Uterine Cancer Review for Health Care Professionals

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Medical Advisor: Dr. X. Zeng
The slides presented are meant to be used as an orientation package for health care providers new to gynecologic oncology; to review the management and treatment of uterine cancers.

Variation across the country can occur in accordance within provincial guidelines.

Remember that not all patients are the same and that some deviation **CAN** and often **does** occur.
Uterus Review

- Pear-shaped, hollow, and fibro muscular organ located in a woman’s pelvis between the bladder and rectum
- Varies greatly in size
- Made up of 3 sections
  - Cervix (lower)
  - Corpus (middle)
  - Fundus (top)
- The inside of the uterus has two tissue layers
  - Endometrium (inner)
  - Myometrium (outer)

Cartwright-Alcarese & O'Sullivan, 2010
The walls of the uterus are composed of muscular tissue called *myometrium* (middle layer).
The superficial (outside layer) of the uterus is called the *serosa* and is continuous with the pelvic peritoneum.
The epithelial membrane (lining of uterus) is called the *endometrium*.
The Role of Estrogen and Progesterone

• *Estrogen* stimulates the uterine lining to proliferate and grow

• *Progesterone* inhibits the proliferative growth effects of estrogen, and provides structural support to the endometrium

• With the withdrawal of progesterone at the end of the menstrual cycle, the structural support to this thickened endometrium is weakened, and shedding of the uterine lining occurs (menses)

Landrum, Zuna & Walker, 2012; Redlin Frazier, 2010
Incidence of Endometrial Cancer

• Most common gynecologic cancer
• Estimated that 6000 Canadian women will be diagnosed in 2014, 920 will die from it
• 4th most common cancer in Canadian women, 8th most common cause of cancer death
• Lifetime risk in Canada is 1 in 38 women
## Endometrial Cancer Risk Factors

<table>
<thead>
<tr>
<th>Lifestyle Factors</th>
<th>Hormonal and Reproductive Factors</th>
</tr>
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<tbody>
<tr>
<td>Age &gt; 50</td>
<td>Early menarche</td>
</tr>
<tr>
<td>Obesity (more than 50 pounds over normal BMI)</td>
<td>Postmenopausal</td>
</tr>
<tr>
<td>Diet/lack of exercise</td>
<td>Late menopause (&gt;55)</td>
</tr>
<tr>
<td>Personal Breast/Colon Cancer History</td>
<td>Endometrial Hyperplasia</td>
</tr>
<tr>
<td>Genetic Factors</td>
<td>Prolonged use of estrogen without opposing progesterone</td>
</tr>
<tr>
<td></td>
<td>Tamoxifen use</td>
</tr>
<tr>
<td></td>
<td>Polycystic Ovarian syndrome</td>
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</tbody>
</table>

Amant Moerman, Neven, Timmerman, Van Limbergen & Vergote, 2005; Burke, 2005; Creasman & Scott Miller, 2012; Farley-Omerod & Fusco, 2010; Lockwood, 2008; Redlin Frazier, 2010; Tiffen & Mahon, 2006
Lynch II Syndrome (HNPCC)

• An inherited disorder that increases the risk of many types of cancer, particularly cancers of the colon (large intestine) and rectum, which are collectively referred to as colorectal cancer.

• People with Lynch syndrome also have an increased risk of cancers of the stomach, small intestine, liver, gallbladder ducts, upper urinary tract, brain, and skin. Additionally, women with this disorder have a high risk of cancer of the ovaries and lining of the uterus (the endometrium).

Ahnen & Axell, 2015
Lynch II Syndrome (HNPCC) “Red Flags”

- Onset of colorectal cancer before age 50
- Onset of endometrial cancer before age 50
- Two or more HNPCC cancers in an individual or family
Endometrial Cancer Risk Factor: Obesity

• Widely recognized risk factor for endometrial cancer
• Strong association between a 5 kg/m2 increase in BMI and endometrial cancer
• Affects both premenopausal and postmenopausal risk for endometrial cancer

Farley-Omerod & Fusco, 2010; Redlin Frazier, 2010; Renehen et al., 2008; Tiffen & Mahon, 2006
Bariatric surgery, which results in dramatic weight loss in formerly severely obese women, reduces the risk of endometrial (uterine) cancer by 71% immediately after weight loss and 81% if healthy weight is maintained after surgery.

Ward et al., 2014
Unopposed Estrogen Exposure

• In an environment of chronically unopposed estrogen exposure (such as seen in obesity), the endometrial layer undergoes a progression of abnormal cellular changes from benign endometrial hyperplasia to endometrial intraepithelial neoplasia (EIN) and endometrial adenocarcinoma
Endometrial Cancer Risk Factor
Selective Estrogen Receptor Modulators

- Used as both treatment and chemoprevention of breast cancer
- SERMS: Tamoxifen, Raloxifene
  - Although Tamoxifen is an anti-estrogen in breast tissue, it paradoxically has estrogen-like properties in the endometrium and ↑ the risk of endometrial cancer
  - It is also associated with thromboembolism and stroke
  - It provides protection against bone loss, osteoporosis and fractures, but does not appear to carry an ↑ of myocardial infarction

Landrum, Zuna & Walker, 2012
# Endometrial Cancer: Risk Reducing Factors

<table>
<thead>
<tr>
<th>Factors</th>
<th>Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of combination oral contraceptives</td>
<td>Diet modifications (low fat, increase fruit and vegetable intake)</td>
</tr>
<tr>
<td>Multiparity</td>
<td>Decrease phyto-estrogen (soy) intake</td>
</tr>
<tr>
<td>Exercise and physical activity</td>
<td>Weight control/loss to reflect ideal BMI of ≤25</td>
</tr>
<tr>
<td>Smoking * (NOT recommended)</td>
<td>Genetic counselling and risk assessment of women at risk</td>
</tr>
<tr>
<td>Mirena IUD</td>
<td></td>
</tr>
<tr>
<td>Tubal Ligation</td>
<td></td>
</tr>
</tbody>
</table>

*Amant et al., 2005; Farley-Omerod & Fusco, 2010; Redlin Frazier, 2010*
Endometrial Cancer: Screening

• No good screening test for endometrial cancer
• The pelvic exam enables the clinician to detect only an abnormally sized uterus
• Sampling of the endometrium is neither cost-effective nor indicated in the general population and is not required before or during HRT (hormone replacement therapy) in asymptomatic women

Amant et.al, 2005; Burke, 2005; Farley-Omerod & Fusco, 2010; Redlin Frazier, 2010; Tiffen & Mahon, 2006;
Endometrial Cancer: Signs & Symptoms

Post menopausal women

- Post menopausal bleeding (PMB) after menopause is the most common symptom
  - About 90% of women diagnosed with endometrial cancer have abnormal uterine bleeding as presenting symptom

Premenopausal women

- Increased menstrual flow and bleeding between periods may be the only symptoms
- Other signs may include:
  - A yellow, watery vaginal discharge
  - Pyometria (accumulation of pus in the uterus)
  - Pain in the hypogastric or lumbosacral areas or the pelvis

Amant et al., 2005; Burke, 2005; Farley-Omerod & Fusco, 2010; Lockwood, 2008; Otto, 2001; Tiffen & Mahon, 2006;
Postmenopausal Bleeding

• Most PMB is caused by benign conditions
  – Most common benign causes are endometrial polyps, sub-mucosal fibroids and atrophy of the endometrium, HRT and Tamoxifen use

• Cancer and hyperplasia are present in 20% of women with PMB

• A biopsy should be performed to evaluate endometrium in women with abnormal uterine bleeding after age 40

Amant et.al, 2005; Farley-Omerod & Fusco, 2010; Lockwood, 2008; Singh et al., 2013
Endometrial Cancer Diagnosis

- Ultrasound (TransVaginal-TVUS) to look at thickness of endometrial lining and localize lesions
  - An endometrium thicker than 16 mm in premenopausal women and in postmenopausal women thicker than 5 mm is a predictor of abnormal endometrial pathology

- Endometrial biopsy to sample lining of the uterus
  - Most cost effective when the prevalence of endometrial cancer is over 15%
  - +/- Hysteroscopy/D&C (Dilatation & Curettage)

- Pathology

- Other Imaging Studies
  - MRI, CT scan, Chest x-ray

Amant et.al, 2005; Farley-Omerod & Fusco, 2010; Lockwood, 2008; Redlin Frazier, 2010;; Tiffen & Mahon, 2006
Endometrial Biopsy/Pipelle

Endometrial biopsy: A catheter is inserted into the uterus through the vagina to remove cells from the uterine lining for examination.

Diagnostic Tests for Uterine Abnormalities
Endometrial Hyperplasia

• An overgrowth of the endometrial lining of the uterus as a result of stimulation of the endometrium
• Typically presents clinically as abnormal bleeding
• Hyperplasia with atypia is a complex pattern with overcrowding of the glands; the presence of atypical cells indicates high risk for the progression to endometrial cancer
  – Endometrial hyperplasia with atypia is considered a precursor state to endometrial cancer

Farley-Omerod & Fusco, 2010; Lockwood, 2008
Endometrial Hyperplasia

- The scientific explanation for the low incidence rates for endometrial hyperplasia is that it is a lesion that is usually unrecognized and asymptomatic until cancer develops.
- Women with cellular atypia is considered to be premalignant; whereas those without atypia are benign. Hysterectomy is the standard of treatment when atypia is present.
- Patients with hyperplasia should be treated with progestins or hysterectomy if atypical cells are associated with the hyperplastic cells.
  - Patient’s age, fertility plans & need for contraception, comorbidities and personal preferences play an important role in the management of these lesions.

Farley-Omerod & Fusco, 2010; Landrum, Zuna & Walker, 2012; Lockwood, 2008
Uterine Cancers: Classification

- The primary types of uterine cancers are adenocarcinoma, sarcomas, mucinous carcinoma, serous carcinoma, clear cell carcinoma and endometrioid carcinoma.

- More than 95% are endometrial adenocarcinomas and less than 5% are sarcomas.

Otto, 2001
Endometrial Cancer

- Neoplasm that occurs within the lining of the uterus
- Arises from the glandular component of the endometrial mucosa
- Divided into 2 subtypes (Type I and Type II)

Amant et al., 2005; Brown, 2008; Farley-Omerod & Fusco, 2010; Lockwood, 2008; Redlin Frazier, 2010; Tiffen & Mahon, 2006;
Endometrial Cancer Subtypes

Type I

- Well or moderately differentiated estrogen dependent subtypes that tend to have a better prognosis (tends to be diagnosed early stage and has a better prognosis). Prolonged exposure to estrogen

Type II

- Aggressive, non-estrogen dependent subtypes such as clear cell and serous which has a poorer prognosis related histologically to a higher grade or poorer differentiation and is more often diagnosed at a late stage, it has a propensity for metastases or because it is a nonendometrioid subtype

Amant et.al, 2005 ; Brown, 2008 ; Farley-Omerod & Fusco, 2010; Lockwood, 2008; Redlin Frazier, 2010; Tiffen & Mahon, 2006;
Endometrial Cancer: Grading

- The grade of the tumour signifies how closely the tumour resembles the tissue of origin.
- In endometrial cancer, the tumor grows in a solid fashion, whereas the normal tissue grows in a glandular fashion.

Lockwood, 2008
# Endometrial Cancer Grading

<table>
<thead>
<tr>
<th>Grade</th>
<th>Differentiation</th>
<th>% of Tumour Showing a Solid Growth Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Well differentiated</td>
<td>5% or less</td>
</tr>
<tr>
<td>II</td>
<td>Moderately differentiated</td>
<td>6% - 50%</td>
</tr>
<tr>
<td>III</td>
<td>Poorly differentiated</td>
<td>&gt; 50%</td>
</tr>
</tbody>
</table>

Lockwood, 2008
Endometrial Cancer

- Morbidity and mortality increases with age and stage, making early diagnosis a priority in order to achieve better outcomes

Redlin Frazier, 2010
## Endometrial Cancer Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Extent of Uterine Involvement</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>Cancer limited to the uterine body (corpus)</td>
</tr>
<tr>
<td>II</td>
<td>Cancer extends into the cervix, but not beyond the uterus</td>
</tr>
<tr>
<td>III</td>
<td>Cancer extends beyond the uterus, but only so far as the peritoneum, adnexa or vagina</td>
</tr>
<tr>
<td>IV</td>
<td>Cancer extends into the bladder, bowel or, to lymph nodes in groin, or to distant sites</td>
</tr>
</tbody>
</table>

![Diagram showing the extent of uterine involvement](image)
Endometrial Cancer

- Endometrial cancer is surgically staged
  - Histological assessment of the hysterectomy specimen remains the gold standard

- Workup for biopsy proven Endometrial Cancer includes a clinical examination. Other diagnostic tests may include Transvaginal Ultrasound, Chest X-ray, CT, MRI.

- CA-125 is a potential tumour marker

Amant et.al, 2005; Brown, 2008; Farley-Omerod & Fusco, 2010; Lockwood, 2008;
Treatment for Endometrial Cancer

- Surgery
  - Hysterectomy
  - Lymphadenectomy
- Radiation Therapy
- Chemotherapy

Redlin Frazier, 2010
Hormone Therapy

• Hormone therapy with Progestin may be considered in certain cases of grade 1 when there is no invasive disease and patient wants fertility preservation

• The use of progestin-secreting IUD has been utilized in cases where surgical morbidity prevents traditional treatment

Montz, Bristow, Bovicelli, Tomacruz & Kurman, 2002; Redlin Frazier, 2010
Endometrial Cancer
Surgical Management

- Depends on the stage and grade of the cancer; considers the usual spread pattern of endometrial cancer to the lymph nodes nearest to the uterus
- Surgery includes Total Hysterectomy and Bilateral Salpingo-Oophorectomy (TH BSO) +/- surgical staging
  - Approach may be abdominal or minimally invasive
  - Removal of the adnexa at time of surgery is thought to be important given that approximately 5% of endometrial cancers have metastatic disease to the ovaries and/or fallopian tubes
  - Removal of the upper vagina does not appear to decrease vault recurrences
- Pelvic +/- para aortic lymph node dissection may be done depending on grade and/or histology of endometrial biopsy

Creasman & Scott Miller, 2012; Redlin Frazier, 2010
Role of Lymphadenectomy

- Pelvic lymphadenectomy, with or without paraortic lymphadenectomy, plays an important role in the surgical staging of endometrial cancer, and thus provides more accurate prognostic information.

- The therapeutic role of lymphadenectomy and its ability to modify adjuvant therapy continues to evolve.
  - Impacts the addition or deletion of radiation/chemotherapy postoperatively.
  - Need to discuss the pros/cons of lymph node dissection and potential for complications in the future.

- Sentinel lymph node mapping may be considered in selected patients.

Creasman & Scott Miller, 2012; Hacker, 2000
Pathologist Review

• Measures the depth of myometrial invasion in relationship to myometrial thickness and the size and location of the tumour and then makes a determination as to the extent of disease

• Examines the specimen(s) microscopically and the histologic subtype, grade and presence of lymphovascular space invasion
Poor Prognostic Features

- Papillary Serous, Clear Cell Histology
- Grade 3 (poorly differentiated)
- More advanced stage
- Myometrial invasion > 50%
- Positive pelvic lymph node(s)
- Positive para-aortic lymph node(s) (highest risk feature)
Carcinosarcoma

- Uterine carcinosarcomas, or formerly referred to as Malignant Mixed Mülllerian tumours (MMMTs), are highly aggressive cancers with a 5-yr survival rate reported as 18-39%
- Usually arise in women older than 65 and commonly present at an advanced stage
- Considered a high-risk variant of endometrial adenocarcinoma because carcinosarcomas share similarities in epidemiology, risk factors, and clinical behavior more closely with endometrial carcinoma as opposed to uterine sarcomas.

Dulko, 2010; Lockwood, 2008; McMeekin, 2012; Penson & Powell, 2014
Carcinosarcoma

• Uterine carcinosarcoma displays both epithelial and stromal differentiation and is further subdivided into homologous and heterologous subtypes based on the sarcomatous component

• Recently, carcinosarcomas have been treated more as a carcinoma rather than sarcoma

• Uterine carcinosarcoma tends to spread by local extension to pelvic structures, but may metastasize with the manner of spread being mainly through the lymphatic system rather than through the blood

Dulko, 2010; Lockwood, 2008; McMeekin, 2012
Adjuvant Treatment

• The need for adjuvant treatment is determined by the final pathology report
• Adjuvant treatment may include:
  – External beam radiotherapy
  – Brachytherapy
  – Chemotherapy
  – Hormonal therapy
GOG Criteria for Determining Adjuvant Radiotherapy Treatment in Stage I or II

1. Patients who are age 70 or older and any 1 of the following risk factors:
   – Tumour grade 2 or 3
   – Outer third myometrial invasion
   – Presence of lymphovascular space involvement.

2. Patients 50 years of age or older and any 2 of the risk factors described above.

3. Patients of any age and all 3 factors described above.

Keys et al., 2004; Kupets & Le, 2013
Radiation Therapy

• Radiation therapy has been the mainstay of adjuvant therapy for endometrial cancer
  – Adjuvant radiotherapy following primary surgery significantly improves pelvic tumour control, but has no measurable impact on overall survival

Creasman & Scott Miller, 2012; Lockwood, 2008
Radiation Therapy

• Treatment may include external beam radiation therapy and/or brachytherapy (intravaginal)

• For patients who are at high risk for recurrence, radiation therapy is used to improve loco regional control

• Radiation therapy utilization has been widely variable

Lockwood, 2008; Redlin Frazier, 2010
Radiation Side Effects

• Depending on area that is irradiated, may include:
  – Skin Changes
  – Bowel Changes
  – Urinary Changes
  – Vaginal Changes
  – Fatigue
  – Psychological

Lockwood, 2008; Smith & McLaughlin, 2012; Redlin Frazier, 2010
Brachytherapy

• Health Care professionals should not underestimate the physiologic and psychological effects of intravaginal radiation therapy

• Women who receive this treatment should be counselled carefully prior to treatment with a mindfulness that it may be humiliating, disturbing and in some cases of previous sexual abuse, an exceptionally difficult treatment to undergo

• Any woman receiving pelvic radiation (external or internal) needs to be advised/taught to use vaginal dilators to maintain vaginal patency and to prevent agglutination

Miles et al., 2012; Redlin Frazier, 2010
Chemotherapy

• The role of chemotherapy in the treatment of endometrial cancer is complex and evolving
  – Was traditionally reserved for patients with recurrent or disseminated cancer

• Systemic therapy may be used
  – In cases of initial advanced disease
    • Advanced and high-risk early-stage
  – At the time of relapse

Amant, et.al, 2005; Creasman & Scott Miller, 2012; Lockwood, 2008; Redlin Frazier, 2010
Chemotherapy

- These therapies are often provided in the outpatient setting
- See next slides for common agents and side effects
- Incidence and severity of any of these side effects is largely dependent of the patient’s characteristics such as diagnosis, stage, performance status, comorbidities and individual treatment regimen
  - agent, dosage and schedule
- Nurses have an essential role in teaching, monitoring and managing side effects related to gynecologic cancer treatments

Hydzik & O’Connor, 2010
Combination of Chemotherapy Agents

• Studies have found the combination of *Cisplatin* or *Carboplatin* with other agents (Doxorubicin, Taxanes—Paclitaxel) to have significant activity in endometrial cancer treatments

• Combining two or more active agents has been an important strategy (Phase III studies)
  – Better response rates when agents are combined compared to used alone

Creasman & Scott Miller, 2012
Paclitaxel

- Often given in combination with Carboplatin
- Has potential for hypersensitivity reactions, patients need to be premedicated with steroids
- Indicated for patients with ovarian cancers, cervical cancers and endometrial cancers.
- Potential side effects:
  - Alopecia
  - Mucositis
  - Myelosuppresion
  - Myalgia, arthralgia
  - Peripheral neuropathy
  - Visual disturbances
  - Ototoxicity
  - Diarrhea
  - Nausea, vomiting
  - Neutrophil nadir—Day 10-12
  - Platelet nadir—Day 8-9
  - Cardiovascular—hypotension, bradycardia, hypertension
  - Injection site reactions—erythema, tenderness, skin discoloration, swelling—extravasation
  - Elderly patients have more myelosuppression, neuropathy and cardiovascular toxicities
Carboplatin

- Usually infused over 60 minutes.
- Often given in combination with Taxol.
  - Taxol should be given before Carboplatin to increase efficiency and limit myelosuppression.
- Indicated for patients with ovarian cancers, cervical cancers and endometrial cancers.

*Side effects:* - ↓Na, ↓Mg, ↓Ca, ↓K
  - Vomiting
  - ↑Creatinine
  - ↑liver function
  - Myleosupression (Neutropenia/thrombocytopenia)
  - Neuropathies
  - Ototoxicity
  - Potential allergic reaction (typically in 2nd line)
Cisplatin

• Pre-treatment hydration VERY important before Cisplatin.
• Compatible with NS (normal saline)

Side effects:

- Significant nausea and vomiting
  – Myelosuppression
  – Nephrotoxicity
  – ↓Mg
  – Neurotoxicity and autotoxicity
Hypersensitivity Reactions

- An exaggerated or inappropriate immune response that may be localized or systemic, occurring during or within hours of a drug administration
  - Medical emergency as can result in respiratory failure, cardiovascular collapse and possibly death
  - Certain classes of chemotherapy agents are more commonly associated with hypersensitivity reactions including the taxanes and platinum compounds

- Can be prevented with (prophylaxis of anaphylaxis)
  - Corticosteroids (Dexamethasone)
  - H₁ Blockers (antihistamines such as Diphenhydramine [Benadryl])
  - H₂ Blockers (Ranitidine)
  - Longer infusion time

Holmes Gobel, 2005; Hydzik & O’Connor, 2010; Myers, 2001; Polovich, White & Kelleher, 2005; Winkeljohn, 2006
Hypersensitivity Reaction

Clinical Manifestations of HSR & Anaphylaxis
- Uneasiness or agitation
- Tightness in chest
- Shortness of breath (dyspnea), with or without wheezing (stridor/bronchospasms), ↓ O₂ sat
- Hypotension
- Tachycardia
- Urticaria (hives) or rash and/or itching
- Flushing
- Periorbital or facial edema (angioedema)
- Lightheadedness or dizziness
- Abdominal cramping, diarrhea, nausea, vomiting
- *Back pain—Paclitaxel HSR is believed to be d/t cremophor vehicle

Hydzik & O’Connor, 2010; Otto, 2001; Polovich, Whitford & Olsen, 2009; Young & Markman, 2000

Image retrieved on April 13, 2015 from:
http://synergyhw.blogspot.ca/2013/01/magnesium-part-3-wrath-of-histamine.html
Doxorubicin

- Anthracycline and Anti-tumour Antibiotic
  - Myelosuppression
  - ↑ Liver Function Tests
  - Nausea & Vomiting
  - Skin Changes/Radiation Recall
  - Skin Hyperpigmentation
  - Mucositis or Esophagitis
  - Diarrhea
  - Alopecia
  - Vein Discolouration
  - Red urine
  - Cardiac Toxicity
    - Maximum lifetime dose 550 mg/m²
  - Potent vesicant
    - Extravasation may lead to tissue necrosis

Hydzik & O’Connor, 2010; Smith & McLaughlin, 2012;
Gemcitabine

- Antimetabolite
  - Myelosuppression
  - Increase Liver Function Tests
  - Diarrhea
  - Flu-like Symptoms
    - Muscle pain, fever, headache, chills, fatigue, nausea and poor appetite
  - Rash
  - May experience alopecia
  - Mucositis
  - Edema

Hydzik & O’Connor, 2010; Smith & McLaughlin, 2012
Hormonal Therapy

• Progestins have been the cornerstone of hormonal treatment of metastatic endometrial cancer, and response is related to the presence of steroid-hormone receptors
• Used with the aim of prolonging progression-free interval
• Used in patients with hormone-dependent Type I tumours
• Types of hormone therapy include progestins and aromatase inhibitors
  – i.e. Provera and Megestrol Acetate (Megace)

Amant, et.al, 2005; Creasman & Scott Miller, 2012; Lockwood, 2008; Tsoref & Oza, 2011
Oral Hormonal Therapies

- Progestin
  - Medroxyprogesterone acetate (Provera®)
  - Megestrol Acetate (Megace®)

- The precise mechanism by which Megace® produces its antineoplastic effects against endometrial carcinoma is unknown at the present time

- Generally, these drugs work by slowing the growth of endometrial cancer cells

- Side effects can include
  - Hot flashes
  - Night sweats
  - Weight gain (from fluid retention and ↑appetite)
  - Worsening of depression
  - For women with diabetes, progestins can cause increased blood sugar levels
  - Rarely, serious blood clots can happen

Creasman & Scott Miller, 2012; Polovich, Whitford & Olsen, 2009; Redlin Frazier, 2010
Follow-up

• Weight loss, pain and vaginal bleeding can suggest recurrent disease, which mostly occurs during the first 2-3 years after primary treatment
• Retrospective data suggest that there is no difference in survival between symptomatic and asymptomatic recurrences or between women with recurrences detected during routine follow-up visits
  – Psychological benefit for most patients (reassured)

Amant, et.al, 2005; Creasman & Scott Miller, 2012; Redlin Frazier, 2010
Follow-Up

- Follow up includes a speculum exam with a bimanual pelvic-rectal exam
- Women need to be counselled to contact their healthcare team in case of vaginal bleeding
  - Surveillance assessments and questions includes: pelvic, leg or back pain, vaginal bleeding, urinary changes, changes in bowel habits
- Surveillance should focus on detection of potentially curable vaginal recurrences

Creasman & Scott Miller, 2012
UTERINE SARCOMAS
Uterine Sarcoma

• Rare type of uterine cancer that forms in the connective or stromal tissues of the uterus
  – Group of aggressive and rare cancers that originate from mesenchymal tissue
    • Embryonic mesoderm from which blood vessels, lymphatic vessels and connective tissue arise

• Two main types of sarcoma
  – Leiomyosarcoma
  – Endometrial stromal sarcoma (low or high grade)

Dulko, 2010; Lockwood, 2008; McMeekin, 2012; Smith & McLaughlin, 2012
Diagnosis of Sarcomas and Clinical Presentation

- Diagnosis is made following histologic evaluation of the tumour.
- Often found incidentally at the time of a hysterectomy or myomectomy.
- Symptoms include postmenopausal or abnormal vaginal bleeding, uterine cramping, uterine enlargement and possible malodorous vaginal discharge.
  - An enlarged uterus is palpated in about 50% of patients with uterine sarcomas, and tumour may be seen protruding from the cervix particularly in women with carcinosarcoma.

Amant et al., 2009; Dulko, 2010; Lockwood, 2008; McMeekin, 2012; Tropé et al, 2012
Uterine Leiomyosarcoma (LMS)

- Most common uterine sarcoma
- Uterine LMS arises within the uterine smooth muscle; therefore, biopsy of the malignant tissue is difficult and many lesions are found only at final pathology
- Rapidly enlarging mass (sometimes thought to be fibroids) should be a red flag
- Median age at diagnosis is in the early 50s, with most cases occurring in women aged 30-50 years
- Risk factors for the development of uterine LMS are not well known

Dulko, 2010; Lockwood, 2008; McMeekin, 2012; Smith & McLaughlin, 2012;
Uterine Leiomyosarcoma (LMS)

- LMS is usually described as a large, inhomogeneous, oval-shaped mass with an area of central necrosis.

- Symptoms
  - Pain
  - Heavy Vaginal Bleeding
  - Presence of a Pelvic Mass

- 50% of women present with Stage 1 disease, which means that the tumour is confined to the uterus.

- No adjuvant therapy has been shown to be effective in prolonging survival.
  - As with other high-risk uterine cancers, it has been managed postoperatively by radiation therapy or chemotherapy.

McMeekin, 2012; Smith & McLaughlin, 2012
Endometrial Stromal Sarcoma (ESS)

- Endometrial stromal sarcoma is a heterogeneous histopathologic entity that is considered less aggressive and has a better outcome than other uterine sarcomas
- ESS account for 7-15% of all uterine sarcomas
- ESS is malignant with as many as 30% of women with low-grade ESS having extra uterine disease at presentation
- Most common symptom is irregular vaginal bleeding
- Standard management is surgery

Dulko, 2010; Lockwood, 2008; McMeekin, 2012
Endometrial Stromal Sarcoma (ESS)

- Begins in connective tissue cells
- ESS is divided into 2 subtypes:
  - Low-grade
  - High-grade
- ESS tumours have usually an slow growing clinical course with an 80-100% 5-yr survival, but approximately 37-60% of patients eventually recur and 15-25% of women die of the disease
- The most powerful predictor of clinical outcome whether measured in terms of survival, number of relapses, or time to first relapse is surgical stage

Dulko, 2010; Lockwood, 2008; McMeekin, 2012
### Staging of Uterine Sarcomas

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I A</td>
<td>Tumor limited to uterus &lt; 5 cm</td>
</tr>
<tr>
<td>I B</td>
<td>Tumor limited to uterus &gt; 5 cm</td>
</tr>
<tr>
<td>II A</td>
<td>Tumor extends to the pelvis, adnexal involvement</td>
</tr>
<tr>
<td>II B</td>
<td>Tumor extends to extra-uterine pelvic tissue</td>
</tr>
<tr>
<td>III A</td>
<td>Tumor invades abdominal tissues, one site</td>
</tr>
<tr>
<td>III B</td>
<td>Tumor invades abdominal tissues, more than one site</td>
</tr>
<tr>
<td>III C</td>
<td>Metastasis to pelvic and/or para-aortic lymph nodes</td>
</tr>
<tr>
<td>IV A</td>
<td>Tumor invades bladder and/or rectum</td>
</tr>
<tr>
<td>IV B</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>
Treatment of Sarcomas

- Standard treatment for sarcomas involves surgical resection of the tumour (exploratory laparotomy)
- Usually involves hysterectomy and bilateral salpingo-oophorectomy +/- lymph node dissection
- CT scan is done to determine local resectability and to rule out extra uterine spread in suspected sarcomas
- If extra uterine disease is known or suspected, a CXR or CT scan is warranted to rule out pulmonary metastasis
Adjuvant Treatment

• Role of radiation therapy is controversial, no studies have shown a survival benefit associated with post-operative radiation therapy
• Therapy may reduce the rate of local recurrences, it has no significant impact on overall survival as most patients with recurrent disease have distant failures
• Useful in palliative setting to distant sites, bone/brain

Amant, 2009; Dulko, 2010; Lockwood, 2008; Smith & McLaughlin, 2012; Tropé et al., 2012;
Adjuvant Treatment

• Most common chemotherapy regimens used include:
  – Docetaxol and gemcitabine
  – Doxorubicin, cisplatin, and ifosfamide
  – Paclitaxel and carboplatin

• No prospective study has shown an improvement in survival outcomes for treatment with chemotherapy

Gockley et al., 2014; McMeekin, 2012
Ifosfamide

- Alkylation agent

- Key points to remember
  - Maintain high fluid intake
  - Administered with **Mesna**
    - For the prevention of urinary tract toxicity (hemorrhagic cystitis)

- Side Effects
  - Myelosuppression
  - N&V
  - Alopecia
  - Hemorrhagic cystitis
  - Neurotoxicity

Hydzik & O’Connor, 2010; Polovich, Whitford & Olsen, 2009
Recurrent Disease

• The treatment of recurrent sarcoma often requires the use of multiple therapeutic modalities
  – Rare cases of resectable, isolated pulmonary metastases may occur
• Enrolment into clinical trials is strongly recommended to facilitate the identification of new active agents for these malignancies
• In women with poorer performance status or multiple co-morbidities, palliative measures and supportive care should be the mainstay of treatment

Dulko, 2010; Smith & McLaughlin, 2012
References


References


References


References


References


References


References


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