was made to minimize the risk of suboptimal surgery and intra operative spillage of cancer cells.

Table 2. Surgical staging in endometrial cancer

Grade 1 and 2 (endometrioid) with <50% myometrial invasion	TH BSO + Peritoneal washings for cytology
Grade 1 or 2 with > 50% myometrial invasion or Grade 1 or 2 without pre-operative MRI or Grade 3 with < 50% myometrial invasion	H BSO + BL Pelvic lymphadenectomy + Peritoneal T washings for cytology*
Grade 3 with > 50% myometrial invasion or Grade 3 without pre-operative MRI	TH BSO + BL Pelvic lymphadenectomy + Peritoneal washings for cytology* +/- Para aortic lymphadenectomy** +/- infra colic omentectomy
Type 2 endometrial cancer (See Appendix)	TH BSO + BL Pelvic lymphadenectomy + Peritoneal washings for cytology* +/- Para aortic lymphadenectomy** And infra colic omentectomy

* A total pelvic nodal count more than 10 is recommended⁴.

**Should be performed if no significant comorbidity or intra operative risk factors.

4.2 Treatment of Stage II endometrial cancer

Simple TH + BSO + B/L Pelvic lymphadenectomy +/- Para aortic lymphadenectomy followed by adjuvant treatment or Radical hysterectomy + BL Pelvic lymphadenectomy +/- Para aortic lymphadenectomy without adjuvant therapy (if no additional risk factors in the post-operative histology).

Traditionally Stage II endometrial cancer was treated with radical hysterectomy (RH). But with current evidence, both RH or simple hysterectomy with adjuvant therapy offers similar survival benefits. However, due to need of adjuvant treatment in some patients who undergo radical hysterectomy, current guidelines favour simple hysterectomy^{3,4}.

4.4 Adjuvant treatment for early endometrial cancer

Post-operative risk assessment should be done in every patient.

All the patients with stage II, III or IV disease on histology should be referred to the clinical oncologist for adjuvant treatment.

Stage I disease is further re classified according to risk of recurrence and patients with intermediate and high risk should be referred to a clinical oncologist for adjuvant treatment.

The aim of adjuvant treatment in early endometrial cancer is to reduce the risk of disease recurrence in high and intermediate risk groups. Table 3 summarizes the different risk groups and recommendations on adjuvant treatment.

4.5 Fertility sparing treatment

All the patients who are offered with fertility sparing treatment should be selected carefully and discussed in a multi-disciplinary setting.

Histology should be assessed by a consultant pathologist with good experience in gynae-oncological disease.

Patients who had initial biopsy by pipelle aspiration should undergo hysteroscopy guided dilatation and curettage as it is superior in assessing the histological grade of the disease⁴.

All the patients should undergo MRI of the pelvis to exclude overt myometrial invasion and pelvic lymph node involvement.

Patients with Grade 1 endometrioid type tumor without myometrial invasion who are willing to undergo assisted reproduction could be offered with conservative treatment^{2,4}.

Medroxy progesterone acetate (MPA) 400-600 mg per day is the treatment of choice^{2,4}.

Table 3. Risk based adjuvant treatment in endometrial cancer

Risk group	Stage and description	Management
Low risk	FIGO grade 1-2, Stage IA, no LVSI	No adjuvant treatment
Intermediate risk	FIGO grade 1, grade 2, LVSI unequivocally positive, regardless of depth of invasion FIGO grade 1- 2, Stage IB, no LVSI FIGO grade 3, Stage IA	Oncology referral to consider adjuvant treatment
High risk	FIGO grade 3, Stage IB	Oncology referral for adjuvant treatment

All the patients should be assessed with endometrial biopsy at 3 monthly interval and repeat MRI scan at 6 months from initiation of treatment. If remission is achieved, these patients should be referred to reproductive medicine specialist for assisted reproduction.

Those patients who do not respond by 6 months should be offered with standard surgical management.

It should be well appreciated that fertility preservation is a non-standard management and inferior to surgical treatment. Therefore strict patient selection criteria is used. Central pathological review of the histology and MRI pelvis would aid in selecting low risk, early-stage patients, with minimal risk of disease progression. Early involvement of the fertility medicine specialist in the management would be helpful in initial decision making and follow up. Assisted reproduction is recommended as soon as remission is achieved and those patients who achieve remission but not planning to become pregnant at the end of 6 months, should continue progesterone treatment and have endometrial biopsy every 3 months. If fertility is not desired by 12 months or unable to conceive by 24 months after initiating hormone treatment, definitive surgical treatment is highly recommended.

4.6 HRT in treated endometrial cancer patients (After TAH BSO)

HRT can be considered in patients with grade 1/2 endometrioid, stage IA disease, without LVSI.

There is limited data on safety of HRT on patients surgically treated with endometrial cancer. Therefore, prescription should be directly supervised by a consultant experienced in managing such patients. It is an acceptable practice to prescribe HRT to surgically managed low risk, early-stage endometrial cancer patients⁶.

4.7 Endometrial cancer diagnosed in a post hysterectomy specimen

When endometrial cancer is diagnosed incidentally in a post hysterectomy specimen, they should be considered for repeat staging surgery (Eg: Salpingo oophorectomy, lymph node assessment, omentectomy).

It is not uncommon to diagnose endometrial cancer

following hysterectomy for benign indications. Proper staging in these patients would aid in avoiding unnecessary adjuvant treatment in low-risk patients. However, patient fitness as well as surgical morbidity should be considered when planning re staging surgery.

4.8 Advanced endometrial cancer (Stage IIIA, IIIB, IIIC and IV in the pre-operative assessment)

Clinical pelvic assessment to assess local invasion by an experienced clinician is required in all patients. CECT scan of chest, abdomen and pelvis should be performed to assess for distant disease.

Debulking surgery: Should be performed only when disease is completely resectable⁷. All the patients should be referred to the oncologist for adjuvant treatment.

Primary oncological management: Radiotherapy with or without chemotherapy is the preferred treatment for patients with inoperable disease confined to pelvis. Patients with stage IV disease are usually managed with chemotherapy.

Palliative surgery: Should be reserved for symptomatic control in situation such as severe genital tract bleeding not responding to radiotherapy/chemotherapy or intestinal obstruction.

Hormone therapy: Can be used in patients with advanced disease not fit enough for surgery, radiotherapy or chemotherapy. Medroxy progesterone acetate 200mg/d can be given for grade 1 and grade 2 endometrioid, endometrial cancer patients⁸.

Advanced endometrial cancer is not common. Inputs from clinical oncologist and radiologist are required before planning treatment in this patient group. Patients with enlarged pelvic lymph nodes only (IIIC) can be managed as mentioned in the above section.

If surgery to improve patient survival, complete macroscopic clearance should be achieved⁷. If this deems not possible on imaging or surgical survey, patient should receive primary oncological treatment rather than sub optimal debulking. Hormonal therapy can be used as 3rd line in well differentiated cancers. Response rate of Grade 3 endometrioid and other histological subtypes is less than 10%.

4.9 Recurrent endometrial cancer

All patients should receive clinical pelvic assessment by an experienced clinician (Senior Registrar or Consultant) and histological confirmation should be done when the lesion is accessible.

CECT scan of the chest, abdomen and pelvis should be performed in all patients before planning invasive treatment.

Recurrence within 1 year of primary treatment or multi focal disease are not suitable for radical surgery or radiotherapy. Surgery, radiotherapy or chemotherapy should be given only in palliative intent. Medroxy progesterone acetate 200mg/d can be considered for symptom control^{2,4}.

No previous radical radiotherapy

Single recurrent lesion in a medically fit patient with a disease-free interval of more than one year can be managed by radical radiotherapy. Need for surgical debulking should be individually assessed in case-based manner.

Previous radiotherapy

Central, isolated pelvic recurrence can be radically excised by pelvic exenteration as these patients are not suitable for further radio therapy. CECT scan or Positron Emission Tomography (PET) scan to exclude any distance metastasis should be done in all patients before selecting for exenterative procedure.

Behavior of endometrial cancer is more complex in

the recurrent disease compared to primary. Therefore inputs from the oncologist and radiologist are required before planning treatment in these patients. Remission period from the primary treatment, anatomical distribution of the disease, previous radio therapy as well as physical fitness/performance status are important variables to consider when managing these patients. Recurrence within 1 year of the primary treatment and multi-focal disease are considered as features of poor prognosis. Previous radical irradiation of the pelvis is associated with cellular changes that prevents the possibility of re-irradiation due to extremely high incidence of organ toxicity (urinary fistula, faecal fistula, skin ulceration, bowel stricture formation, ureteric stricture formation etc). Therefore, Pelvic exenteration is the only curative option for resectable recurrent disease in patients who had previous radical radio therapy.

4.10 Follow up

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

Follow up frequency should be dictated by risk of recurrence of the cancer.

History: Ask for vaginal bleeding or discharge, new onset persistent lower limb swelling, recent change of bladder/bowel habits.

Examination: All patients should have abdominal examination including inguinal area for lymphadenopathy with speculum and per vaginal examination.

Follow up interval – risk based follow up is recommended.

Table 4. Risk based follow up intervals in endometrial cancer

Low risk of recurrence	FIGO grade 1, Stage IA, IB, no LVSI or FIGO grade 2, Stage IA no LVSI And No adjuvant treatment	6 monthly clinical assessment for at least 2 years
Intermediate/high risk of recurrence	All other patients	3 to 4 monthly follow up for first 2 years. 6 monthly follow up for another 3 years. (total 5 years)

Follow up setting – follow up can be conducted in a gynaecological oncology centre or general gynaecology unit. Follow up should be done by a experienced clinician (Registrar or above level).

5. Clinical governance

Patients presenting with postmenopausal bleeding, postmenopausal discharge or any other symptom suggestive of endometrial cancer should have an urgent endometrial sampling with the aim of obtaining a histopathology report within 14 days of presenting to the specialist gynaecological service.

Where available a hysteroscopy and endometrial biopsy should be performed as the gold standard test.

The definitive treatment of a histologically confirmed case of endometrial cancer, should be aimed to occur within 6 weeks from the date of biopsy. 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. FIGO staging of endometrial cancer

I	Tumor confined to the corpus uteri
IA	No or less than half myometrial invasion
IB	Invasion equal to or more than half of the myometrium
II	Tumor invades cervical stroma, but does not extend beyond the uterus
III	Local and/or regional spread of the tumor
IIIA	Tumor invades the serosa of the corpus uteri and/or adnexae
IIIB	Vaginal involvement and/or parametrial involvement
IIIC	Metastases to pelvic and/or para aortic lymph nodes
IV	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA	Tumor invasion of bladder and/or bowel mucosa
IVB	Distant metastasis, including intra abdominal metastases
	Distant metastasis, including intra-abdominal metastases and/or inguinal nodes

2. Histopathology classifications of endometrial cancer

Type 1 endometrial cancer	Endometrioid carcinoma	Grade 1 – Well differentiated
		Grade 2 – Moderately differentiated.
		Grade 3 – Poorly or undifferentiated
Type 2 endometrial cancer	<ol style="list-style-type: none"> 1. Mucinous adenocarcinoma. 2. Serous adenocarcinoma. 3. Clear cell adenocarcinoma. 4. Neuroendocrine tumors. Mixed carcinoma	All are considered as poorly differentiated / Grade 3