GYNECOLOGICAL MALIGNANCIES

By Dr. Stephen Welch

For the most part, gynecological cancers can be treated for cure. As with the majority of solid tumour cancers, if gynecologic cancers are discovered at an early stage, surgery can be curative, and other treatments, such as radiotherapy or chemotherapy may be given post-operatively to consolidate treatment (ie. adjuvant treatment). All modalities of treatment can be considered in order to palliate symptoms and control disease growth, even if cure is not possible. As such, a multidisciplinary approach to the treatment of gynecologic cancers is necessary. The most common gynecologic cancers (cervical, endometrial and ovarian) are discussed below. Rarer cancers of the gynecologic tract include sarcomas, germ cell tumours, gestational trophobastic tumours, vulvar and vaginal cancers.

1. **CERVICAL CARCINOMA**

- **Epidemiology** – In Canada, 1,350 new cases of invasive cervical cancer are diagnosed annually. Approximately 400 deaths per year occur from this disease.
- Age**:** The median age at diagnosis is 47 years. 47% of women with invasive cervical cancer are diagnosed under 35 years of age. Older women (age > 65) account for 10% of all cervical cancer diagnoses.
- Risk factors: Incidence is inversely related to socio-economic status. Risk increases with early age of first coitus, total number of sexual partners and number of sexual partners before age 20. Increased risk with sexually transmitted diseases, like gonorrhea, syphilis, herpes simplex, trichomonas and chlamydia. With genital warts, the risk is increased 3-fold. Smoking is strongly associated.
- Etiology: Most cervical cancers originate in the transformation zone where metaplasia occurs (squamo columnar junction). More than 95% of cervical cancers are associated with infections with the human papilloma virus (HPV). HPV types 6 and 11 are usually found in benign condylomata acuminata, low-grade dysplasias and laryngeal papilomas. HPV types 16 and 18 (less commonly types 31, 33, 35 and 39) are most highly associated with high-grade dysplasias and carcinomas.

- **Prevention –**
- **Screening:** Screening programs with Papanicolaou smears (ie. Pap tests) have significantly reduced the incidence of advanced cervical cancer. Pap smears are recommended on an annual basis for sexually active women over the age of 18, in order to detect pre-cancerous lesions (squamous intraepithelial lesions, or SILs) before they become more invasive. The management of SILs is discussed below. If women have had three consecutive normal pap smears, they may be safely screened at less frequent intervals (every 2-3 years).

- **HPV vaccine:** Since HPV infection plays a necessary role in the development of cervical cancer, vaccination against HPV prior to potential exposure by sexual transmission is a reasonable prevention strategy. The first HPV vaccine (Gardasil) was approved by Health Canada in July 2006. Clinical trials have suggested these vaccines to be safe and effective in preventing HPV infection. Although their use remains controversial, the National Advisory Committee on Immunization recommends HPV vaccination for females between the ages of 9 and 26.

- **Clinical factors -**
- **Symptomatology**: The most common complaint is abnormal vaginal bleeding, including post-coital bleeding, post-menopausal bleeding, or irregular periods. As the tumor increases in size, the patient may complain of vaginal discharge. In advanced cases, the patient may experience pelvic pain or urinary symptoms. With metastatic disease, the symptoms depend on the site of metastases.
  Clinical examination includes general physical examination for anemia, supraclavicular adenopathy, and inguinal adenopathy. Pelvic examination involves speculum examination, bimanual as well as rectal examination.
- **Diagnosis**: Cervical Intraepithelial Neoplasia (CIN) and early invasive carcinomas of the cervix are usually asymptomatic and discovered only with routine screening. An abnormal pap smear should be evaluated by colposcopy and diagnostic cone biopsies should be performed if indicated. Any abnormal area such as ulceration should be biopsied.
- **Investigations** include a CBC and renal function, and imaging to assess for metastatic disease (either chest x-ray and ultrasound of the liver, or CT scan of thorax, abdomen and pelvis). MRI is superior to a CT scan in determining the depth of tumor invasion and disease extension to the pelvic side walls. MR is also helpful in differentiating pelvic soft tissue fibrosis, necrosis or edema, from recurrent pelvic cancer.
- **Histological Classification**
  - squamous cell carcinoma (75% to 85%)
  - adenocarcinoma (10% to 15%)
  - rare subtypes include: adenosquamous, clear cell carcinoma (diethyl stilbesterol exposure in utero), small cell carcinomas of the cervix (neuro-endocrine in origin), adenoid cystic carcinoma, glassy cell carcinoma and sarcomas.
- **Staging** - The most commonly used system is the International Federation of Gynecology and Obstetrics (FIGO). The FIGO is a clinical staging and involves pelvic examination under anaesthesia with cystoscopy and proctoscopy. Radiologic studies, which may be used, include an intravenous pyelogram, barium enema, chest x-ray and skeletal x-rays. The alternative staging system that is available is the AJC staging, TNM classification (T = tumor, N = node, M = metastasis).

FIGO	Site	AJC
Stage I A1 A2	Micro invasive carcinoma with minimal stromal invasion. Measurable invasion <= 5mm	T1a N0 M0
Stage I B	Invasive cancer confined to the cervix >5mm	T1b N0 M0
Stage II A	Extension to vagina (not lower third)	T2a N0 M0
Stage II B	Extension to parametrium	T2b N0 M0
Stage III A	Extension to lower one third of vagina	T3a N0M0
Stage III B	Extension to pelvic side wall / hydronephrosis	T1-3a N1 M0 T3b N_{any}M0
Stage IV A Stage IV B	Extension to bladder / rectum / beyond true pelvis Distant metastases	T4 N_{any} M0 T_{any} N_{any} M1

- **Treatment** : Multidisciplinary approach involving the gynecologic, radiation and medical oncologists is essential to plan and manage these patients.

a) Cervical Dysplasia and Carcinoma in situ:

Cervical intraepithelial neoplasia (CIN I to III) are usually treated with local methods. These include cryotherapy, electrocautery, excision, conization and laser therapy. Hysterectomy is also used to treat cervical dysplasias and carcinoma in situ. The recurrence rate following cone biopsy is approximately 3% compared with recurrence rate of about 1% following hysterectomy. Almost 97% of women can be cured with cone biopsy, routine hysterectomy for non-invasive disease is not warranted.

b) Invasive Cervical Carcinoma:

Both surgery and radiation therapy are used as primary modalities in the treatment of cervical carcinoma. The choice treatment modality depends on the size and stage of the lesion, as well as the patient's age and general medical condition.

- Surgery:

Surgery is used to treat early cancers in stage I. The surgical procedure includes radical hysterectomy with pelvic lymphadenectomy (Wertheim's hysterectomy). The uterus, cervix, surrounding parametrial tissues, cardinal ligaments, and upper vagina are removed. In young women the ovaries are not removed and the ovarian function

is preserved. It may also be used in previously irradiated patients with recurrent disease.

- Radiotherapy:
  Radiotherapy remains very effective in the treatment of cervical carcinoma. All stages may be treated with radiation, it is nearly always used in patients with stages higher than stage I. External beam radiation to the pelvis followed by intracavitary radiation is the standard treatment.

- Chemotherapy:
  Chemotherapy is used along with radiation as a radiosensitizer. A meta-analysis of randomized clinical trials has shown that adding cisplatin to radiation improves survival compared to radiation alone. Cisplatin is usually given weekly during radiotherapy. Chemotherapy can also be used in a neo-adjuvant setting to decrease the tumor bulk prior to radical surgery.
  Chemotherapy is given with palliative intent for systemic disease. Again, cisplatin is the most active drug in this disease. Combination therapy with another drug, topotecan, has been shown to prolong survival compared to cisplatin alone for patients with advanced cervical cancer.

- **Results and Prognosis**:
  - 5-year survival – 90% for stage I
    70% for stage II
    40% for stage III
    5%- 10% for stage IV.

2. **ENDOMETRIAL CARCINOMA:**
   - **Epidemiology:** Most prevalent cancer of the female genital tract. About 4,100 new cases are diagnosed annually in Canada. Early diagnosis and effective treatment reduce the death rate to less than 750 per annum.
   - Age: Majority are post menopausal, median age of diagnosis is 61yrs.
   - Risk factors:
     - Obesity – 10 fold increase in relative risk for endometrial carcinoma, due to a relative increase in free estrogen secondary to a decrease in sex hormone-binding globulin and increased aromatization of circulating androgens into estrone.
     - Oral contraceptives or post-menopausal estrogen replacement without progestins – 1.7 to 8.0% increase in relative risk. Tamoxifen therapy for breast cancer slightly increases the risk of low grade endometrial cancer (1 in 10,000).
     - Estrogen-secreting tumors, polycystic ovarian syndrome.
     - Nulliparity and anovulation.

- Hereditary – women with a family history of breast, ovarian or colon cancer are at higher risk for development of endometrial cancer. An autosomal dominant mechanism has been proposed.
- Endometrial hyperplasia and cytological atypia within the hyperplasia increases the risk of developing endometrial cancer from 1.6% to 23%.

- **Histological Classification:**

Type of Tumor	Incidence
Endometrioid adenocarcinoma	60%
Adenoacanthoma	20%
Adenosquamous carcinoma	7%
Clear cell carcinoma	5%
Papillary serous carcinoma	5%
Secretory adenocarcinoma	1.5%
Mucinous adenocarcinomas	1.5%

- **Clinical factors:**
- Symptomatology - Abnormal uterine bleeding occurs in more than 90% of the patients with endometrial cancer. (Only 15% to 20% of patients presenting with postmenopausal bleeding have endometrial cancer). Premenopausal women present with menometrorrhagia.
- Patterns of spread – typically spreads by invasion of the myometrium. Can also extend into the lower uterine segment and to the endocervix. Intraperitoneal spread through transtubal migration or from transmural invasion of the myometrium. Lymphatic spread may result in pelvic and paraaortic lymph node involvement. Haematogenous dissemination can occur rarely with pulmonary or hepatic spread.
- Diagnosis – Fractional dilatation and curettage is the standard diagnostic procedure. Out patient suction-curettage is an alternative, has a false negative rate of <3%. Rarely an abnormal pap smear with atypical endometrial cells in an asymptomatic patient may prompt further investigation. Pap smears are not indicated for screening or diagnosis. Hysteroscopy with endometrial biopsies or curettage may further decrease the false negative rates.
- Investigations – Haematological investigations - CBC, renal and hepatic function. CT scan of the thorax, abdomen and pelvis to assess extent of disease. Surgical staging is necessary to determine several prognostic pathological features that correlate with risk of recurrence (see below).

- **Staging:**

FIGO and AJCC TNM classification

FIGO	SITE	AJCC
Stage 0	In Situ	Tis
Stage I	Confined to corpus A.limited to endometrium	T1 N0 M0

	B.<50% myometrium C.>50%myometrium	
Stage II	Extension to cervix A.endocervix glandular B. stroma	T2N0M0
Stage III	Extension beyond uterus / within true pelvis A. serosa / adnexa / cytology B. vaginal metastases C. pelvic / paraaortic nodes	T3N1M0
Stage IVA	Extension to mucosa of bladder / rectum or beyond true pelvis	T4N0M0
Stage IV B	Distant metastases	T_{any} N_{any} M1

- **<u>Prognostic Factors</u>** correlating with the risk of recurrence:
  - high grade tumors
  - deep myometrial invasion
  - gross intra peritoneal disease
  - positive lymphnodes
  - lymphatic and vascular space tumor invasion
  - positive peritoneal cytology
  - age >60 years
  - histology (papillary serous / clear cell)

  75% of the patients present with stage I disease.
  With deep muscle invasion and high grade tumors, nodal spread is 20% to 60% in pelvic and 10% to 30% in para-aortic nodal regions.

- **<u>Treatment</u> :**
  - <u>Surgery</u>:

    Total abdominal hysterectomy with bilateral salpingo oophorectomy. As part of surgical staging, peritoneal cytology, pelvic and para-aortic nodal sampling and omental biopsies should be done. Surgical staging provides prognostic information in order to justify the addition of adjuvant radiotherapy or chemotherapy.
  - <u>Radiotherapy:</u>

    Adequate surgical staging will determine whether the patient should receive pelvic radiation, pelvic and para-aortic radiation or whole abdominal radiation. Primary treatment with radiation is used in patients who are not candidates for surgery. External beam radiation treatment to the pelvis is recommended for patients at high risk for local recurrence post surgery. In addition, high dose rate intracavitary brachytherapy is used to decrease the risk of vaginal vault recurrence.

- Hormonal Therapy:
  Hormonal therapy, with progestational agents like medroxyprogesterone (Provera) and megestrol acetate (Megace), is used to treat advanced, recurrent or metastatic disease. The treatment is well tolerated and the side effects are minimal. In general, the response rates are around 10%, but higher response and control rates are seen in low-grade tumors that are estrogen and / or progresterone receptor positive.
- Chemotherapy:
  Patients with high-risk endometrial cancer (lymph node spread, papillary serous histology) are often offered adjuvant chemotherapy, sequentially with adjuvant radiotherapy. Chemotherapy is also used with palliative intent for patients with recurrent or metastatic endometrial cancer. Combination therapy appears to be more effective than single-agent therapy for advanced endometrial cancer. Carboplatin and paclitaxel is the most commonly used regimen.

- **Results and Prognosis:** 5 year survival for Stage I carcinoma (all grades inclusive) is about 75%, Stage II is 57%, Stage III is 30% and Stage IV is 10%

3. OVARIAN CANCER:

- **Epidemiology:** Ovarian cancer is the second most common gynecologic cancer. Although it ranks seventh in incidence among cancers affecting women, ovarian cancer ranks fifth in absolute mortality among cancer-related deaths. Approximately 2,400 Canadian women are diagnosed with ovarian cancer annually and there are nearly 1700 ovarian cancer-related deaths in Canada per year. The majority is diagnosed at advanced stages (III or IV), as early diagnosis is difficult due to lack of early symptoms.
- Age: Epithelial ovarian tumors are most common and the median age of presentation is 59yrs. Malignant germ cell tumors present at a younger age.
- Risk factors: Increased risk with nulliparity, non-white race and family history. Asbestos exposure has been weakly linked to ovarian epithelial cancer.
- Genetic factors: Familial ovarian cancers-autosomal dominant with variable penetration for epithelial tumors. Relationship also exists between breast, colon and ovarian cancers.

- **Histological classification**:

Epithelial Tumors (85% - 90%)
Benign, Borderline malignancy, Malignant (grades I,II, and III)
- Serous (50%)
- Mucinous (10%)
- Endometrioid (20%)
- Clear cell (4%)

• Unclassified/ undifferentiated (15%)
Stromal Tumors • Sex cord stromal tumors (3%-8%) - granulosa-theca (estrogen producing) - Sertoli-Leydig (virilizing) • Non-specialized stroma - Mixed mesodermal tumour - Lymphomas - Leiomyosarcomas
Germ Cell Tumors (2%-4%) • Dysgerminoma (1%-2%) • Embryonic differentiation - Benign cystic teratoma (beta) - Malignant teratoma (AFP, HCG negative) • Extraembryonic differentiation - Endodermal Sinus tumour / Embryonal carcinoma (AFP positive) Choriocarcinoma (rare, BHCG positive)
Secondary (metastatic) carcinomas (ie. Krukenburg tumours)

- **Clinical Factors:**
- Symptomatology**:** the most common presentation for ovarian cancer is vague abdominal pain and bloating. Abdominal distension and fluid retention, related to ascites, can also be the presenting complaint. Ovarian cancer patients can develop bowel obstruction, due to extrinsic compression of small or large bowel by peritoneal disease.
- Patterns of spread: locally invasive, intraperitoneal spread (IP), lymphatic and hematological. IP metastases show a predilection for the omentum and the diaphragmatic surfaces, resulting in peritoneal tumor implants and ascites formation. Lymphatic spread includes abdominal, pelvic and retroperitoneal nodes, less commonly inguino-femoral nodes and lymph nodes above the diaphragm. Pleural space can be invaded through extension across the diaphragm. Hematological spread to lung, liver and brain can occur.
- Diagnosis: history and physical, pelvic examination, pelvic ultrasound, CT of abdomen and pelvis, chest x-ray, serum tumor markers, cytology of ascitic and pleural fluids (if present), and histological confirmation (biopsy).
- Serum tumor markers for ovarian cancer- AFP, beta HCG for germ cell tumors; CA-125 for epithelial tumors.

- **Staging**: Ovarian cancers are surgically staged, using the FIGO staging system. Staging laparotomy is usually combined with the definitive surgery (see below).

FIGO and AJCC TNM classification

FIGO	SITE	AJCC
Stage I	Limited to ovaries A.limited to one ovary B. limited to both ovaries C. capsule rupture / tumor on ovarian surface / malignant cells in peritoneal fluid	T1 N0 M0
Stage II	Extension to pelvic organs A.uterus / fallopian tube only B. involvement of other pelvic tissues C. malignant cells in peritoneal fluid	T2N0M0
Stage III	Extension to peritoneum beyond pelvis A. microscopic focus B. macroscopic< 2 cm C. macroscopic > 2 cm or lymph nodes metastases	T3N0M0 Or T_{any} N1 M0
Stage IV	Distant Metastases (excludes peritoneal metastases) • Pleural effusion (with positive cytology) • Visceral organ metastases	T_{any} N_{any} M1

- **Treatment:**
- **Epithelial tumors**:

Benign and borderline malignancies are treated surgically and fertility-sparing surgery is often possible. Borderline malignancies can recur, are generally slow-growing and do not respond well to chemotherapy or radiotherapy.

***Malignant* epithelial ovarian cancer**

Surgery:

Total abdominal hysterectomy with bilateral salpingo-oophorectomy and removal of all gross / macroscopic disease (ie. complete cytoreduction). *Optimal debulking of peritoneal disease is associated with improved survival in epithelial ovarian cancer.* To assess the extent of the disease locally, at the time of laparotomy, cytologic washings of the upper abdomen and the diaphragm, infracolic omentectomy, pelvic and para aortic lymph nodal sampling and random peritoneal biopsies are also performed.

Adjuvant therapy:

After surgery, further treatment depends on the grade of the tumor, amount of residual disease post primary surgery (microscopic,

macroscopic <2cms, macroscopic >2cms), stage of the disease and age of the patient. For example, despite optimal cytoreductive surgery, up to three-quarters of patients with stage III ovarian cancer will ultimately relapse and die from their cancer. In most instances, adjuvant therapy is recommended to improve chances of cure.

Currently, the standard of care for adjuvant therapy is six cycles of intravenous (IV) chemotherapy (carboplatin and paclitaxel). Recent reports have suggested that delivering chemotherapy directly into the peritoneal cavity (intraperitoneal, or IP, chemotherapy) is associated with higher cure rates than IV chemotherapy for early-stage ovarian cancer. IP chemotherapy is more toxic and requires at a cancer center experienced in this technique.

For patients with stage IV disease or with very bulky disease platinum-based chemotherapy can be given first, followed by a second look laparotomy. Ideally, a tissue biopsy is done before chemotherapy to establish the correct diagnosis. Prognosis in these cases depends on response to chemotherapy and the resectability of the residual disease at second look laparotomy.

Recurrent ovarian cancer:

Recurrence rates despite initial therapy are high. The intention of treatment for most recurrent epithelial ovarian cancers is palliative. Options for treatment include surgery, radiation, chemotherapy and hormonal therapy.

The prognosis for recurrent ovarian cancer depends greatly on two factors: bulk of recurrent disease and time between last treatment with chemotherapy to subsequent relapse (ie. treatment-free interval). Those individuals with a long treatment-free interval (> 12 months) tend to respond better to subsequent treatments. These individuals are often treated with combination chemotherapy (similar to adjuvant), but also may be candidate for a second surgical debulking. Patients whose disease recurs shortly after completing adjuvant chemotherapy (< 6 months) have a poorer prognosis. These patients can be treated with non-platinum chemotherapy drugs, such as liposomal doxorubicin, topotecan or etoposide, but response rates are only 10-15%. Alternatively, hormonal therapy, using tamoxifen, with limited side-effects, but slightly lower chance for response, can be used. Radiotherapy is generally limited to patients with focal areas of pain, and short course are given for symptom relief.

As patients with advanced, recurrent ovarian cancer commonly develop some degree of bowel obstruction, the palliative management of bowel obstruction is important. Surgical palliation by means of a defunctiong colostomy may be possible. Medications including octreotide and dexamethasone have also been used to control symptoms.

Prognosis:
Stages IA and IB, grade I or II have an excellent prognosis with 5year survival over 90%. Stages IC and II and poorly differentiated tumours (grade III), the survival is lower, with 5-year survival of 45% to 60%. For Stage III disease, the survival depends on status after surgical cytoreduction. With small volume residual disease and optimal adjuvant treatment, 10-year survival of up to 30% has been reported. The prognosis for bulky Stage III disease and stage IV is poor, with very few patients surviving to 5 years.

- **Stromal tumours**
  These tumours are quite rare. Surgery is the mainstay of treatment. For advanced or recurrent sex-cord stromal tumors, treatment is palliative. These cancers can respond to hormonal therapy (tamoxifen or leuprolide) or cisplatin-based chemotherapy. Sarcomas are treated in similar fashion to soft-tissue sarcomas arising elsewhere in the body.

- **Germ cell tumours**
  This is a very aggressive cancer that predominantly affects young women. These rare tumours are very responsive to chemotherapy. The combination of bleomycin, etoposide and cisplatin is effective in eradicating germ cell tumours in > 90% of cases.

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