CREOG Review
Gynecologic Oncology
2016
## American Cancer Society Statistics 2014

<table>
<thead>
<tr>
<th>New Cases by Site</th>
<th>Deaths by Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Lung</td>
</tr>
<tr>
<td>231,840</td>
<td>71,660</td>
</tr>
<tr>
<td>Lung</td>
<td>Breast</td>
</tr>
<tr>
<td>105,590</td>
<td>40,290</td>
</tr>
<tr>
<td>Colo-Rectal</td>
<td>Colo-Rectal</td>
</tr>
<tr>
<td>63,610</td>
<td>19,850</td>
</tr>
<tr>
<td>Uterus</td>
<td>Pancreas</td>
</tr>
<tr>
<td>54,870</td>
<td>19,850</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Ovary</td>
</tr>
<tr>
<td>47,230</td>
<td>14,180</td>
</tr>
<tr>
<td>N-H Lymphoma</td>
<td>Leukemia</td>
</tr>
<tr>
<td>32,000</td>
<td>10,240</td>
</tr>
<tr>
<td>Ovary</td>
<td>Uterus</td>
</tr>
<tr>
<td>21,290</td>
<td>10,170</td>
</tr>
</tbody>
</table>
Gynecologic Malignancies
2015

<table>
<thead>
<tr>
<th>Location</th>
<th>New</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterus</td>
<td>54,870</td>
<td>10,170</td>
</tr>
<tr>
<td>Ovary</td>
<td>21,290</td>
<td>14,180</td>
</tr>
<tr>
<td>Cervix</td>
<td>12,900</td>
<td>4,100</td>
</tr>
<tr>
<td>Vulva</td>
<td>4,100</td>
<td>1,080</td>
</tr>
</tbody>
</table>
Ovarian Cancer
Ovarian Cancer Screening

No effective screening test

• **PLCO (Prostate, Lung, Colorectal & Ovarian Cancer Screening)**
  - 34,261 women, aged 55-74 with ovaries and without symptoms
  - Randomized to no intervention vs. annual TV sono and CA-125
  - For every 1 patient found to have ovarian cancer 20 additional women had surgery.
  - No survival advantage for those women diagnosed with ovarian cancer due to screening compared to those not screened.

• **ROCA (Risk of Ovarian Cancer Algorithm) CA-125 followed by sono**
  - 3,238 low risk women, ages 50-74 (USA Trial)
  - 200,000 low risk women, ages 50-74 (United Kingdom Collaborate Trial)
  - Both show specificity of 99.8% (lack of disease)
  - Both have Positive Predictive Value of 35-37%
Pelvic Mass Assessment
Risk Factors

• Age
• Symptoms
• Family history
• Examination
• Tumor markers

• Sonographic characteristics
  • Unilocular vs. complex
  • Unilateral vs. Bilateral
  • Septations, papillary growth
  • Ascites
Pelvic Mass Triage

• OVA-1
  • Five markers (CA-125, transthyretin, apolipoprotein A 1, beta-2 macroglobulin, and transferrin)
  • Abnormal score for premenopausal women is > 5, and > 4.4 for postmenopausal women.
  • OVA-1 and physical assessment showed a high negative predictive value (95%), but a 35% positive predictive value.
  • Not a screening test, but for use in patients with a known pelvis mass to help decide on referral.

• ROMA (Risk of Ovarian Malignancy Algorithm)
  • HE4 human epididymis protein, and CA-125
  • Proprietary
  • 93% sensitivity
Pelvic Mass Referral

• ACOG and SGO Joint Recommendations 2002

• Postmenopausal patient
  • Elevated CA-125
  • Ascites
  • Nodular or fixed pelvic mass
  • Evidence of abdominal or distant metastasis
  • Family history of one or more first degree relatives with ovarian or breast cancer

• Premenopausal Patient
  • Very elevated CA-125 (>200 units/mL)
  • Ascites
  • Evidence of abdominal or distant metastasis
  • Family history of one or more first degree relatives with ovarian or breast cancer
Ovarian Mass in Pregnancy

Adnexal Mass (asymptomatic)

Repeat Ultrasound (16-18 weeks)

- Resolution
  - Routine OB Care

- Persistent Mass

  - Symptomatic
  - No suspicious features

  - Suspicious Features
    - (≥30% size, solid component, excrescences, increased vascularity/low resistance on color flow Doppler, ascites)

    - Laparoscopic Evaluation (18-22 weeks)
    - Surveillance through pregnancy

DiSaia & Creasman, 2012
Ovarian Cancer Staging
FIGO 2014

• **Stage I**  Growth limited to the ovaries
  - Ia  Growth limited to one ovary, no tumor on external surface, and capsule intact, negative washings.
  - Ib  Growth limited to both ovaries, otherwise like IA
  - Ic  Tumor limited to 1 or both ovaries
    - 1C1  Surgical spill
    - 1C2  Capsule rupture before surgery, or tumor on ovarian surface
    - 1C3  Malignant cells in the ascites or peritoneal washings

• **Stage II**  Growth involving one or both ovaries with pelvic extension (below pelvic brim), or primary peritoneal cancer
  - IIa  Extension and/or metastases to the uterus and/or Fallopian tubes
  - IIb  Extension to other pelvic intraperitoneal tissues
  
  (Note: old Stage IIC has been eliminated)
Ovarian Cancer Staging
FIGO 2014

- Stage III: Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes.

- IIIA (Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis)
  - IIIA1 Positive retroperitoneal lymph nodes only
    - IIIA1(i) Metastasis ≤ 10 mm
    - IIIA1(ii) Metastasis > 10 mm
  - IIIA2 Microscopic extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes

- IIIB Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.

- IIIC Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.
Ovarian Cancer Staging
FIGO 2014

- Stage IVA  Pleural effusion with positive cytology
- Stage IVB  Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity)

- Major Recommendations:
  - Histologic type including grading should be designated at staging
  - Primary site (ovary, Fallopian tube or peritoneum) should be designated where possible
  - Tumors that may otherwise qualify for Stage I but involved with dense adhesions justify upgrading to Stage II if tumor cells are histologically proven to be present in the adhesions.
2014 FIGO Staging for Ovarian Cancer

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OVARIAN CANCER
HISTOLOGY

OVARY

EPITHELIAL

Germ Cell

STROMAL
EPITHELIAL OVARIAN CANCER
HISTOLOGY (W.H.O.)

- SEROUS
- MUCINOUS
- ENDOMETRIOD
- CLEAR CELL
- TRANSITIONAL CELL
- MIXED EPITHELIAL
- UNDIFFERENTIATED
- UNCLASSIFIED
GERM CELL TUMORS

HISTOGENESIS

GERM CELL

- DYSGERMINOMA
- TOTIPOTENTIAL CELL TUMORS

TOTIPOTENTIAL CELL TUMORS

- EMBRYONAL CARCINOMA
  - EXTRAEMBRYONIC STRUCTURES
    - ENDODERMAL SINUS TUMOR (YOLK SAC)
    - CHORIOCARCINOMA
  - EMBRYONAL CARCINOMA
    - EMBRYONIC ECTODERM, ENDODERM, MESODERM
    - TERATOMA
      - MATURE
      - MONODERMAL
      - IMMATURE
GERM CELL TUMORS
PATHOLOGY

- DYSGERMINOMA
- EMBRYONAL CARCINOMA
- ENDODERMAL SINUS TUMOR
- CHORIOCARCINOMA
- MIXED GERM CELL TUMORS
Endodermal Sinus Tumor
Schiller-Duval Body
Immature Teratoma

Immature neural tube
GERM CELL TUMORS
CHARACTERISTICS

- **AGE DISTRIBUTION**
  - MOST COMMONLY SECOND AND THIRD DECADES OF LIFE

- **SIGNS AND SYMPTOMS**
  - RAPID GROWTH OF ABDOMINAL MASS
  - SYMPTOMS OF ACUTE ABDOMEN

- **PREGNANCY**
  - MOST COMMON OVARIAN MALIGNANCY ASSOCIATED WITH PREGNANCY
OVARIAN STROMAL TUMORS
PATHOLOGY

- GRANULOSA CELL TUMORS
- THECOMA/FIBROMA
- SERTOLI-LEYDIG CELL TUMORS (ANDROBLASTOMA)
- GYNANDROBLASTOMA
- SEX CORD TUMOR WITH ANNULAR TUBULES
- SCLEROSING STROMAL CELL TUMORS
STROMAL TUMORS
CHARACTERISTICS

- GRANULOSA CELL TUMORS
  - MAY OCCUR IN ALL AGES, ALTHOUGH 50% OCCUR POSTMENOPAUSAL
  - SYMPTOMS INCLUDE MENSTRUAL IRREGULARITIES OR POSTMENOPAUSAL BLEEDING
  - SOLID OR CYSTIC
  - BILATERAL IN 2% OF CASES
  - MAY PRODUCE ESTROGEN
  - JUVENILE GRANULOSA TUMOR
Granulosa Cell Tumor
Call-Exner bodies
Epithelial Ovarian Cancer

Therapy

- With the exception of Stage IA, Grade 1, the goal is TAH, BSO with no gross (visible) residual disease.
  - Primary cytoreductive surgery vs. Interval cytoreductive surgery following three cycles of chemotherapy

- Combination chemotherapy with a taxane and platinum compound is the Gold Standard

- Intraperitoneal/Intravenous Taxol/Platinum may improve overall survival for patients with no gross residual disease.

- Addition of a tyrosine kinase inhibitor (bevacizumab/Avastin) has prolonged disease free survival.
Gonadal Stromal Tumors of the Ovary

Therapy

- Surgical treatment is primary
- Risk of recurrent disease is low and may be years later.
- Chemotherapy has been used, but it’s effectiveness is unclear.
  - BEP- Bleomycin, Etoposide, Platinum
- Because recurrences are late and unpredictable, the benefit of chemotherapy is hard to measure.
Germ Cell Tumors of the Ovary

Therapy

- Because of the young age of the patients, and effectiveness of chemotherapy, surgery is more conservative. Salpingo-oophorectomy, and biopsy of any metastatic disease. Fertility preservation.

- Tumor markers are followed.

- Bleomycin, Etoposide, Cisplatin (BEP)

- Vinblastine, Bleomycin, Cisplatin (BVP)
Genetic Risk and Risk Reduction Surgery
Syndromes Associated with Increased Risk of Gynecologic Cancer

- **Hereditary Breast & Ovarian Cancer (HBOC)**
  - BRCA1 and BRCA2
- **Lynch/Hereditary Non-Polyposis Colorectal Cancer (HNPCC)**
  - MLH1, MSH2, MSH6, PMS2
- **Cowden Syndrome**
  - PTEN
- **Li Fraumeni Syndrome**
  - TP53
- **Peutz-Jeghers Syndrome**
  - STK11/LKB1
## Risk of Malignancy by Gene Mutation

<table>
<thead>
<tr>
<th>Gene</th>
<th>Breast</th>
<th>Ov/FT/Per</th>
<th>Uterus</th>
<th>Colon</th>
<th>Cervix</th>
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</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>65-85%</td>
<td>39-46%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRCA2</td>
<td>45-85%</td>
<td>10-27%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLH1</td>
<td>4-20%</td>
<td>20-54%</td>
<td>25-50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH2</td>
<td>7.5-24%</td>
<td>21-49%</td>
<td>25-50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH6</td>
<td>0-13.5%</td>
<td>16-71%</td>
<td>25-50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMS2</td>
<td></td>
<td>15%</td>
<td>25-50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTEN</td>
<td>50%</td>
<td></td>
<td>19-28%</td>
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<td></td>
</tr>
<tr>
<td>TP53</td>
<td>60%</td>
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<tr>
<td>STK11/LKB1</td>
<td>50%</td>
<td>21% sex cord stromal tumor</td>
<td></td>
<td></td>
<td>10% adenoma malignum</td>
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</table>
Genetic counseling and testing should be offered to: Women AFFECTED with

- High grade epithelial ovarian/tubal/peritoneal cancer
- Breast cancer ≤ 45 years
- Breast cancer with close relative with breast cancer ≤ 50 years or close relative with epithelial ovarian/FT/Per cancer at any age
- Breast cancer ≤ 50 years with limited family history
- Breast cancer with ≥ 2 close relatives with breast cancer at any age
- Breast cancer with ≥ 2 close relatives with pancreatic cancer, aggressive prostate cancer (Gleason Score ≥ 7)
- Two breast primaries, with the first diagnosed prior to age 50
- Triple negative breast cancer ≤ 60 years
- Breast cancer and Ashkenazi Jewish ancestry
- Pancreatic cancer with ≥ 2 close relatives with breast, Ov/FT/Per, pancreatic, or aggressive prostate cancer (Gleason Score ≥ 7)
Genetic counseling and testing should be offered to: Women UNAFFECTED with cancer, but with:

- A first degree relative or several close relatives that meet one of the previous criteria
- A close relative carrying a known BRCA1 or BRCA2 mutation
- A close relative with male breast cancer
Genetic counseling and assessment should be offered to those patients with an increased likelihood of Lynch Syndrome

• Patients with endometrial or colorectal cancer with evidence of microsatellite instability or loss of a DNA mismatch repair protein (MLH1, MSH2, MSH6, PMS2) on immunohistochemistry.

• Patients with a first-degree relative affected with endometrial or colorectal cancer who was either diagnosed before age 60 years or who is identified to be at risk for Lynch Syndrome by a systematic clinical screen that incorporates a focused personal and medical history.

• Patients with a first or second degree relative with known mutation in a mismatch repair gene.
# Ovarian Cancer Types

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td>Low-grade Serous</td>
<td>High-grade Serous</td>
</tr>
<tr>
<td></td>
<td>Clear Cell</td>
<td>High-grade Endometrioid</td>
</tr>
<tr>
<td></td>
<td>Low-grade Endometrioid</td>
<td>Undifferentiated</td>
</tr>
<tr>
<td></td>
<td>Mucinous</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transitional</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Borderline</td>
<td></td>
</tr>
<tr>
<td><strong>Common Genetic Defects</strong></td>
<td>ARIDIA</td>
<td>PS3</td>
</tr>
<tr>
<td></td>
<td>BRAF</td>
<td>BRCA</td>
</tr>
<tr>
<td></td>
<td>B-Catenin</td>
<td>AKT</td>
</tr>
<tr>
<td></td>
<td>KRAS</td>
<td>NOTCH3</td>
</tr>
<tr>
<td></td>
<td>PTEN</td>
<td>PAX8</td>
</tr>
<tr>
<td></td>
<td>MAPK</td>
<td>PIK3CA</td>
</tr>
<tr>
<td></td>
<td>MEK</td>
<td></td>
</tr>
<tr>
<td><strong>Proportion of Cancers (%)</strong></td>
<td>20-25</td>
<td>75-80</td>
</tr>
<tr>
<td><strong>Primary tissue of origin</strong></td>
<td>Ovarian surface epithelium</td>
<td>Fallopian tube</td>
</tr>
<tr>
<td><strong>Pathway to cancer</strong></td>
<td>Cortical inclusion cysts or tuboperitoneum nest transformations or endometriosis</td>
<td>PS3 Mutation in distal fallopian tube to STIC to invasive carcinoma</td>
</tr>
<tr>
<td><strong>Clinical Behavior</strong></td>
<td>Slow growing</td>
<td>Rapid growing</td>
</tr>
<tr>
<td></td>
<td>Indolent to Aggressive</td>
<td>Aggressive</td>
</tr>
</tbody>
</table>

STIC = Serous tubal intraepithelial carcinoma
Fallopian Tube as Source/Facilitator for Ovarian Cancer

- Pathologic findings at Risk Reducing Salpingo-oophorectomy (RRSO)
- Epithelial changes and genotoxic injury to the fallopian tube epithelium.
- Decreased incidence following tubal ligation.
Pathologic Findings at RRSO for BRCA Mutation Carriers

• Lifetime risk for ovarian cancer is 1.6% in the general population and 60% for BRCA1 and 30% for BRCA2 Carriers.

• 98% risk reduction following RRSO.

• No premalignant lesions of the ovary identified.

• STIC (serous tubal intraepithelial carcinoma) identified in fallopian tubes of 5-10% of women.

• STIC incidence is higher in BRCA1 vs. BRCA2 mutation carriers.

• p53 mutations identified in the cellular proliferation, similar to invasive HGSC.
Uterine Cancer
# Endometrial Cancer

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factors</td>
<td>Unopposed estrogen</td>
<td>Age</td>
</tr>
<tr>
<td>Race</td>
<td>White &gt; Black</td>
<td>White = Black</td>
</tr>
<tr>
<td>Differentiation</td>
<td>Well differentiated</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>Histology</td>
<td>Endometrioid</td>
<td>Non-endometrioid</td>
</tr>
<tr>
<td>Stage</td>
<td>I/II</td>
<td>III/IV</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Favorable</td>
<td>Not favorable</td>
</tr>
<tr>
<td>Ploidy</td>
<td>Diploid</td>
<td>Aneuploid</td>
</tr>
</tbody>
</table>
Uterine Carcinoma
Histology

• Endometrioid
• Adenosquamous
• Mucinous
• Papillary serous
• Clear cell
• Undifferentiated
Uterine Sarcoma

Histology

- Endometrial Stromal Tumors
  - Stromal nodule, Low-grade, High-grade sarcoma
- Smooth muscle tumor of uncertain malignant potential
- Leiomyosarcoma
  - Epithelioid
  - Myxoid
- Mixed endometrial stromal and smooth muscle tumor
- Undifferentiated endometrial sarcoma
- Adenosarcoma
- Carcinosarcoma (formerly malignant mixed mesodermal tumor)
**Uterine Cancer**

**Tamoxifen use**

- Used for breast cancer therapy and breast cancer prevention
- NSABP trial with 2,843 node-negative, ER-positive breast cancer were randomized to Tamoxifen 20 mg/day vs. placebo,
- The annual hazard rate for endometrial cancer was
  - 0.2/1,000 in the placebo group
  - 1.6/1,000 in the Tamoxifen group.
- Subepithelial stromal hypertrophy makes TV sonography difficult to interpret.
- Atrophic endometrium and endometrial polyps are common in symptomatic women.
### 2009 FIGO Uterine Cancer Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>The carcinoma is confined to the corpus uteri</td>
</tr>
<tr>
<td>IA</td>
<td>No or &lt; ½ myometrial invasion</td>
</tr>
<tr>
<td>IB</td>
<td>Invasion ≥ ½ of the myometrium</td>
</tr>
<tr>
<td>Stage II</td>
<td>Tumor involves the cervical stroma, but does not extend beyond the uterus</td>
</tr>
<tr>
<td>Stage III</td>
<td>Local and/or regional spread of the tumor</td>
</tr>
<tr>
<td>IIIA</td>
<td>Tumor invades the serosa of the corpus uteri and/or adnexae</td>
</tr>
<tr>
<td>IIIB</td>
<td>Vaginal and/or parametrial involvement</td>
</tr>
<tr>
<td>IIIC</td>
<td>Metastases to the pelvic and/or para-aortic lymph nodes</td>
</tr>
<tr>
<td>IIIC1</td>
<td>Positive pelvic lymph nodes</td>
</tr>
<tr>
<td>IIIC2</td>
<td>Positive para-aortic lymph nodes with or without positive pelvic lymph nodes</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Tumor invades the bladder and/or bowel mucosa</td>
</tr>
<tr>
<td>IVA</td>
<td>Tumor invades bladder and/or bowel mucosa</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes</td>
</tr>
</tbody>
</table>

Note: All tumors are Graded 1, 2 or 3. Endocervical gland involvement is to be considered Stage I. Positive cytology has to be reported separately without changing stage.
FIGO 2009
Updated Endometrial Cancer Staging

• Myometrial invasion is consolidated into two groups IA and IB
• Stage IIA cervical mucosal involvement deleted
• Stage not altered by (+) cytology IIIA
• Node involvement segregated into pelvic and aortic
Endometrial Cancer Therapy

• Hysterectomy, BSO and Lymphadenectomy
• The lymphadenectomy helps establish prognosis and guide postoperative therapy decisions. The lymphadenectomy may not alter survival.
• Prognostic factors guiding post-operative therapy
  • Grade
  • Histology
  • Myometrial invasion
  • Vascular space invasion
  • Node status
Cervical Cancer
Carcinoma of the Cervix
FIGO 2009

Stage I  The cancer is strictly confined to the cervix
( extension to the corpus should be disregarded)
IA  Invasive carcinoma which can be diagnosed only by microscopy with deepest invasion
≤ 5 mm and largest extension ≤ 7 mmIA1 Measured stromal invasion of ≤ 3.0 mm in depth and largest extension of
≤ 7.0 mmIA2 Measured stromal invasion of > 3.0 mm and not > 5.0 mm with an extension of not
> 7.0 mmIB  Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than
IA
IB1 Clinically visible lesion ≤ 4.0 cm in greatest dimension
IB2 Clinically visible lesions > 4.0 cm in greatest dimension
Stage II  Cervical cancer invades beyond the uterus, but not to the pelvic sidewall or to the
lower third of the vagina
IIA  Without parametrial invasionIIA1 Clinically visible lesion ≤ 4.0 cm in greatest dimensionIIA2 Clinically visible lesion > 4.0 cm in greatest dimensionIIB  With obvious parametrial invasion
Stage III  The tumor extends to the pelvic sidewall and/or involves lower third of the vagina
and/or causes hydronephrosis
IIIA  Tumor involves the lower third of the vagina, with no extension to the pelvic sidewall
IIIB  Extension to the pelvic sidewall and/or hydronephrosis or non-functioning kidney
Stage IV  The carcinoma has extended beyond the true pelvis or has involved (biopsy proven)
the mucosa of the bladder or rectum. Bullous edema, as such, does not permit a case
to be allotted to Stage IV.
IVA  Spread of the growth to adjacent organs
IVB  Spread to distant organs
2009 FIGO Update
Cervical Cancer

• All macroscopically visible lesions are allotted to Stage IB
• Minimal or microscopic invasion IA1 to include squamous and glandular lesions
• Vascular/lymphatic invasion should not change the stage allotment
• IIA subdivided into Lesion ≤ 4.0 cm or > 4.0 cm
Cervical Carcinoma
Microinvasion by SGO

- Less than or equal to 3 mm stromal invasion
- Absence of vascular space involvement
# Cervical Cancer Therapy

<table>
<thead>
<tr>
<th>FIGO Stage</th>
<th>Fertility Preservation</th>
<th>Standard Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA1 SCCA (no LVSI) or AIS</td>
<td>Conization</td>
<td>Extrafascial hysterectomy</td>
</tr>
<tr>
<td>IA1 with LVSI</td>
<td>Conization &amp; Laparoscopic lymphadenectomy</td>
<td>Extrafascial hysterectomy ± lymphadenectomy</td>
</tr>
<tr>
<td>IA2 or occult IB1</td>
<td>Radical trachelectomy with lymphadenectomy</td>
<td>Modified radical hysterectomy, lymphadenectomy</td>
</tr>
<tr>
<td>IB1-IIBA</td>
<td>As above for IB1 ≤ 2 cm</td>
<td>Radical hysterectomy, lymphadenectomy</td>
</tr>
<tr>
<td>IB2-IVA</td>
<td></td>
<td>Radical hyst, lymphadenectomy (select cases), or Chemoradiation</td>
</tr>
<tr>
<td>IVB, persistent and/or recurrent</td>
<td></td>
<td>Palliative Cisplatin/Taxol, +/- XRT, or Taxol/Topotecan/bevacizumab</td>
</tr>
</tbody>
</table>
Cervical Carcinoma
Postoperative Adjuvant Therapy- Chemoradiation

• Intermediate Risk
  • > 1/3 stromal invasion, LVSI, tumor diameter > 4 cm

• High Risk
  • Positive nodes, positive margins, microscopic disease in the parametrium

Pelvic radiation or chemoradiation reduced the risk of recurrence, and improved progression-free and overall survival.
GTN
Gestational Trophoblastic Neoplasia

• Definition
  • Plateaued, rising, or prolonged persistence of elevated hCG values after molar evacuation, histologic diagnosis of choriocarcinoma, invasive mole or PSST, or identification of metastasis.
GTN

FIGO requirements for postmolar GTN

• 4 values or more of plateaued hCG (±10%) over at least 3 weeks: days 1, 7, 14 and 21

• A rise of hCG of 10% or greater for three values or more over at least 2 weeks: days 1, 7 and 14.

• Persistence of hCG beyond 6 months

• Histologic diagnosis of choriocarcinoma, invasive mole, or PSTT (placental site trophoblastic tumor)

• Metastatic disease without established primary site with elevated hCG; pregnancy has been excluded.
GTN Evaluation

• Complete physical and pelvic exam, baseline hematologic, hepatic and renal functions
• Baseline quantitative hCG level
• Chest radiograph or CT scan of chest
• Brain MRI or CT scan
• CT or MRI of abdomen and pelvis.
### GTN Staging System: FIGO, 2009

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical/Pathological Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Disease confined to the uterus</td>
</tr>
<tr>
<td>II</td>
<td>GTN extends outside the uterus, but is limited to the genital structures</td>
</tr>
<tr>
<td>III</td>
<td>GTN extends to the lungs, with or without known genital tract involvement</td>
</tr>
<tr>
<td>IV</td>
<td>All other metastatic sites</td>
</tr>
</tbody>
</table>
**GTN Scoring System: High Risk = 7 or higher**

<table>
<thead>
<tr>
<th></th>
<th>Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Less than 40</td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td>Mole</td>
</tr>
<tr>
<td>Interval months from index</td>
<td>Less than 4</td>
</tr>
<tr>
<td>pregnancy</td>
<td></td>
</tr>
<tr>
<td>Pretreatment hCG (IU/L)</td>
<td>Less than $10^3$</td>
</tr>
<tr>
<td>Largest Tumor Size (including uterus)</td>
<td>---</td>
</tr>
<tr>
<td>Site of metastases</td>
<td>Lung</td>
</tr>
<tr>
<td>No. of metastases</td>
<td>---</td>
</tr>
<tr>
<td>Previous failed chemotherapy</td>
<td>---</td>
</tr>
</tbody>
</table>
GTN
Treatment Options

• Non-metastatic and Low-risk Metastatic GTN
  • Methotrexate: Weekly, or daily for 5 days q 14 days, or Day 1,3,5 and 7 with folinic acid Days 2,4,6 and 8 q 14 days
  • Dactinomycin: IV daily for 5 days 2 14 days, or IV bolus q 14 days

• High-risk metastatic GTN
  • EMA/CO
    • Etoposide, MTX, Actinomycin-D, Cyclophosphamide and Oncovin (vincristine)
Vulvar Cancer
Vulvar Cancer Staging
FIGO 2009

Stage I
Tumor confined to the vulva
IA Lesions ≤ 2 cm in size, confined to the vulva or perineum and with stromal invasion ≤ 1.0 mm, no nodal metastasis
IB Lesions > 2 cm in size or with stromal invasion > 1.0 mm, confined to the perineum, with negative nodes

Stage II
Tumor of any size with extension to adjacent perineal structures (1/3 lower vagina, 1/3 lower urethra, anus) with negative nodes

Stage III
Tumor of any size with or without extension to adjacent perineal structures (1/3 lower vagina, 1/3 lower urethra, anus) with positive inguino-femoral lymph nodes
IIIA (i) With 1 lymph node metastasis (≥ 5 mm), or (ii) 1-2 lymph node metastases (< 5 mm)
IIIB (i) With 2 or more lymph node metastases (≥ 5 mm), or (ii) 3 or more lymph node metastases (<5 mm)
IIIC With positive nodes with extracapsular spread

Stage IV
Tumor invades other regional (upper 2/3 of the urethra or upper 2/3 of vagina), or distant structures
IVA Tumor invades any of the following: (i) upper 2/3 of urethra or vaginal mucosa, bladder mucosa, rectal mucosa, and/or fixed to pelvic bone, or (ii) fixed or ulcerated inguino-femoral lymph nodes
IVB Any distant metastasis including pelvic lymph nodes

Depth of invasion is defined as the measurements of the tumor from the epithelial stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion
### 2009 Staging

**Tumor Characteristics**

<table>
<thead>
<tr>
<th>$T_0$</th>
<th>Carcinoma in situ</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_1$</td>
<td>Tumor confined to the vulva, perineum or both.</td>
</tr>
<tr>
<td>$T_{1A}$</td>
<td>Stromal invasion no greater than 1.0 mm. $\leq$ 2 cm. in greatest dimension</td>
</tr>
<tr>
<td>$T_{1B}$</td>
<td>Stromal invasion $&gt; 1.0$ mm. of $&gt; 2$ cm. greatest dimension</td>
</tr>
<tr>
<td>$T_2$</td>
<td>Tumor any size extending to anus, urethra or lower 1/3 of the vagina</td>
</tr>
<tr>
<td>$T_3$</td>
<td>Tumor of any dimension with adjacent spread to upper urethra, bladder, rectum or pubic bone</td>
</tr>
</tbody>
</table>
## 2009 Staging
Regional Node Status

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$N_0$</td>
<td>Regional nodes negative</td>
</tr>
<tr>
<td>$N_{1a}$</td>
<td>Spread to 1 or 2 nodes, $\leq 5$ mm</td>
</tr>
<tr>
<td>$N_{1b}$</td>
<td>Spread to 1 node with $&gt; 5$ mm area</td>
</tr>
<tr>
<td>$N_{2a}$</td>
<td>3 or more nodes with $\leq 5$ mm area</td>
</tr>
<tr>
<td>$N_{2b}$</td>
<td>2 or more nodes with $&gt; 5$ mm area of spread</td>
</tr>
<tr>
<td>$N_{2c}$</td>
<td>Nodal spread with extracapsular spread</td>
</tr>
<tr>
<td>$N_3$</td>
<td>Ulcerated or fixed nodes</td>
</tr>
</tbody>
</table>
## 2009 Staging
### Distant Metastases

<table>
<thead>
<tr>
<th>$M_x$</th>
<th>Presence of distant metastases cannot be assessed.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$M_0$</td>
<td>No distant metastases.</td>
</tr>
<tr>
<td>$M_1$</td>
<td>Distant metastases or positive pelvic lymph nodes.</td>
</tr>
<tr>
<td>Stage</td>
<td>T</td>
</tr>
<tr>
<td>-----------</td>
<td>----</td>
</tr>
<tr>
<td>Stage 0</td>
<td>$T_0$</td>
</tr>
<tr>
<td>Stage I</td>
<td>$T_1M_0N_0$</td>
</tr>
<tr>
<td>Stage IA</td>
<td>$T_{1A}N_0M_0$</td>
</tr>
<tr>
<td>Stage IB</td>
<td>$T_{1B}N_0M_0$</td>
</tr>
<tr>
<td>Stage II</td>
<td>$T_2N_0M_0$</td>
</tr>
<tr>
<td>Stage IIIa</td>
<td>$T_1, T_2, N_{1a}, N_{1b}, M_0$</td>
</tr>
<tr>
<td>Stage IIIb</td>
<td>$T_1, T_2, N_{2a}, N_{2b}, M_0$</td>
</tr>
<tr>
<td>Stage IIIc</td>
<td>$T_1, T_2, N_{2c}, M_0$</td>
</tr>
<tr>
<td>Stage IVa</td>
<td>$T_1N_2, N_3, M_0, T_3N_{any}, M_0$</td>
</tr>
<tr>
<td>Stage IVb</td>
<td>$T_{any}N_{any}, M_1$</td>
</tr>
</tbody>
</table>
Prognostic Factors

• Lymph node status
• Clinical stage
• Lesion size
• Depth of invasion
• Presence of vascular space invasion
Early Invasive Cancer
ISSVD Definition

• 2 cm. or less in diameter
• Depth of invasion of 1 mm. or less
• 1% risk of inguinal node metastases
Vulvar Cancer Therapy

• Management of the Primary Vulvar Lesion
• Management of the Region at Risk for Metastatic Disease
• Minimize Toxicity Without Compromising Cure
Surgical Options
Treatment of the Primary Lesion

• Wide local excision
• Radical Hemivulvectomy, Wide Local Excision
• Radical Vulvectomy
• Radical Vulvectomy with Pre-op Chemotherapy or Radiation
• Radical Vulvectomy with Anovulvectomy or Pelvic Exenteration
Surgical Options
Treatment of Inguinal Lymph Nodes

1. No therapy

2. Ipsilateral superficial inguinal node dissection (Separate incision)

3. Ipsilateral superficial and deep inguinal node dissection (Separate incision or *en bloc* resection with vulvar lesion)

4. Bilateral superficial and deep inguinal node dissection (Separate incisions)
Surgical Options
Treatment of Inguinal Lymph Nodes

5. Bilateral superficial and deep femoral node dissection (Separate or *en bloc* resection with vulvar lesion)

6. Unilateral or bilateral, superficial and deep femoral, and pelvic node dissection

7. Any of the above with post-operative radiation therapy
Surgical Therapy
Primary Lesion

• Adequate, clear surgical margins required
• 2 cm. margin, medial, lateral and deep
• Radical Vulvectomy *en bloc* resection carries a high wound breakdown rate (60%)
• Radical hemi-vulvectomy, wide local excision, or vulvectomy with separate groin incision offers lower morbidity and equal local control
Inguinal Triangle

Floor

- Inguinal ligament
- Anterior superior iliac spine (ASIS)
- Sartorius m.
- Iliacus m.
- Adductor longus m.
- Pectineus m.
- Psoas m.
- Pubic tubercle
Early Invasive Carcinoma

• < 2 cm Diameter
• 1 mm or < stromal invasion
• low risk of nodal spread (<1%)
• May be treated by wide local excision only without groin node dissection
Paget’s Disease of the Vulva
Paget’s Disease of the Vulva

- Intraepithelial proliferation of atypical glandular-type cells.
- Derived from the stratum germinativum of the epidermis
- Associated with adenocarcinoma of the sweat gland in 14-19% of patients
- Risk of metachronous carcinoma (breast, cervix, basal cell of skin, esophagus) in 26-43% of patients.
Vulvar Melanoma
Vulvar Melanoma

- 10% or < of vulvar malignancies.
- 1.3% of melanomas in women
- 0.108/100,000 women/year
- Median age is 66 years
Vulvar Melanoma

- Symptoms include vulvar mass, bleeding or pruritis
- Diagnosis is made by full thickness dermatome punch biopsy
- Pathology
  - Superficial spreading melanoma
  - Nodular melanoma
  - Acral lentiginous melanoma
Vulvar Melanoma Staging

- Clarks Levels (Anatomic)
- Breslows System (Depth of invasion)
- Chung’s System (Combination of above)
- American Joint Committee on Cancer Staging for Melanoma
### American Joint Committee on Cancer Staging for Melanoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Primary melanoma (&lt;0.75) mm thick and/or Clark’s level II (N(_0)M(_0))</td>
</tr>
<tr>
<td>IB</td>
<td>Primary melanoma (0.75-1.50) mm thick and/or Clark’s level III</td>
</tr>
<tr>
<td>IIA</td>
<td>Primary melanoma (1.51-4.0) mm thick and/or Clark’s level IV</td>
</tr>
<tr>
<td>IIB</td>
<td>Primary melanoma (&gt;4.0) mm thick and/or Clark’s level V</td>
</tr>
<tr>
<td>III</td>
<td>Regional node and/or in-transit metastases (T(<em>{\text{any}}),N(</em>{1-2}),M(_0))</td>
</tr>
<tr>
<td>IV</td>
<td>Systemic metastases (T(<em>{\text{any}}),N(</em>{\text{any}}),M(_1))</td>
</tr>
</tbody>
</table>

Beahrs 1992
Radiation Therapy
Radiation Oncology
Principles

• External Irradiation (Teletherapy)
  • Linear accelerators

• Local Irradiation (Brachytherapy)
  • Intracavitary Irradiation
    • Cesium or iridium (HDR)
  • Interstitial Irradiation
    • Iridium or cesium
Radiation Effect
## Radioactive Isotopes

<table>
<thead>
<tr>
<th>Radioisotope</th>
<th>Radiation emitted</th>
<th>Half-life</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>technetium-99m</td>
<td>$\gamma$</td>
<td>6 h</td>
<td>medical diagnosis for heart, bone, lung, brain, thyroid, blood flow</td>
</tr>
<tr>
<td>iodine-131</td>
<td>$\beta, \gamma$</td>
<td>8 d</td>
<td>treatment of diseases of the thyroid</td>
</tr>
<tr>
<td>iridium-192</td>
<td>$\beta, \gamma$</td>
<td>74 d</td>
<td>used as an internal radiotherapy source</td>
</tr>
<tr>
<td>fluorine-18</td>
<td>$\beta^+ \beta$</td>
<td>1.8 h</td>
<td>positron emission tomography (PET) to study brain function and to diagnose epilepsy, heart diseases and certain types of cancer</td>
</tr>
<tr>
<td>iodine-123</td>
<td>$\beta, \gamma$</td>
<td>13.2 h</td>
<td>diagnosis of thyroid diseases and some cancers</td>
</tr>
<tr>
<td>cobalt-60</td>
<td>$\beta, \gamma$</td>
<td>5.3 y</td>
<td>gamma radiation for cancer treatment</td>
</tr>
<tr>
<td>caesium-137</td>
<td>$\beta, \gamma$</td>
<td>30 y</td>
<td>thickness gauges in industry radiography of machinery and welds irradiation of food (not in Australia—yet)</td>
</tr>
<tr>
<td>americium-241</td>
<td>$\alpha$</td>
<td>432 y</td>
<td>smoke detectors</td>
</tr>
<tr>
<td>gold-198</td>
<td>$\beta, \gamma$</td>
<td>2.7 d</td>
<td>radio-tracer to follow movements of sewage and other wastes through waterways movement of sand in river beds and ocean floors (erosion)</td>
</tr>
<tr>
<td>zinc-65 and manganese-54 (produced together)</td>
<td>$\beta^+ \beta$, E.C.</td>
<td>244 d, 312 d</td>
<td>follow heavy metals in waste water from mining</td>
</tr>
</tbody>
</table>
Inverse Square Law

\[ \frac{S}{4\pi r^2} = I \]

The energy twice as far from the source is spread over four times the area, hence one-fourth the intensity.
Therapeutic Effect vs. Toxicity

![Graph showing the relationship between dose and therapeutic ratio](image)

- Blue line: Probability of local tumor control
- Yellow line: Probability of complications

Therapeutic Ratio vs. Dose

Shifts in Therapeutic Ratio
Chemotherapy
<table>
<thead>
<tr>
<th>TABLE 2: Chemotherapeutic agents^a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alkylating agents</strong></td>
</tr>
<tr>
<td>- Nitrogen mustards: chlorambucil, cyclophosphamide, estramustine, ifosfamide, mechlorethamine, melphalan</td>
</tr>
<tr>
<td>- Aziridine: cliofera</td>
</tr>
<tr>
<td>- Alkyl sulfonate: busulfan</td>
</tr>
<tr>
<td>- Nitrosourea: carmustine, lomustine, streptozocin</td>
</tr>
<tr>
<td>- Platinum complexes: carboplatin, cisplatin, oxaliplatin</td>
</tr>
<tr>
<td>- Nonclassic alkylators: altretamine, dacarbazine, procarbazine, temozolomide</td>
</tr>
<tr>
<td><strong>Antimetabolites</strong></td>
</tr>
<tr>
<td>- Folate analogs: methotrexate, pemetrexed</td>
</tr>
<tr>
<td>- Purine analogs: fludarabine, mercaptopurine, thioguanine</td>
</tr>
<tr>
<td>- Adenosine analogs: cladribine, pentostatin</td>
</tr>
<tr>
<td>- Pyrimidine analogs: capecitabine, cytarabine, 5-fluorouracil, gemcitabine</td>
</tr>
<tr>
<td>- Substituted urea: hydroxyurea</td>
</tr>
<tr>
<td><strong>Natural products</strong></td>
</tr>
<tr>
<td>- Antitumor antibiotics: bleomycin, daunomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, mitoxantrone, mitomycin, valrubicin</td>
</tr>
<tr>
<td>- Epipodophyllotoxins: etoposide, teniposide</td>
</tr>
<tr>
<td>- Microtubule agents: docetaxel, paclitaxel, vinblastine, vincristine, vinorelbine</td>
</tr>
<tr>
<td>- Camptothecin analogs: irinotecan, topotecan</td>
</tr>
<tr>
<td>- Enzyme: asparaginase</td>
</tr>
<tr>
<td><strong>Targeted agents</strong></td>
</tr>
<tr>
<td>- Monoclonal antibodies: alemuzumab, bevacizumab, cetuximab, panitumumab, rituximab, trastuzumab</td>
</tr>
<tr>
<td>- Molecularly targeted therapies: bortezomib, dasatinib, erlotinib, gefitinib, imatinib, lapatinib, sorafenib, sunitinib, temsirolimus</td>
</tr>
</tbody>
</table>

^aFor a comprehensive table of drug information including dosages and toxicities, see Appendix 4.
MOA of some anticancer drugs

Antimetabolites
- 6-Mercaptopurine
- 6-Thioguanine
- Methotrexate → DHFR
- Hydroxyurea

- 5-Fluorouracil
- Cytarabine
- Gemcitabine

Etoposide
- Topoisomerase II inhibitor - DNA break

Purine Synthesis

Pyrimidine Synthesis

Ribonucleotides

Deoxyribonucleotides

DNA

RNA

Proteins

Enzymes

Microtubules

Alkylating agents
- Alkylation → Alter structure & function of DNA by cross linking and/or fragmenting DNA

Antibiotics

L-Asparaginase

Vinca Alkaloids → prevent polymerization

Taxans → enhance polymerization
Summary of MOA and site of action of chemotherapeutic agents

- 6-Mercaptopurine
- 6-Thioguanine
- Methotrexate
  - Inhibit purine ring synthesis
  - Purines and pyrimidines
  - Ribonucleotides
- Hydroxyurea
  - Inhibit ribonucleotide reductase
- Methotrexate
  - Inhibit dTMP synthesis
  - Deoxyribonucleotides
- 5-Fluorouracil
- Cytarabine
  - Inhibit DNA synthesis
- Bleomycin
- Doxorubicin
- Daunorubicin
- Dactinomycin
- Alkylating agents
- Nitrosoureas
- Cisplatin
- L-Asparaginase
- Vinca alkaloids
  - Inhibit microtubule function
  - microtubules
- Paclitaxel
- Colchicine
  - Protein tyrosin kinase inhibitor
  - Block activity
- Enzymes

DNA
  - Scission of DNA
  - Intercalate DNA
  - Cross-link DNA
  - Inhibit protein synthesis
  - Proteins
  - RNA
  - Proteins