PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

GYNECOLOGIC CANCER

ENDOMETRIAL

Site Group: Gynecologic – Endometrial

Original Author: Dr. Stephane Laframboise
Reviewer: Dr. Stephanie Lheureux

1. Introduction

Uterine cancer is the most common cancer in the female reproductive tract, and represents the 4th most common cancer overall in women. It is highly curable at early stage, with a survival rate of >80%. Most (95%) cancers of the uterus arise from the endometrium, referred to as *endometrial cancer,* while only 5% arise from the myometrium or the stroma of the endometrium, referred to as *uterine sarcoma.* Endometrial cancer is the most common gynaecological tumour in developed countries, and its incidence is increasing.

2. Prevention:

The most important risk factor associated with endometrial cancer is excess of estrogen, highly associated with obesity, diabetes, early age at menarche, nulliparity, late-onset menopause, older age (≥55 years), use of tamoxifen and can be associated with use of estrogen supplements/hormone replacement therapy, and occasionally from estrogen producing tumors.

3. Screening and Early Detection

No specific screening is recommended in the general population. Most women with endometrial cancer will present with abnormal bleeding, either with irregular cycles and/or excessive bleeding in the premenopausal woman, and any bleeding in the post menopausal woman. In other uterine cancers or with advanced disease at time of presentation, women may complain of pelvic and abdominal discomfort, pain, bloating, or presence of a mass, gastrointestinal or genitourinary symptoms, or constitutional symptoms.

4. Diagnosis

FIGO Staging - Carcinoma of the Endometrium 2009	
Stage 1*	Tumour confined to the corpus uteri
1A*	No or less than half myometrial invasion
1B*	Invasion equal to or more than half of the myometrium
Stage 2*	Tumour invades cervical stroma, but does not extend beyond the uterus**
Stage 3*	Local and/or regional spread of the tumour
3A*	Tumour invades the serosa of the corpus uteri and/or adnexae***
3B*	Vaginal and/or parametrial involvement***
3C*	Metastases to pelvic and/or para-aortic lymph nodes***
3C1*	Positive pelvic nodes
3C2*	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
Stage 4*	Tumour invades bladder and/or bowel mucosa, and/or distant metastases
4A*	Tumour invasion of bladder and/or bowel mucosa
4B*	Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes
*	Either Grade 1, Grade 2, or Grade 3
**	Endocervical glandular involvement only should be considered as Stage 1 and no longer as Stage 2
***	Positive Cytology has to be reported separately without changing the stage

Initial evaluation:
History and Physical examination: including bimanual and rectopelvic exam, Pap smear and biopsy (see below).
Laboratory testing: CBC and chemistry profile as indicated
Imaging: CT of abdomen, pelvic and thorax, MRI

Endometrial Biopsy:
Most patients with abnormal bleeding or any episodes of postmenopausal bleeding will require an evaluation (to r/o other causes of vaginal bleeding) and likely will require an endometrial biopsy for diagnosis. An endocervical biopsy and occasionally a vagina biopsy of any suspicious lesion may be required. This can be done in clinic, or less commonly with require a Dilation and Curettage (D&C) with or without hysteroscopy. Management will be determined based on histological type, grade and metastatic work up.

5. Pathology

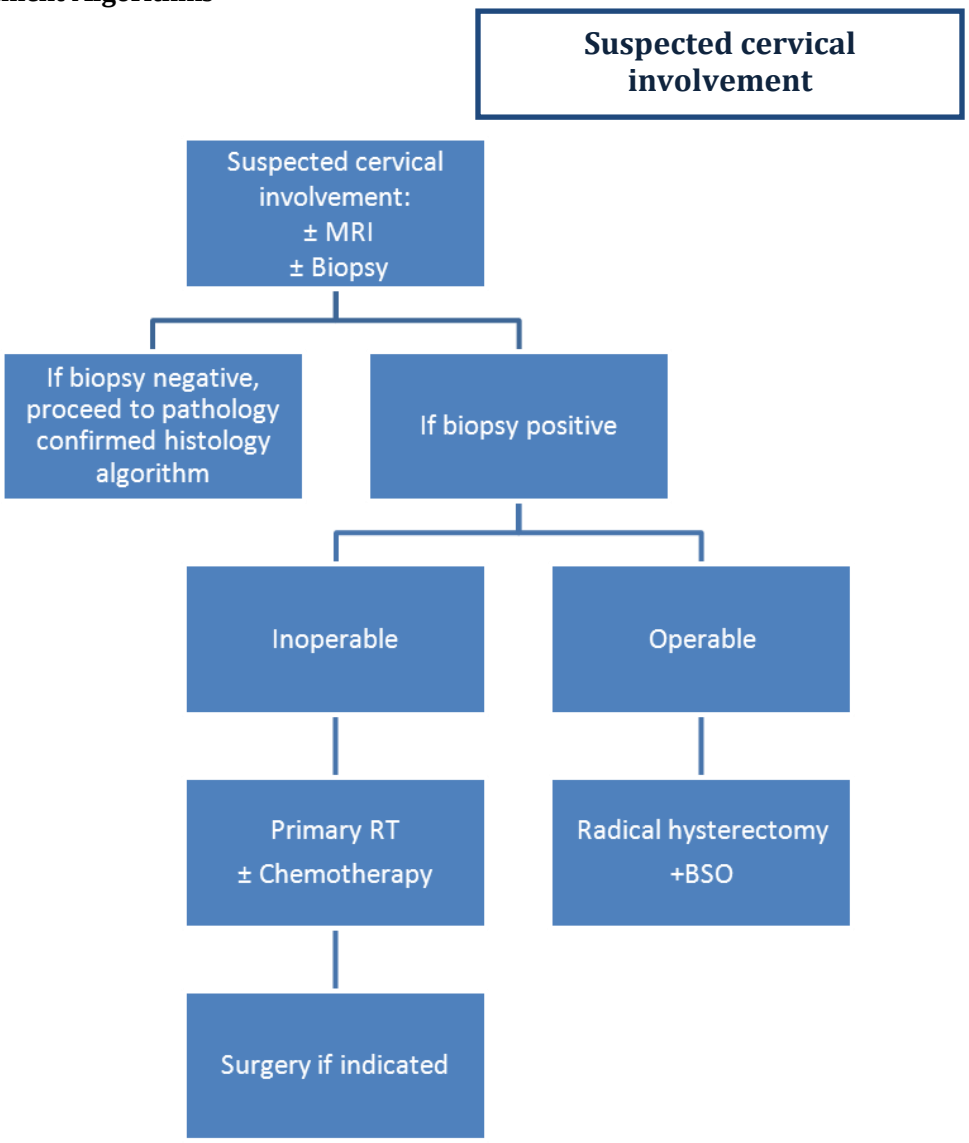
Endometrial cancer:
Endometrioid is the most common histological cell type , other subtypes are papillary serous ,clear cell and mixed tumors representing . Rare tumors are mucinous, squamous or undifferentiated types.
Immunohistochemistry including ER, PR, MMR and TP53 are recommended.

Carcinosarcomas (also known as Malignant mullerian mixed tumors) are composed of malignant epithelial and stromal tissues. These cancers are commonly seen in older women and have a poor prognosis.

Uterine Sarcoma:
Leiomyosarcomas (LMS) represent 30% of all sarcomas, often diagnosed in younger women and are highly aggressive tumor, often with metastases (lung) at time of presentation. Endometrial stromal sarcomas (ESS) represent 15% of all sarcomas and tend to present in younger women. Low grade ESS have an overall good prognosis. Patients diagnosed with sarcoma are followed by the sarcoma group.

6. Management

6.1 Management Algorithms



Pathology confirmed histology

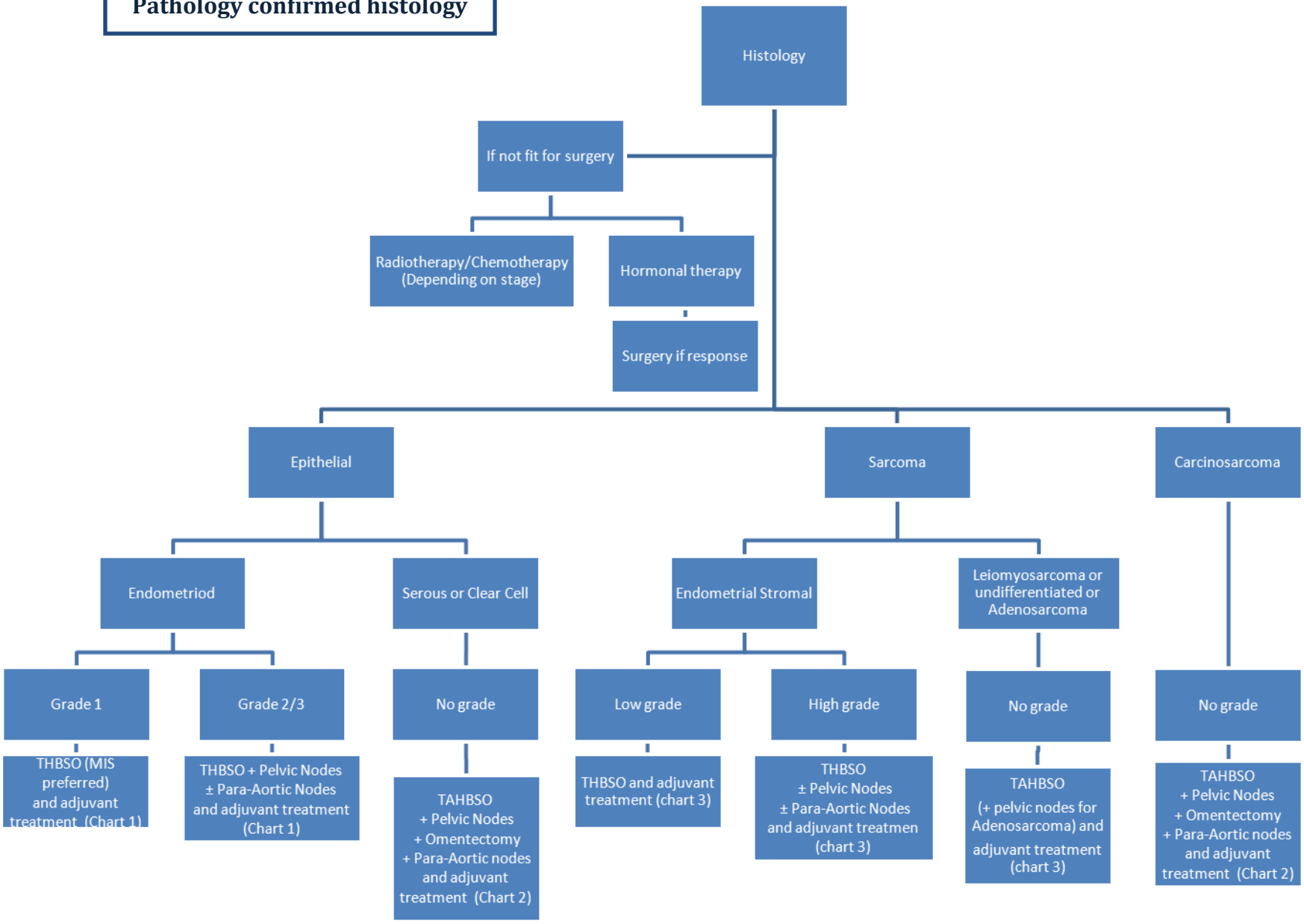
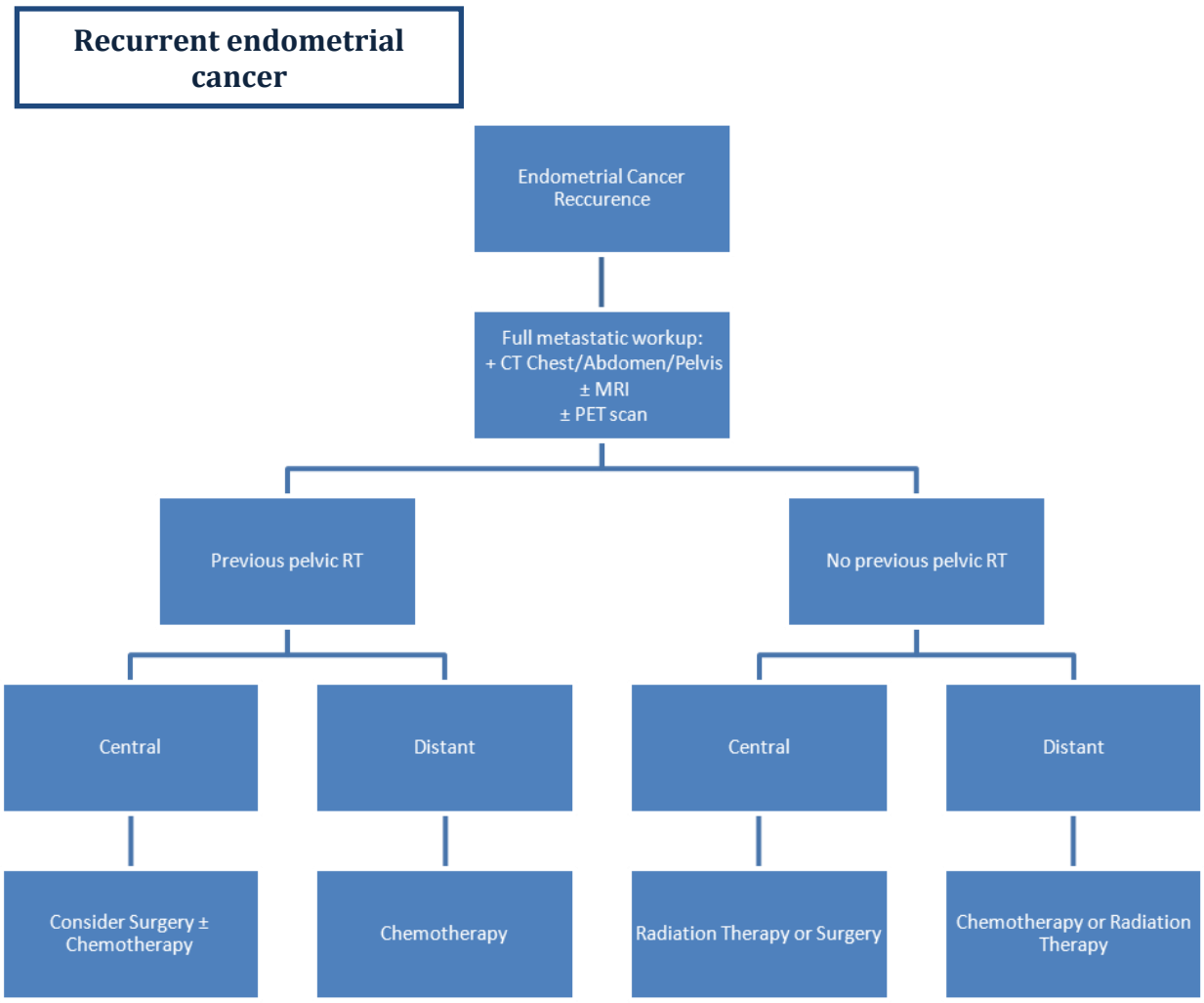


Chart 1: Adjuvant treatment for Endometrioid Histology

Stage	Nodal Status	LVI or Age > 60	Grade 1/2	Grade 3
1A	Unknown	No	Observe	VB or Pelvic RT. If 1A polyp only then observe.
		Yes	Observe or VB	Pelvic RT or VB
	Negative	No	Observe	VB. If 1A polyp only then observe.
		Yes	Observe or VB	Pelvic RT (or VB)
1B	Unknown	No	VB or observe	Pelvic RT
		Yes	VB or observe (if one risk factor only) or Pelvic RT (if 2 risk factors)	
	Negative	No	Observe or VB	
		Yes	VB or Observe (if one risk factor only) or Pelvic RT(small field) (if 2 risk factors)	Pelvic RT
2	Pelvic RT+VB			
3A	PORTEC 3 protocol or sequential Pelvic RT +/- chemo +/- VB			
3B	Pelvic RT + VB +/- chemo +/- surgery			
3C	PORTEC 3 protocol or sequential Chemo + Pelvic +/- PA RT +/- VB			
4	Chemo +/- RT +/- Hormones			

Chart 2: Adjuvant treatment for clear cell, serous and carcinosarcoma			
Stage	**Nodes**	**Clear Cell**	**Serous / Carcinosarcoma**
1A	Unknown	Chemo-Pelvic RT or Pelvic RT	Chemo- Pelvic RT
	Negative	Chemo-RT (Pelvic RT or VB) or Pelvic RT; if polyp only observe	Chemo-RT (Pelvic RT or VB); if polyp only observe
1B	Chemo-Pelvic RT		
2	Chemo / RT (Pelvic RT +VB)		
3A	PORTEC 3 protocol or sequential Chemo- Pelvic RT		
3B	Pelvic RT+ VB ± Chemo ± Surgery		
3C	PORTEC 3 protocol or sequential Chemo ± RT (pelvic+/- PA RT +/-VB)		
4	Chemotherapy +/ - palliative XRT		



6.2 Surgery

Grade 1: Endometrioid histology:
A minimally invasive (MIS) or laparotomy approach; MIS preferred if feasible.
Evaluation of the abdominal and pelvic carvity, peritoneal surfaces, and pelvic and para aortic nodal areas
Hysterectomy and bilateral salpingo-ophorectomy
If there is evidence of cervical involvement consider radical hysterectomy. If known deep myometrial invasion, proceed to pelvic and para aortic node dissection be completed

Grade 2 or Grade 3 endometrioid histology:
A minimally invasive (MIS) or laparotomy approach; MIS preferred if feasible.
Evaluation of the abdominal and pelvic cavity, peritoneal surfaces, and pelvic and para aortic nodal areas
Hysterectomy and bilateral salpingo-ophorectomy plus pelvic and para aortic node dissection

High grade histologies:
A minimally invasive (MIS) or laparotomy approach; MIS preferred if feasible.
Evaluation of the abdominal and pelvic cavity, peritoneal surfaces, and pelvic and para aortic nodal areas
Hysterectomy and bilateral salpingo-ophorectomy plus pelvic and para aortic node dissection +/- omentectomy.

6.3 Chemotherapy:

First line treatment for endometrial cancers: Taxol and Carboplatin. Clinical trials are also an option.

For sarcomas, Patients are followed by the sarcoma group.

6.4 Radiation Therapy

- External Beam Radiotherapy
    - Clinical target volume (CTV)p: vagina and parametria
    - CTVn: pelvic lymph nodes including the pre-sacral lymph nodes anterior to S1-S3, + the para-aortic lymph nodes.
    - Dose: 45 Gy in 1.8 Gy daily fractions
- Adjuvant Intravaginal Brachytherapy alone
    - Cylindrical vaginal applicator
    - Upper 1/2 of the vagina (maximum of 4 cm)
    - 21 Gy in three 7 Gy HDR fractions prescribed at a depth of 0.5 cm
- Adjuvant Intravaginal Brachytherapy after EBRT
    - Cylindrical vaginal applicator
    - Upper 1/3 of the vagina
    - 11 Gy in two 5.5 Gy HDR fractions prescribed at a depth of 0.5 cm

6.5 Other Therapy

- Hormone therapy particularly in recurrent grade 1 endometrioid cancer – hormone receptors positive
- Clinical trial
- Consider access to Pembrolizumab for patients with recurrent endometrial cancer – MSI positive
- interventional radiology

6.6 Oncology Nursing

Refer to general oncology nursing practices

7. Supportive Care

7.1 Patient Education

Refer to general patient education practices

7.2 Psychosocial Care

Refer to general psychosocial oncology care guidelines

7.3 Symptom Management

Refer to general symptom management care guidelines

7.4 Clinical Nutrition

Refer to general clinical nutrition care guidelines

7.5 Palliative Care

Refer to general oncology palliative care guidelines

8. Follow-up Care

Aim of follow up is to identify side effects of the treatment, to help women recover from their cancer diagnosis and to identify recurrence.

For serous, clear cell, carcinosarcoma:
Every 3 months for 2 years after completion of treatment, then every 6 months to 5 years.
± Vaginal dilators for 6 months after completion of brachytherapy to prevent vaginal stenosis
± CA-125
± CT/MRI
+ genetic counselling for patients with family history or endometrial, colon or ovarian cancer. Patients with high grade serous endometrial cancer can be offered genetic counselling at our centre regardless of age or family history.

For endometrioid histology:
Every 3-6 months for 2 years after completion of treatment, then every 6 months to 5 years.

± CT/MRI
+ genetic counselling for patients with family history or endometrial, colon or ovarian cancer.

For sarcomas:
Every 3 months for 2 years after completion of treatment, then every 6 months
± CT/MRI

Recurrence:
Recurrence in endometrial cancer can be central/ pelvic, side wall pelvic or distant. When a recurrence is detected a full metastatic workup should be completed including a CT scan of thorax/abdomen and pelvis.

1. Central pelvic. Recurrence at the vaginal vault in non-radiated patients can be successfully treated with EBRT /brachytherapy and in some selected patients with surgery.
2. Sidewall pelvic: In non-radiated patients, radiation can be considered as well as chemotherapy (Carbo/paclitaxel)
3. Distant: Consideration for chemotherapy or progestational agents.
4. Clinical Trials

References

https://www.cancercareontario.ca/en/pathway-maps/endometrial-cancer

Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet. 2016 Mar 12;387(10023):1094-1108.