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Gynecologic Cancers: Staging, prognostic factors, and management

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Objectives

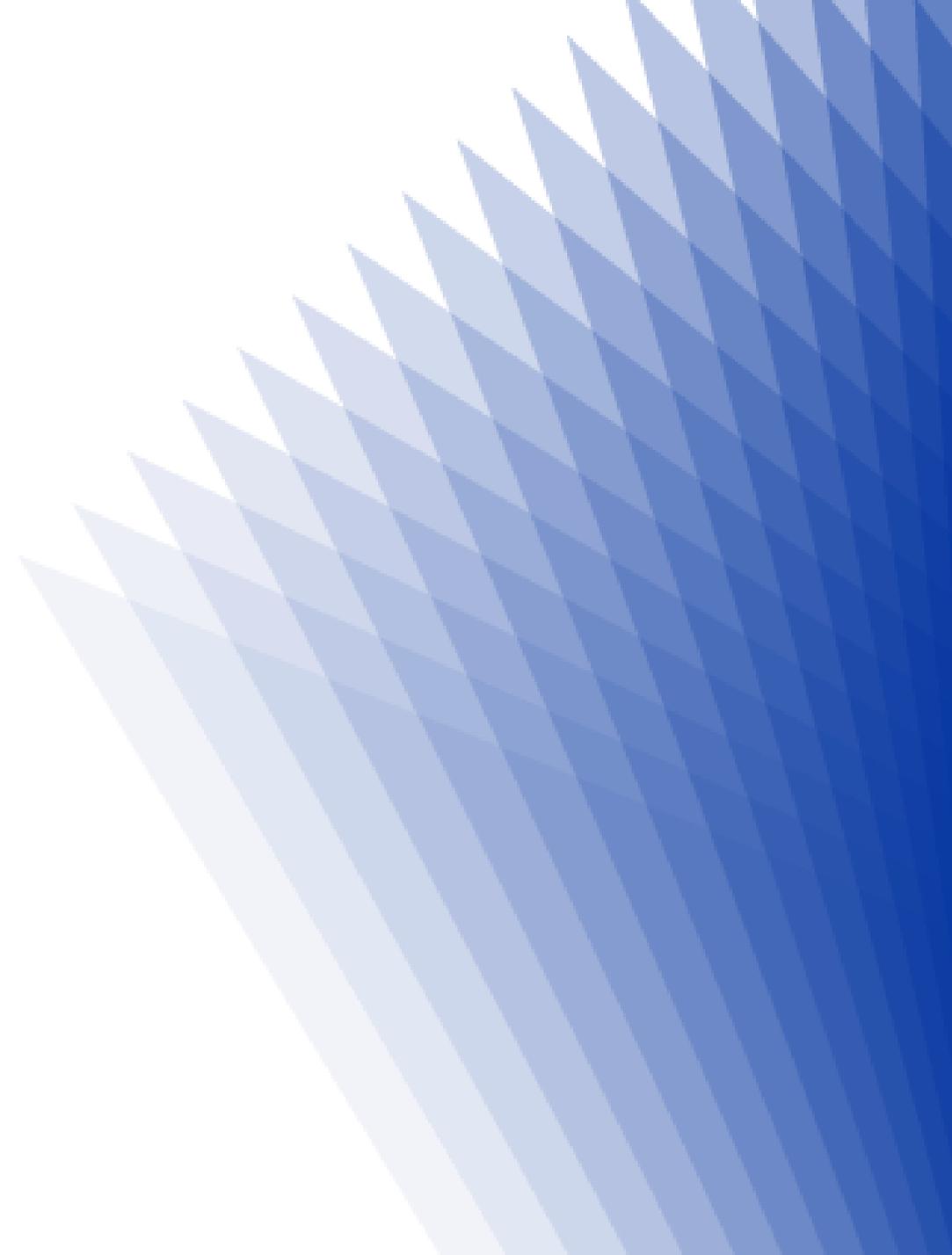
- Review staging, prognostic factors, and general NCCN-based management guidelines for ovarian, uterine, and cervical cancers



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Ovarian Cancer



Ovarian Cancer Statistics

- Estimated New Cases: 22,000
- Estimated Deaths: 13,770
- Leading cause of gynecologic cancer death
- Fifth leading cause of cancer death in women

New Cases



	Female	
Breast	281,550	30%
Lung & bronchus	116,660	13%
Colon & rectum	69,980	8%
Uterine corpus	66,570	7%
Melanoma of the skin	43,850	5%
Non-Hodgkin lymphoma	35,930	4%
Thyroid	32,130	3%
Pancreas	28,480	3%
Kidney & renal pelvis	27,300	3%
Leukemia	25,560	3%
All sites	927,910	

Deaths



	Female	
Lung & bronchus	62,470	22%
Breast	43,600	15%
Colon & rectum	24,460	8%
Pancreas	22,950	8%
Ovary	13,770	5%
Uterine corpus	12,940	4%
Liver & intrahepatic bile duct	9,930	3%
Leukemia	9,760	3%
Non-Hodgkin lymphoma	8,550	3%
Brain & other nervous system	8,100	3%
All sites	289,150	

Risk factors

- Northern European descent/ Ashkenazi Jews
- Nulliparous
- Late menopause
- Infertility
- Talc (controversial)
- Hereditary (10-15% of all epithelial ovarian cancer)
 - BRCA 1 & 2
 - HNPCC

- Birth control pills decrease the risk of ovarian carcinoma by 50%

Ovarian Cancer Symptoms

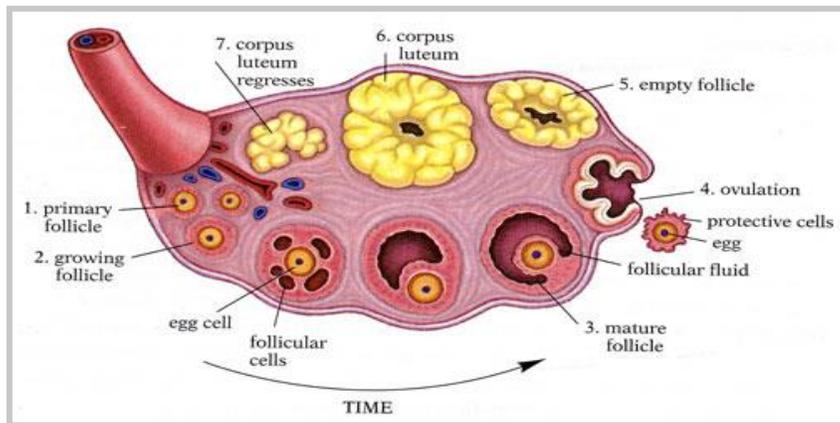
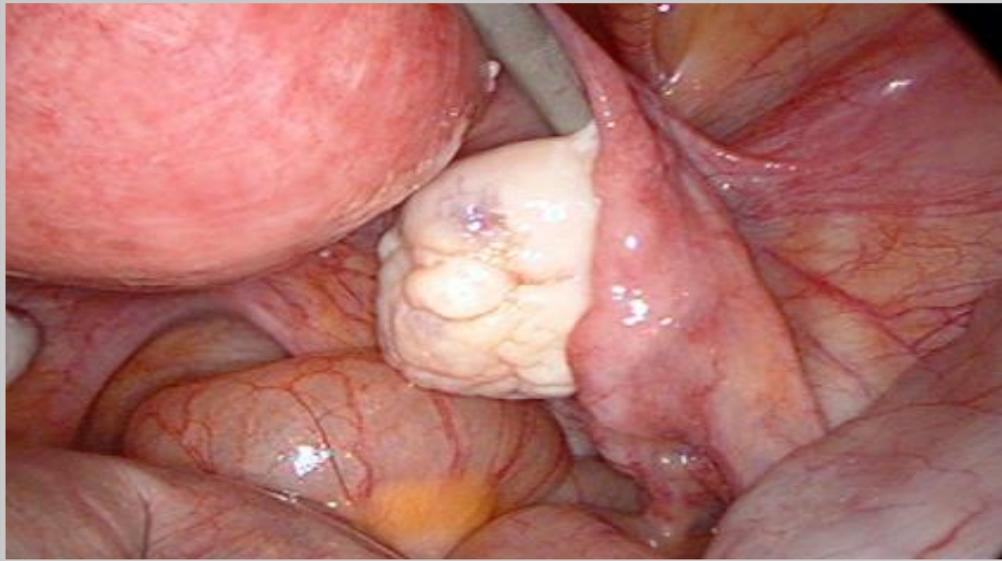
- **Vague and nonspecific pelvic, abdominal, and menstrual symptoms**
 - Pelvic or abdominal pain
 - Urinary frequency or urgency
 - Increased abdominal size or bloating
 - Difficulty eating or feeling full
- **Most suspicious when present less than 1 year or more than 12 days a month**



Diagnosis

- Excision and pathologic evaluation (gold standard)
- Vaginal ultrasound
 - UK ovarian ultrasound experience (asymptomatic women)
 - 89 cancers among 35,000 screenings
 - Sensitivity 86%, Specificity 70%, PPV 10%
- CA 125
 - **Not reliable for diagnosis** (better suited for following treatment response)
 - 50% of stage I cancers do not have elevated CA 125's
 - Endometriosis, PID, hepatitis, CHF all cause false positive results

Histologic Types of Ovarian Cancer



1. Epithelial Ovarian Cancer (90%)

- Serous/Papillary serous (80%)
- Mucinous (10%)
- Endometrioid (10%)
- Clear Cell
- *Borderline Tumors*

2. Sex-cord Stromal Tumors

- Granulosa Cell Tumors
- Fibrosarcoma
- Sertoli-Leydig Tumors

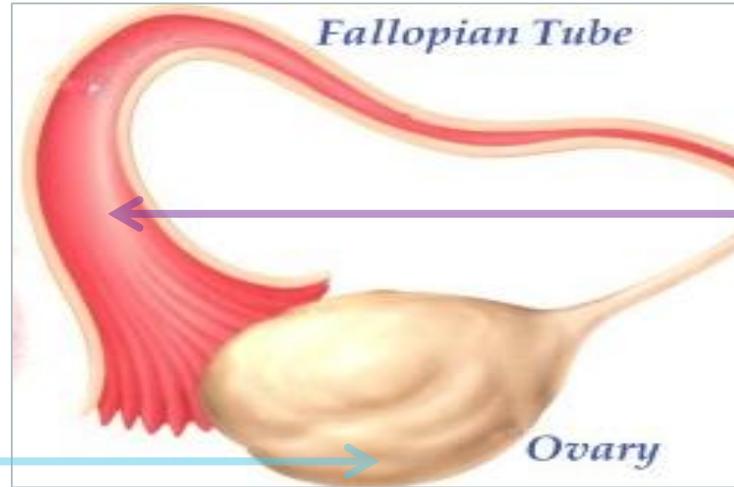
3. Germ Cell Tumors

- Dysgerminoma
- Yolk Sac Tumors
- Embryonal Carcinoma
- Choriocarcinoma
- Teratomas

Two Types of Ovarian Cancer

Type I

- low grade serous or endometrioid cancers
- arise from transformation of epithelial cysts
- less aggressive

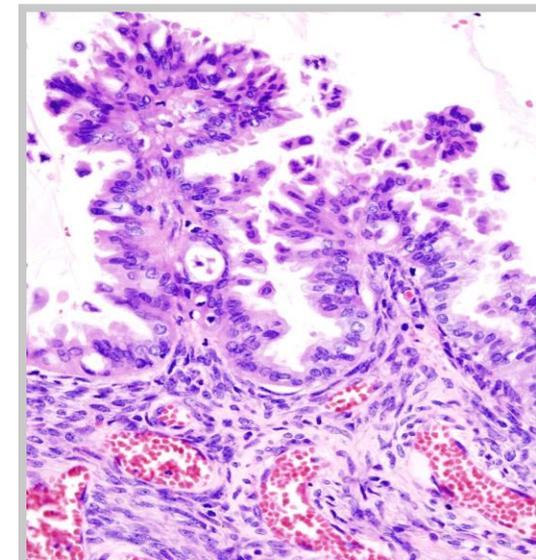


Type II

- high grade, poorly differentiated tumors
- may arise from tubal intraepithelial carcinoma
- biologically aggressive

Ovarian Borderline Tumors

- Also called low malignant potential (LMP) tumors or atypical proliferative tumors
 - Recent CAP protocols do not use “LMP”
- Usually occur in premenopausal women
- Cytologic characteristics of cancer but no definite invasion microscopically
- Usually early stage with overall good prognosis
- However, there can be metastatic implants with invasive components
- Borderline tumors can be serous or mucinous histology



Ovarian Carcinosarcomas

- Also called mixed Mullerian mesenchymal tumors (MMMT) contain both malignant epithelial and sarcomatous elements
- Clonality suggests that this is a metaplastic carcinomas, with both components arising from an epithelial precursor, and the sarcomatous component resulting from transdifferentiation

Ovarian Cancer Grade

- Serous ovarian cancer is either referred to as low grade (most grade 1) or high grade (most grade 2 or 3 tumors)
- Grades 1, 2, or 3 used for endometrioid, mucinous, and stage IC tumors.

Surgical Staging of Ovarian Cancer

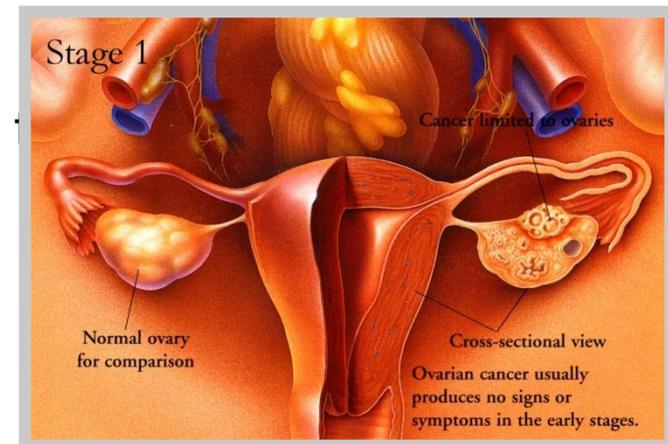
- Inspection of all peritoneal surfaces
- Pelvic washings
- Total abdominal hysterectomy, bilateral salpingo-oophorectomy
 - Fertility sparing surgery reasonable if appears confined to ovary
- Pelvic and aortic lymph node sampling
- Peritoneal biopsies (bladder, posterior cul de sac, pelvic sidewalls, colic gutters, diaphragm, and any suspicious lesions/adhesions)
- Omentectomy
- Appendectomy (if indicated)

Ovarian Cancer Staging

- Ovarian cancer is classified primarily as stages I to IV using FIGO (International Federation of Gynecology and Obstetrics) staging system
 - Included in AJCC Cancer Staging Manual 8th Edition and effective for all cancer cases recorded on or after January 1, 2018
- FIGO stage and grade are important considerations for prognosis and treatment recommendations
- Less common ovarian cancers (LCOC) are also staged using FIGO/AJCC (8th edition) ovarian cancer staging system

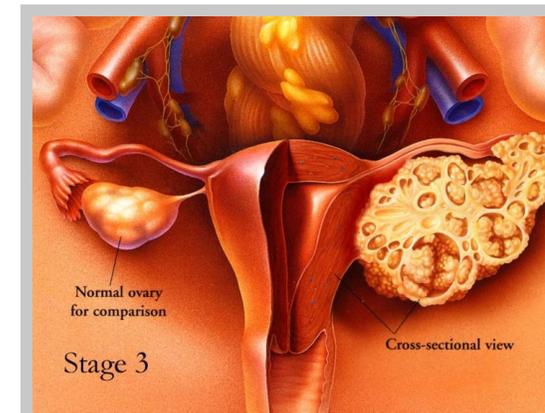
FIGO Ovarian Cancer Staging (TNM, AJCC 8th ed, 2017)

- Stage I (T1) — Tumor confined to ovaries
 - IA (T1a) — Tumor limited to one ovary; capsule intact; no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings
 - IB (T1b) — Tumor involves both ovaries; capsule intact; no tumor on ovarian surface; negative washings
 - IC (T1c) — Tumor limited to one or both ovaries
 - IC1 (T1c1) – Surgical Spill
 - IC2 (T1c2) – Capsule rupture before surgery or tumor on surface of ovary
 - IC3 (T1c3) – Malignant cells in the ascites or washings
- Stage II (T2) — Pelvic extension or implants
 - IIA (T2a) — Extension or implants on uterus and/or fallopian
 - IIB (T2b) — Extension or implants to other pelvic structures



FIGO Ovarian Cancer Staging (TNM, AJCC 8th ed, 2017)

- Stage III (T3) — Peritoneal implants outside of the pelvis and/or metastases to the retroperitoneal lymph nodes
 - IIIA — Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis
 - IIIA1 (N1) – Positive retroperitoneal lymph nodes only
 - IIIA1(i) (N1a) – Metastasis \leq 10 mm
 - IIIA1(ii) (N1b) – Metastasis $>$ 10 mm
 - IIIA2 (T3a) – Microscopic, extrapelvic (above the brim) peritoneal involvement with or without positive lymph node
 - IIIB (T3b) — Macroscopic, extrapelvic peritoneal \leq 2 cm in size, with or without positive lymph nodes (includes extension to capsule of liver/spleen)
 - IIIC (T3c) — Macroscopic, extrapelvic peritoneal $>$ 2 cm in size, with or without positive lymph nodes (includes extension to capsule of liver/spleen)
- Stage IV (M1) — Distant metastasis excluding peritoneal metastasis
 - IVA (M1a) – Pleural effusion with positive cytology
 - IVB (M1b) – Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)



- Surgery
 - 1) Comprehensive surgical staging versus cytoreductive surgery as indicated for Stages IA-IV followed by adjuvant chemotherapy; or
 - 2) Neoadjuvant chemotherapy with interval debulking surgery, followed by adjuvant chemotherapy for unresectable Stage IIIC-IV.
- Chemotherapy
 - 1) Multi-agent chemotherapy with 3-6 cycles of intravenous taxane/carboplatin for Stage 1A-C; or
 - 2) Intravenous or intraperitoneal taxane/carboplatin for 6 cycles for Stage II-IV.

Ovarian Cancer Survival

5-year Survival Rates

**<30% Localized
and Regional**

- Stage I
- Stage II

~80-95%

>70% Distant

- Stage III
- Stage IV

~28%

~50%

Chemotherapy

- Gold standard following debulking surgery is Platinum and Taxane based chemotherapy
- Response rate of 80%
- Tumors resistant to this combination are refractory to most other types of chemotherapy
- Despite this therapy and the upfront responsiveness, 70% of patients with Stage III disease will recur
- Nearly 100% of patients who have recurrent ovarian cancer will die from their disease

Better Bullet

- New combinations of chemotherapy (Carboplatin/Taxol and Avastin with/without PARP inhibition)
- Intraperitoneal chemotherapy offers a survival advantage for optimally debulked ovarian cancer
- Dose Dense Chemotherapy (weekly Taxol) also has a survival advantage over traditional therapy
- Both IP and dose dense chemotherapy have higher morbidity than standard therapy
- New agents under study (ie Parp inhibitors, immunotherapy, other targeted agents)

Recurrent Disease

- Chronic, relapsing disease
- Salvage chemotherapy (Doxil, Gemzar, Taxotere, Avastin etc) most utilized
- Most produce clinical responses, thereby, keep patients alive longer
- Women living on average 4 to 5 years with ovarian cancer
- Some live 8 to 9 years with the disease
- Inevitably, the cancer becomes resistant to chemotherapy and the patient dies of bowel obstruction and malnutrition

Recurrence, Clinical Considerations

1. Goals of management
2. Extent and nature of recurrence
3. Prior therapy – type and duration of response
4. Toxicity associated with prior treatment

NCCN Guidelines - OVARY



NCCN Guidelines Version 1.2020 Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

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PRINCIPLES OF SYSTEMIC THERAPY

Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)^j/Fallopian Tube/Primary Peritoneal Cancer^k

Recurrence Therapy for Platinum-Sensitive Disease^l (alphabetical order)

Preferred Regimens	Other Recommended Regimens ^r	Useful in Certain Circumstances
Carboplatin/gemcitabine ² ± bevacizumab ^{e,m,n,3} Carboplatin/liposomal doxorubicin ⁴ ± bevacizumab ^{e,5} Carboplatin/paclitaxel ⁶ ± bevacizumab ^{e,m,n,7} Cisplatin/gemcitabine ⁸ <u>Targeted Therapy (single agents)</u> Bevacizumab ^{e,m,9,10} Niraparib ^{o,11} Olaparib ^{p,12} Rucaparib ^{q,13}	Carboplatin/docetaxel ^{14,15} Carboplatin/paclitaxel (weekly) ¹⁶ Capecitabine Carboplatin ^{s,2} Cisplatin ⁶ Cyclophosphamide Doxorubicin <u>Targeted Therapy</u> Niraparib/bevacizumab ^{e,17} Pazopanib (category 2B) ¹⁸ <u>Hormone Therapy</u> Aromatase inhibitors (anastrozole, exemestane, letrozole) Leuprolide acetate Megestrol acetate Tamoxifen	Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Vinorelbine <u>Targeted Therapy (single agents)</u> Entrectinib or larotrectinib (for <i>NTRK</i> gene fusion-positive tumors) ^t Trametinib (for low-grade serous carcinoma) ²⁰ <u>Hormone Therapy</u> Fulvestrant (for low-grade serous carcinoma) <u>Immunotherapy</u> Pembrolizumab (for microsatellite instability-high [MSI-H] or mismatch repair-deficient [dMMR] solid tumors) ^{t,21}

NCCN Guidelines - OVARY



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PRINCIPLES OF SYSTEMIC THERAPY

Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)/Fallopian Tube/Primary Peritoneal Cancer^k

Recurrence Therapy for Platinum-Resistant Disease (alphabetical order)

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
<u>Cytotoxic Therapy</u> Cyclophosphamide (oral)/bevacizumab ^{e,22} Docetaxel ²³ Etoposide, oral ²⁴ Gemcitabine ^{25,26} Liposomal doxorubicin ^{25,26} Liposomal doxorubicin/bevacizumab ^{e,m,27} Paclitaxel (weekly) ²⁸ Paclitaxel (weekly)/bevacizumab ^{e,m,27} Topotecan ^{29,30} Topotecan/bevacizumab ^{e,m,27} <u>Targeted Therapy (single agents)</u> Bevacizumab ^{e,m,9,10} Niraparib ^{0,11} Olaparib ^{p,12} Rucaparib ^{q,13}	<u>Cytotoxic Therapy^f</u> Capecitabine Cyclophosphamide Doxorubicin Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Sorafenib/topotecan ³¹ Vinorelbine <u>Targeted Therapy (single agents)</u> Pazopanib (category 2B) ¹⁸ <u>Hormone Therapy</u> Aromatase inhibitors (anastrozole, exemestane, letrozole) Leuprolide acetate Megestrol acetate Tamoxifen	<u>Immunotherapy</u> Pembrolizumab (for MSI-H or dMMR solid tumors) ^{t,21} <u>Hormone Therapy</u> Fulvestrant (for low-grade serous carcinoma) <u>Targeted Therapy (single agents)</u> Entrectinib or larotrectinib (for <i>NTRK</i> gene fusion-positive tumors) ^t Trametinib (for low-grade serous carcinoma) ²⁰

A few notes:

- All patients with high grade serous ovarian cancer should see a genetic counselor and consider germline testing for BRCA testing
- NCCN guidelines support tumor molecular testing prior to initiation of therapy for persistent/recurrent disease, if not previously done
 - “Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Testing recommended to include at least: BRCA1/2, and microsatellite instability or DNA mismatch repair if not previously done. Evaluation of homologous recombination deficiency can be considered. Additional somatic tumor testing can be considered at the physician’s discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy option.”



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Endometrial Cancer

Endometrial Cancer

- Accounts for nearly 50% of new gynecologic cancers in the US
- 4th most common cancer in women in US
- 6th most common cause of cancer death in women in US
- 2017 estimates:
 - 61,380 new cases
 - 10,920 deaths

Estimated New Cases

		Males		Females		
Prostate	161,360	19%		Breast	252,710	30%
Lung & bronchus	116,990	14%		Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%		Colon & rectum	64,010	8%
Urinary bladder	60,490	7%		Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%		Thyroid	48,470	6%
Kidney & renal pelvis	40,610	5%		Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%		Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%		Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%		Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%		Kidney & renal pelvis	23,380	3%
All Sites	836,150	100%	All Sites	852,630	100%	

Estimated Deaths

		Males		Females		
Lung & bronchus	84,590	27%		Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%		Breast	40,610	14%
Prostate	26,730	8%		Colon & rectum	23,110	8%
Pancreas	22,300	7%		Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,610	6%		Ovary	11,888	6%
Leukemia	14,300	4%		Uterine corpus	10,920	4%
Esophagus	12,720	4%		Leukemia	10,200	4%
Urinary bladder	12,240	4%		Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%		Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%		Brain & other nervous system	7,080	3%
All Sites	318,420	100%	All Sites	282,500	100%	

Siegel R et al. CA: A Cancer Journal for Clinicians, 67 (1): 7-30, 5 JAN 2017

Endometrial Cancer

- **Average age of onset is 60 years**
 - Most common in sixth and seventh decade
 - 75-85% occur in women 50 years and older
 - Rare in women younger than 30, reported in patients as young as 16
- **Most common in Caucasian women**
 - African American women have a 40% lower risk of developing disease, but 54% greater risk of dying from disease

Endometrial cancer is one of the “good cancers”...

Most women are diagnosed with disease confined to the uterus

- 73% are stage I
- 10% are stage II
- 5-year survival reported as high as 96% in patients with localized disease



Two types of endometrial cancer

	TYPE 1 (70-80%)	TYPE 2 (10-20)
Molecular alterations	Microsatellite instability and mutations in PTEN (80%), PIK3CA, K-ras, β -catenin	P53 mutations (90%), HER2/neu amplification and overexpression
Hormone sensitivity	Yes – related to obesity, estrogen excess	No - arises from endometrial atrophy
Precursor lesion	Hyperplasia	Endometrial intraepithelial neoplasia
Histologic grade	Low	High
Histologic subtype	Endometrioid	Serous, clear cell
Behavior	Favorable	Aggressive
5-year survival	85%	43%

Risk factors

• Nulliparous	2x
• Late menopause	2.4x
• Diabetes	2.8x
• HTN	1.5x
• Obesity >30lbs	3x
• Obesity >50lbs	10x
• Unopposed estrogen	9.5x
• Tamoxifen*	2-3x

Diagnosis

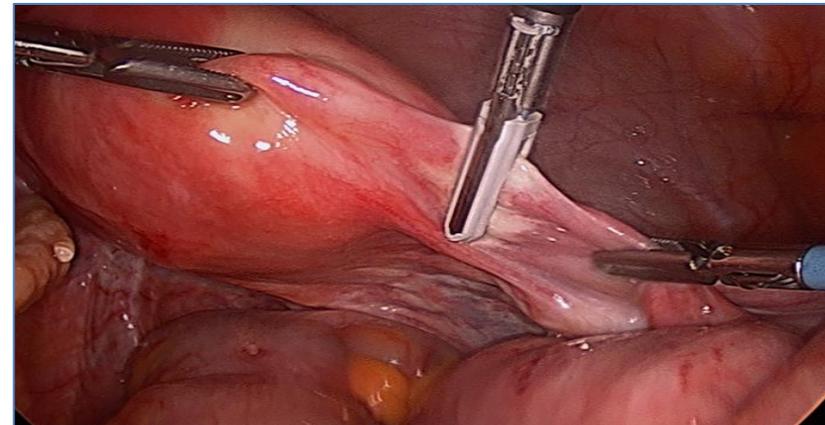
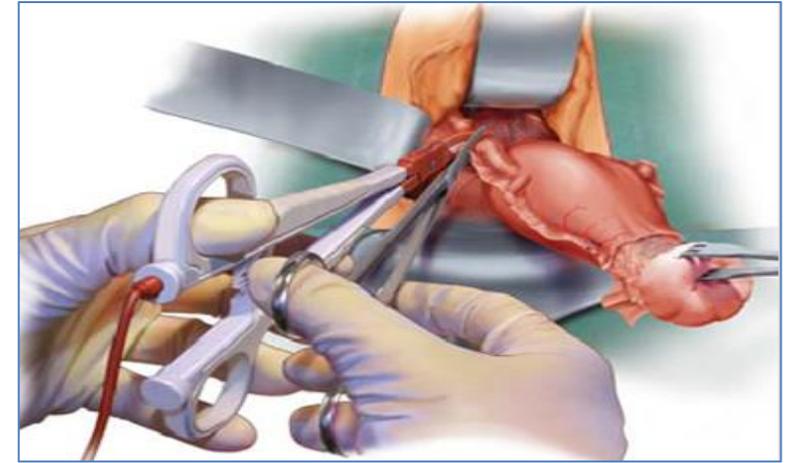
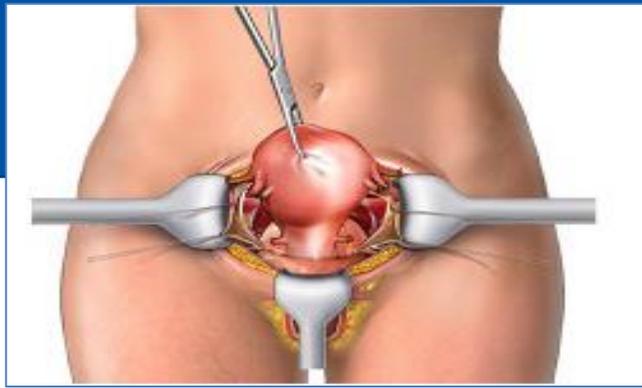
- Endometrial biopsy
- Dilatation and curettage (D&C)
 - 90% accuracy in detecting endometrial cancer
- Vaginal ultrasound
 - Endometrial thickness (ET) evaluated in 205 **postmenopausal** women
 - No cancers detected with an ET < 5 mm
 - PPV 87%, Sensitivity 100%, Specificity 96%

Surgical staging

- Total hysterectomy, bilateral salpingo-oophorectomy
- Pelvic and aortic lymphadenectomy
- For serous cancers - omentectomy, peritoneal biopsies and washings

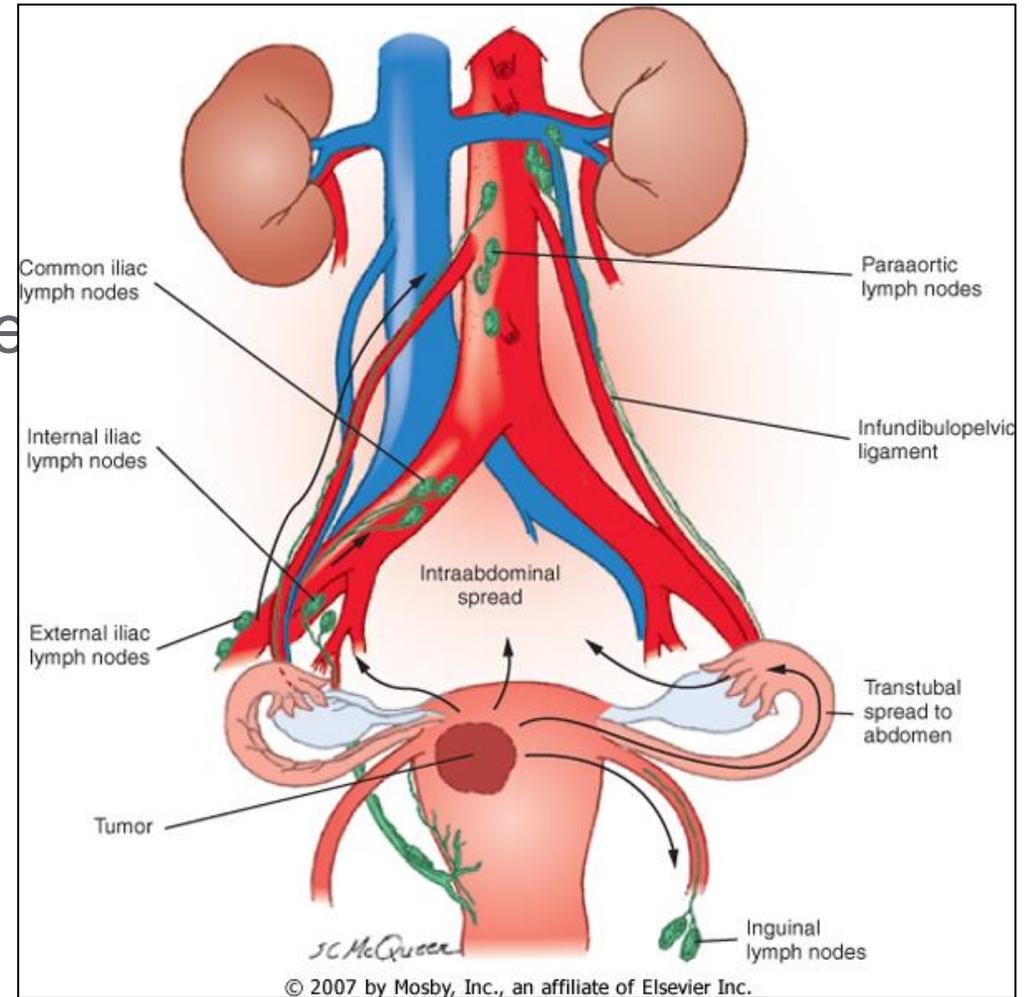
Surgical approach

- Laparotomy
- Vaginal
- Minimally-invasive
 - Laparoscopy
 - Robotic surgery



FIGO staging, 2010 (AJCC)

- Stage I (T1): confined to uterus
 - IA (T1a): inner ½
 - IB (T1b): outer ½
- Stage II (T2): cervical stromal involvement
- Stage III (T3): extra-uterine spread
 - IIIA (T3a): serosal/adnexal involvement
 - IIIB (T3b): vaginal/parametrial involvement
 - IIIC1 (N1a): pelvic nodal involvement
 - IIIC2 (N2a): aortic nodal involvement
- Stage IV: regional, distant metastases
 - IVA (T4): bowel or bladder mucosa
 - IVB (M1): distant metastases



Primary treatment

- **Surgery**
- **Radiation**
 - Medically inoperable
 - 15% survival decrement per stage
 - Most die of other causes
- **Hormonal therapy**
 - May consider for young women who desire future fertility
 - Only appropriate in grade 1 cancers without evidence of myometrial invasion
 - MRI most sensitive to detect myometrial invasion
 - CT to rule out metastatic disease
 - Tumor must be hormone receptor positive
 - Megace 80-100 mg BID
 - Resample with D&C in 3 months – if persistent disease at 6-9 months, consider hysterectomy

Adjuvant treatment after primary surgery

- **Low-risk** endometrial cancer
 - Grade 1, confined to the endometrium
 - Risk of recurrence is very low following surgical treatment alone
- **Intermediate-risk** endometrial cancer
 - Confined to uterus, invades the myometrium or occult cervical stromal invasion
 - Adverse prognostic factors define low and high-intermediate-risk patients
 - deep myometrial invasion
 - grade 2 or 3 differentiation
 - presence of lymphovascular invasion within the cancer
- **High-risk** endometrial cancer
 - Stage III or higher, regardless of histology or grade, or serous or clear cell carcinoma, regardless of stage
 - High risk of relapse and death

Defining a high-intermediate risk (HIR) group

HIGH-INTERMEDIATE RISK

Age ≥ 70 with one risk factor

Age ≥ 50 with two risk factors

Age ≥ 18 with three risk factors

Risk Factors:

- Grade 2 or 3 tumor
- (+) lymphovascular space invasion
- Deep myometrial invasion

- Approximately one-third of the patients fall into HIR group
- HIR group represents 2/3 of recurrences and 2/3 of all cancer related deaths in GOG #99
- Cumulative incidence of recurrence for HIR group is 26%

Adjuvant treatment High-intermediate risk group

- Radiation therapy reduces the risk of local recurrence, but does not improve overall survival (GOG 99)
 - Pelvic radiation resulted in a reduction in local recurrence
 - 2 versus 9%, HR 0.42, CI 0.21 – 0.83
 - No statistically significant reduction in risk of death
 - HR 0.73, 90% CI 0.43-1.26
- Radiation therapy can be administered as vaginal brachytherapy, pelvic RT, or intensity-modulated RT

Adjuvant treatment High risk endometrial cancer

- Lack of a uniform approach to the treatment of women with high-risk endometrial cancer
- Generally, patients with extra-uterine disease confined to the pelvis or vagina (stage III) are treated with chemotherapy
 - Adjuvant chemotherapy is associated with improvement in both PFS and OS, regardless of whether RT is used

Choice of chemotherapy

High risk endometrial cancer

Carboplatin and paclitaxel is the standard-of-care

- GOG 209 compared carboplatin plus paclitaxel with TAP
 - 1300 women with chemotherapy-naïve advanced endometrial cancer, including women with stage III disease
 - carboplatin and paclitaxel results in an equivalent overall response rate, similar PFS, and is also less toxic

Combined modality treatment High risk endometrial cancer

- Combined modality approach may be considered in some patients
 - Radiation after completion of six cycles of chemotherapy
 - RT “sandwiched” in between three cycles of chemotherapy before and after radiation treatment
 - Chemoradiation therapy followed by systemic chemotherapy as in RTOG 9708
- Radiation adds toxicity to chemotherapy but has been shown to be feasible in multiple studies.

NCCN Guidelines - Endometrial



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NCCN Guidelines Version 1.2020 Endometrial Carcinoma

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SYSTEMIC THERAPY FOR RECURRENT, METASTATIC, OR HIGH-RISK DISEASE

<p><u>Chemotherapy Regimens^{a,b}</u></p> <p><u>Preferred Regimens</u></p> <ul style="list-style-type: none"> • Carboplatin/paclitaxel (category 1 for carcinosarcoma)¹ • Carboplatin/paclitaxel/trastuzumab^c (for stage III/IV or recurrent HER2-positive uterine serous carcinoma)² <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> • Carboplatin/docetaxel^d • Cisplatin/doxorubicin³ • Cisplatin/doxorubicin/paclitaxel^{e,f,3} • Carboplatin/paclitaxel/bevacizumab^{e,g,4} • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel⁵ • Albumin-bound paclitaxel^h <p><u>Useful In Certain Circumstances</u></p> <ul style="list-style-type: none"> • Pembrolizumab^l (for MSI-H/dMMR tumors) • Larotrectinib or entrectinib for <i>NTRK</i> gene fusion-positive tumors (category 2B)^e 	<p><u>Adjuvant Treatment When Used for Uterine-Confined Disease</u></p> <p><u>Preferred Regimens</u></p> <ul style="list-style-type: none"> • Carboplatin/paclitaxel <p><u>Hormone Therapy^m</u></p> <p><u>Preferred Regimens</u></p> <ul style="list-style-type: none"> • Medroxyprogesterone acetate/tamoxifen (alternating) • Megestrol acetate/tamoxifen (alternating) • Progestational agents <ul style="list-style-type: none"> ▶ Medroxyprogesterone acetate ▶ Megestrol acetate ▶ Levonorgestrel intrauterine device (IUD) (for select fertility-sparing cases) • Aromatase inhibitors • Tamoxifen • Fulvestrant <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> • Everolimus/letrozole (for endometrioid histology)
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Mesenchymal tumors of the uterus

- Malignant mesenchymal tumors:
 - uterine leiomyosarcoma (uLMS) – 63%
 - endometrial stromal sarcoma (ESS) – 21%
 - undifferentiated uterine sarcoma (UUS) – less common
 - rarer subtypes: adenosarcoma, rhabdomyosarcoma, PEComa
- Carcinosarcomas considered and treated as high grade epithelial tumors (metaplastic carcinomas)

Uterine sarcomas: histologies and prognosis

Good	Bad	Really, Really Bad
Endometrial Stromal Sarcoma	Leiomyosarcoma	High Grade Undifferentiated Sarcoma
Adenosarcoma	Carcinosaroma	Adenosarcoma with Sarcomatous Overgrowth

Staging Sarcomas (LMS, ESS, Adenosarcoma)

Stage I: Tumor confined to uterus

- LMS/ESS
 - IA Tumor <5cm
 - IB Tumor ≥5cm
- Adenosarcomas
 - IA Tumor limited to endometrium
 - IB Invasion to <1/2 myometrium
 - IC Invasion to >1/2 myometrium

All

Stage II: Pelvic extension

- IIA Adnexal Involvement
- IIB Extension to extrauterine pelvic tissue

Stage III: Abdominal metastases

- IIIA Abdominal mets, one site
- IIIB Abdominal mets, >one site
- IIIC Mets to pelvic and/or para-aortic nodes

Stage IV: Distant metastases

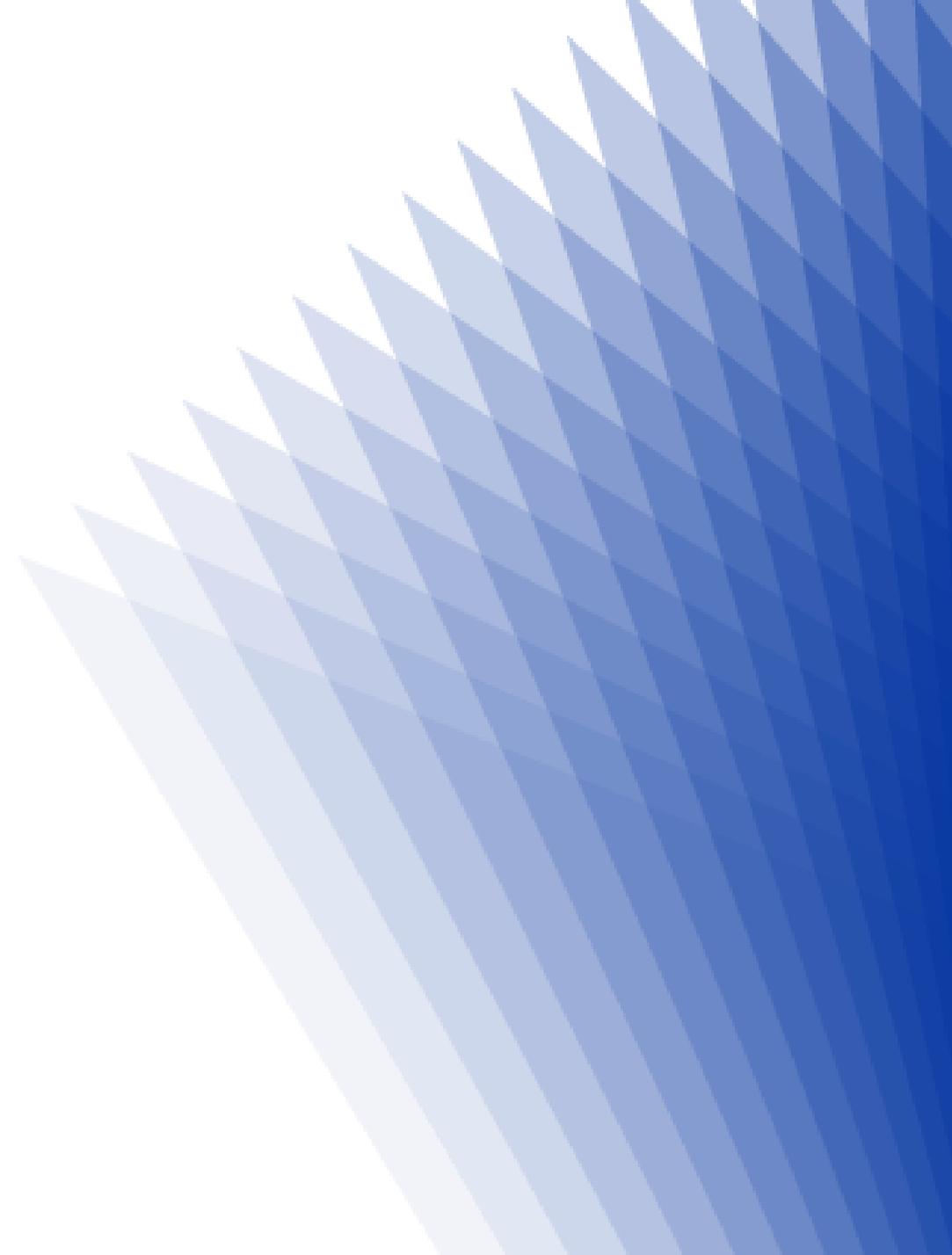
- IVA Extension to bladder and/or rectal mucosa
- IVB Distant mets



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An NCI-Designated Cancer Center

Cervical Cancer



Cervical Cancer

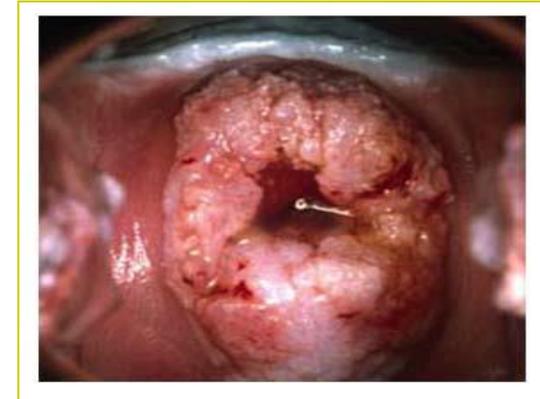
- 3rd most common cancer among women world wide
- Estimated 475,000 new cases
 - 250,000 deaths annually worldwide
- 12th most common cancer among women in the United States
- Estimated 12,360 new cases each year
 - 4,020 deaths annually from cervical cancer

Who Develops Cervical Cancer?

- 50% of women diagnosed with cervical cancer have not had a Pap test in 5 years
- 25% of all cervical cancers are diagnosed in women older than 65
- In women older than 65, it is estimated that over 50% have not had a Pap test in the past 10 years
- Bottom Line – most women with cervical cancer did not get Pap tests

Cervical Cancer Presenting Symptoms

- Early stages
 - Abnormal vaginal bleeding
 - Post-coital bleeding
 - Malodorous vaginal discharge
- Locally advanced
 - Ureteral or bladder outlet obstruction (and resultant symptoms)
- Regional LN involvement:
 - Back pain
 - Unilateral leg swelling
 - Neuropathic pain



Classic Risk Factors for Cervical Cancer

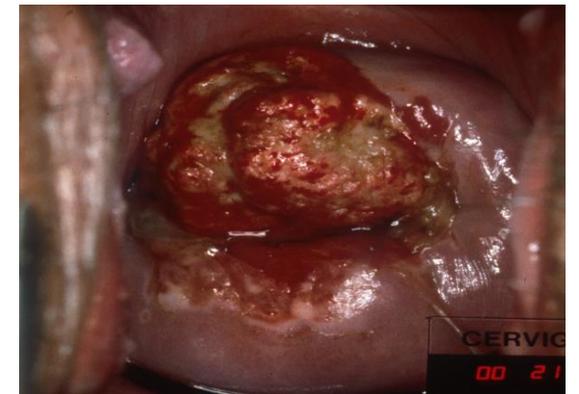
- Early first age of sexual contact
- Multiple sexual partners
- Smoking
- Multiple sexually transmitted diseases
- Immunocompromised
- Lower socio-economic class
- Family history is **not** a risk factor

Main Risk Factors for Cervical Cancer

- Human papillomavirus (HPV) is the cause of cervical cancer
- Estimated that 80% of men and women will have been exposed to the virus by the age of 50
- Smoking is an important cofactor for malignant transformation

Cervical Cancer Staging

- In 2018, the International Federation of Gynecology and Obstetrics (FIGO) expanded the list of tests and procedures that may be used in assigning stage to include imaging and pathologic findings where available
- Lymph node metastases are now included
- Still considered clinical staging since invasive surgery is not required
- Changes aim to improve the ability of stage to predict prognosis and plan treatment



Cervical cancer staging, FIGO 2018

Stage I Carcinoma confined to cervix

- **IA** Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm
 - IA1 Stromal invasion less than 3mm
 - IA2 Stromal invasion of 3mm but less than 5mm
- **IB** Invasive carcinoma with measured deepest invasion ≥ 5 mm (greater than Stage IA), lesion limited to the cervix
 - **IB1** Invasive carcinoma ≥ 5 mm depth of stromal invasion, and <2 cm in greatest dimension
 - **IB2** Invasive carcinoma ≥ 2 cm and <4 cm in greatest dimension
 - **IB3** Invasive carcinoma ≥ 4 cm in greatest dimension

Cervical cancer staging, FIGO 2018

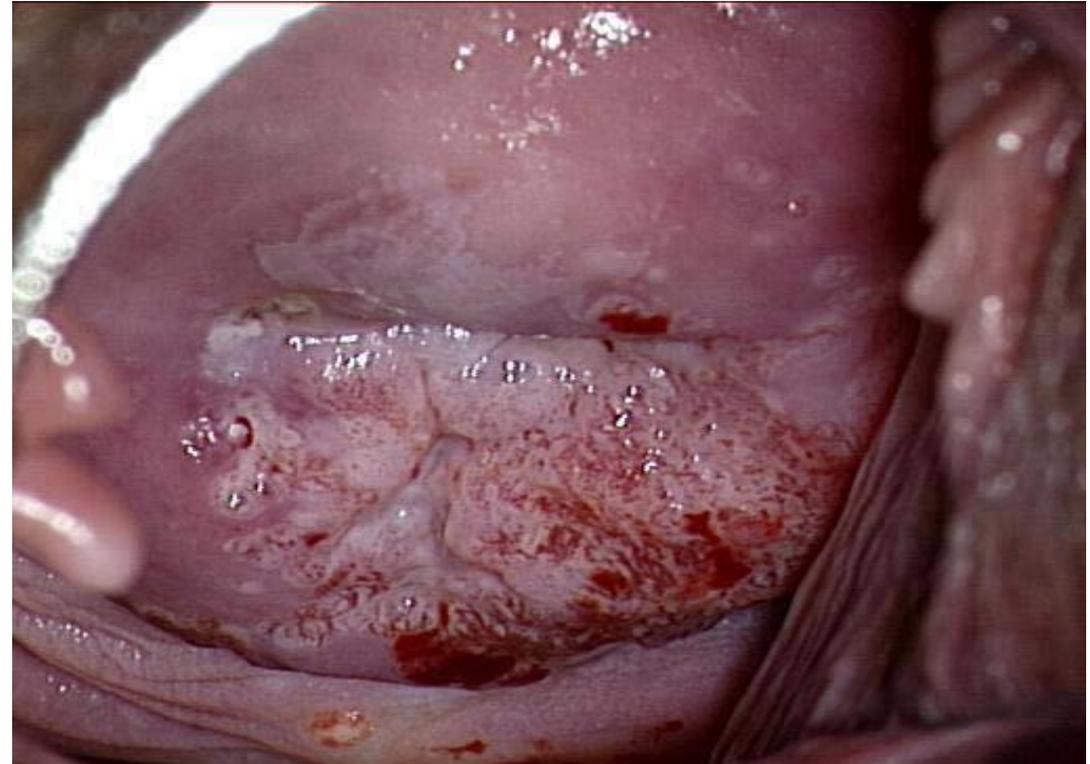
- **Stage II** Invades beyond uterus, but not to pelvic wall or lower 1/3 vagina
 - **IIA** Upper 2/3 vagina without parametrial involvement
 - **IIA1** Invasive carcinoma <4 cm in greatest dimension
 - **IIA2** Invasive carcinoma ≥4 cm in greatest dimension
 - **IIB** With parametrial involvement, but not to pelvic sidewall
- **Stage III** Involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes
 - **IIIA** Involves lower 1/3 vagina, no extension to sidewall
 - **IIIB** Extends to pelvic wall and/or hydronephrosis
 - **IIIC** Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)
 - **IIIC1** Pelvic lymph node metastasis only
 - **IIIC2** Para-aortic lymph node metastasis
- **Stage IV** The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum
 - **IVA** Invades mucosa of bladder or rectum, and/or extends beyond true pelvis (bullous edema does not count)
 - **IVB** Distant mets

Cell Types

- Squamous (90%)
 - Large cell keratinizing
 - Large cell non-keratinizing
- Adenocarcinoma (10%)
 - Incidence is increasing ~30%
- Adenosquamous
- Small cell
 - Neuroendocrine tumor

Survival Rates

- IA 93%
- IB 80%
- IIA 63%
- IIB 58%
- IIIA 35%
- IIIB 32%
- IVA 16%
- IVB 15%



Management Carcinoma in situ

- Cold knife conization
- Extradascial hysterectomy
- Intracavitary radiation (for medically ill)
 - No need for pelvic RT since no risk of (+) LN

Treatment

Stage IA1

1. Conization with post-cone ECC
2. Extrafascial hysterectomy

Stage IA2 – IB1

1. Radical trachelectomy/LND
2. Modified radical hysterectomy/LND

Stage IB2

1. Modified radical hysterectomy/LND
2. Chemoradiation therapy followed by extrafascial hysterectomy

Radical Hysterectomy

- Objective is to remove the cervical cancer, uterus and tissue adjacent to the uterus:
 - Parametrial tissue
 - Complete pelvic lymphadenectomy (internal, external, common iliac nodes and obturator nodes)
 - Upper 2 cm of the vagina
 - Higher morbidity than a simple hysterectomy



Treatment

- Stages II-IVB receive radiation (XRT) and chemotherapy
- XRT given in two phases
- 1st 5-6 weeks of external beam radiation
 - Total dose 45 to 50 Gy
 - Or 180 to 200 cGy each day
 - Cisplatin 40 mg/m² Q week
- 2nd Brachytherapy
 - HDR or LDR
 - Positions a radioactive implant adjacent to the carcinoma

Advanced/ Recurrent disease

- Main stay is chemotherapy
- Advanced (IVA & IVB) palliative XRT and chemo
- Recurrent- chemotherapy
- Cisplatin/Taxol/Avastin

NCCN Guidelines - CERVIX



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 1.2020 Cervical Cancer

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SYSTEMIC THERAPY REGIMENS FOR CERVICAL CANCER^a

Chemoradiation		
<p>Preferred Regimens</p> <ul style="list-style-type: none"> • Cisplatin • Carboplatin if patient is cisplatin intolerant 		
Recurrent or Metastatic Disease		
First-line combination therapy ^{b,c}	Possible first-line single-agent therapy ^c	Second-line therapy ^e
<p>Preferred Regimens</p> <ul style="list-style-type: none"> • Cisplatin/paclitaxel/bevacizumab^{d,1} (category 1) • Carboplatin/paclitaxel/bevacizumab^d <p>Other Recommended Regimens</p> <ul style="list-style-type: none"> • Cisplatin/paclitaxel (category 1)^{2,3} • Carboplatin/paclitaxel^{4,5} (category 1 for patients who have received prior cisplatin therapy) • Topotecan/paclitaxel/bevacizumab^{d,1} (category 1) • Topotecan/paclitaxel¹ • Cisplatin/topotecan⁶ 	<p>Preferred Regimens</p> <ul style="list-style-type: none"> • Cisplatin³ <p>Other Recommended Regimens</p> <ul style="list-style-type: none"> • Carboplatin⁷ • Paclitaxel^{8,9} 	<p>Preferred Regimens</p> <ul style="list-style-type: none"> • Pembrolizumab for PD-L1–positive^f or MSI-H/dMMR tumors⁹ <p>Other Recommended Regimens (All agents listed here are category 2B unless otherwise noted)</p> <ul style="list-style-type: none"> • Bevacizumab^d • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Ifosfamide • Irinotecan • Mitomycin • Pemetrexed • Topotecan • Vinorelbine <p>Useful in Certain Circumstances</p> <ul style="list-style-type: none"> • Larotrectinib or entrectinib for <i>NTRK</i> gene fusion-positive tumors (category 2B)



Division of Gynecologic Oncology



Thank You!



