

Overview of Gynecologic Oncology

"The Blue Book"

R. Kevin Reynolds, MD
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www.med.umich.edu/obgyn/gynonc

Gyn Oncology.....734-764-9106
Cancer Center Answer Line800-865-1125

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Special thanks to William Burke, MD, and to Catherine Christen, PharmD

Favorite Quotes

"Statistics are no substitute for judgment."
Henry Clay

"A leading authority is anyone who has guessed right more than once."
Frank A. Clark

"Well done is better than well said."
Ben Franklin

"Trust me. I'm a doctor"
Donald H. Chamberlain, MD

"To err is human; to repeat the error is sometimes cause for concern."
"Good surgery is like a ballet!"
George W. Morley, MD

"Try not. Do or do not. There is no try."
Yoda

"If your ship doesn't come in, swim out to it."
Jonathan Winters

Breast Cancer

I. Incidence: Most common cancer of women in US. 212,000 new cases in 2006, with 40,970 deaths (Jemal). Incidence increasing 1-2% annually. Average lifetime risk of developing breast cancer is 10%.

II. Epidemiology

A. Risk factors

1. Cumulative Likelihood of Developing Breast Cancer, By Age And Risk Factors

Age	Relative Risk Coefficient			Risk Factors
	1	2	5	
20-40	0.5%	1.0%	2.5%	1 Menarche \geq 14y, no breast biopsies, first birth \leq 20y, no first degree relatives with breast cancer
20-50	1.7%	3.4%	8.3%	
30-50	1.7%	3.3%	8.1%	
30-60	3.2%	6.3%	14.9%	2 One first degree relative with breast cancer first birth \geq 30y, menarche $<$ 12y, one prior breast biopsy
40-60	2.8%	5.5%	13.1%	
40-70	4.4%	8.6%	20.0%	
50-70	3.2%	6.4%	15.1%	5 Two first degree relatives with breast cancer, one relative with breast cancer and one prior breast biopsy
50-80	4.4%	8.5%	19.9%	
60-80	3.0%	5.9%	14.0%	

Assumes well screened population

2. Risk of positive family history, between ages 30-70

Mother or Sister's Lesion	Risk
Premenopausal, unilateral	7%
Postmenopausal, unilateral	18%
Premenopausal, bilateral	51%
Postmenopausal, bilateral	25%

3. Other risk factors: endometrial/ovarian cancer, prior radiation exposure, atypical benign breast disease (ductal or lobular hyperplasia), obesity, low parity, early menarche, high socioeconomic status

B. Etiology. Estrogen, progesterone, prolactin implicated. Two temporal sets of etiologies:

1. Premenopausal cancers influenced by genetic linkage, and ovarian-pituitary dysfunction. Several pedigrees exist: site specific, breast-ovary, and Lynch II family cancer syndrome. Genes BRCA-1 and BRCA-2 implicated in many familial cases
2. Postmenopausal cancers influenced by obesity, dietary fat intake, and hormones.

III. Pathology

A. Benign lesions

1. Nipple discharge. Present in 75% of women. Discharge associated with: duct ectasia (green); benign intraductal papilloma and cancer (serous or bloody). Likelihood of cancer: serous discharge (6%), bloody discharge (13-20%). Evaluate suspicious discharge with ductogram and excision. Cytology rarely helpful.
2. Fibrocystic change. Present in up to 75% of women. No longer considered an accurate diagnostic term.
3. Cysts. Common during reproductive years. Probably develop due to estrogen. Evaluate palpable mass by FNA. If clear fluid obtained without residual mass, then repeat exam in 1 month. If bloody fluid obtained, or if mass persists, submit cytology specimen, order mammogram, and perform biopsy.
4. Fibroadenoma. Most common benign tumor of breast. Peak incidence age 20-30. Usually firm, well circumscribed, and solitary. FNA often diagnostic. Phylloides tumors can mimic fibroadenoma. Lobular CIS reported in these tumors occasionally. Biopsy appropriate.

2. Papilloma, intraductal. Associated with bloody discharge. Palpable subareolar lesions in 30%. Evaluate with ductogram and excision. B. Premalignant lesions. May be either precursors or marker lesions.

B. In-Situ Lesions

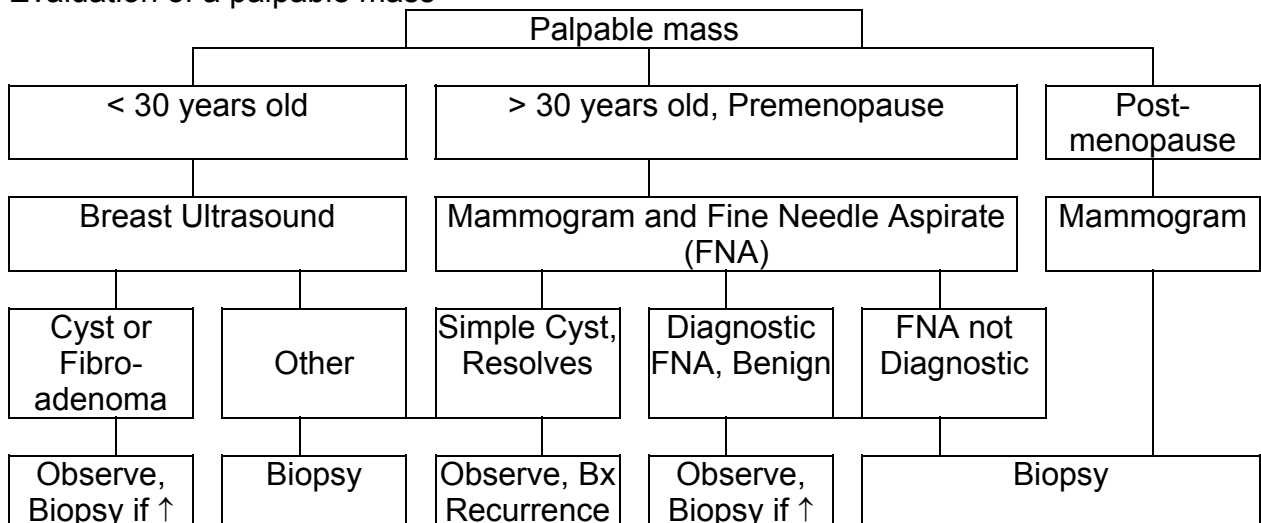
1. Ductal carcinoma in situ. Average age 55y. Represents 10-20% of new breast cancers. Often multifocal: up to 60% have residual DCIS after biopsy, 12% associated with cancer in contralateral breast, and 21-30% associated with cancer in ipsilateral breast. Lifetime breast cancer risk increased 10x. Treatment controversial. Options include excision +/- radiation, or mastectomy.
2. Lobular carcinoma in situ. Average age 45y. Usually an incidental finding (not detected on clinical or mammogram exam) in premenopausal women. Multifocal: 60-90% have residual LCIS after biopsy, 30-50% associated with LCIS in contralateral breast, and 25% associated with cancer in either breast (usually ductal). Treatment controversial. Options include bilateral mastectomy, or excision with close followup.

C. Malignant lesions

1. Ductal carcinoma
 - a. Infiltrating ductal carcinoma: 80% of breast cancers (53% pure, 28% mixed ductal patterns). Arise in myoepithelial cells around duct. Marked desmoplastic response can cause skin dimple or nipple retraction. In inflammatory carcinoma, a poor-prognosis subtype, dermal lymphatics contain tumor.
 - b. Comedocarcinoma: 5% of breast cancers. Predominantly intraductal tumor.
 - c. Medullary carcinoma: 6% of breast cancers. Arise in ductal epithelium. Tumors bulky, soft, often necrotic. Less likely to spread than infiltrating ductal tumors. Prognosis good (85-90% 5y survival).
 - d. Papillary carcinoma: < 1% of breast cancers. Commonly involves multiple ducts.
 - e. Colloid carcinoma: < 1% of breast cancers. Bulky, gelatinous, mucin-containing tumors with relatively good prognosis.
2. Lobular carcinoma: 5% of breast cancers. Arise in acinar cells and terminal ducts. Usually multicentric.
3. Paget's disease: 2% of breast cancers. Arises from mammary ducts. Clinical appearance of eczematoid nipple.
4. Sarcoma: < 1% of breast cancers. Cystosarcoma phylloides has benign and malignant types, and is most common sarcoma of breast. Metastases rare. Treatment usually simple mastectomy.

IV. Diagnosis

A. Evaluation of a palpable mass



B. Screening

1. Breast examination. Most breast cancers present as palpable mass. 10-15% of cancers detectable only by clinical exam. Best to examine shortly after menses.
2. Mammography
 - a. Recommended frequency (ACS): Baseline exam between 35-40y. Every other year between ages 40-50. Annually after age 50. Only 25-35% of women are currently screened following the guidelines. Ultrasound more effective for women < 35y.
 - b. Efficacy: 42% of breast cancers detectable only by mammography. Regularly screened women have 30-40% less breast cancer mortality, and 25% fewer cases are advanced stage at diagnosis. False negative rate 10-15%.
 - c. Technique: Breasts compressed. Radiation dose 0.1cGy. Cancers typically have irregular contour or calcifications of variable size or linear arrangement.

V. Staging

American Joint Committee on Cancer TNM Clinical Breast Cancer Staging System, 2002

Tx	Primary tumor not assessable
T0	No evidence of primary tumor
Tis	Carcinoma in situ. DCIS Ductal carcinoma in situ LCIS Lobular carcinoma in situ Paget's disease if no underlying tumor present
T1	Tumor ≤ 2cm
mic	Microinvasion ≤ 0.1 cm
a	Tumor ≤ 0.5 cm
b	Tumor > 0.5 cm, and ≤ 1cm
c	Tumor > 1cm, and ≤ 2cm
T2	Tumor > 2cm, and ≤ 5cm
T3	Tumor >5cm. May include invasion of pectoral fascia or muscle
T4	Any size with direct extension to chest wall or skin
a	Extension to chest wall not including pectoralis muscle
b	Edema (including <i>peau d'orange</i>), ulceration, or ipsilateral satellite nodules
c	Both T4a and T4b
d	Inflammatory carcinoma

Nx	Regional lymph nodes not assessable
N0	No regional lymph node involvement
N1	Metastases to movable ipsilateral axillary nodes
N2 a	Metastases to fixed or matted ipsilateral axillary nodes
b	Metastases to clinically apparent (exam or imaging) ipsilateral internal mammary nodes in the absence of axillary nodes
N3 a	Metastases to ipsilateral infraclavicular lymph nodes without axillary or internal mammary nodes
b	Metastases to ipsilateral internal mammary and ipsilateral axillary nodes
c	Metastases to ipsilateral supraclavicular lymph nodes

<u>Pathologic (pN)</u> based on axillary dissection. If sentinel nodes done, denote with (sn)	
	postscript
pNx	Regional nodes cannot be assessed (previously removed or not removed)
pN0	No regional lymph node metastases, no additional exam for isolated tumor cells (ITC) ITC defined as individual tumor cells or clusters ≤ 0.2 mm detected by immunohistochemistry (IHC), molecular methods or histologic verification. Usually no evidence of proliferation or stromal reaction
pN0(i -)	No regional lymph node metastases, negative IHC
pN0(i +)	No histologic evidence of regional lymph node metastases, positive IHC, no IHC clusters > 0.2 mm
pN0(mol -)	No regional lymph node metastases, negative molecular findings with reverse transcriptase polymerase chain reaction (RT-PCR)
pN(mol +)	No regional lymph node metastases, positive molecular findings with reverse transcriptase polymerase chain reaction (RT-PCR)
pN1	Metastases in 1-3 axillary nodes, and/or internal mammary nodes with microscopic disease detected by sentinel node dissection without clinically apparent disease on exam or imaging
mi	Micrometastasis > 0.2 mm and ≤ 2 mm
a	Micrometastases in 1-3 axillary nodes
b	Metastases in internal mammary nodes with microscopic disease detected by sentinel node dissection but not clinically apparent
c	Metastases in axillary and internal mammary nodes with microscopic disease detected by sentinel node dissection but not clinically apparent
pN2	Metastases in 4-9 axillary nodes or in clinically apparent internal mammary nodes in the absence of axillary node metastases
a	Metastases in 4-9 axillary nodes with at least one tumor deposit of > 2 mm
b	Metastases clinically apparent internal mammary nodes in the absence of axillary node metastases
pN3	Metastases in ≥ 10 axillary nodes, or in infraclavicular nodes, or in clinically apparent internal mammary nodes in the presence of ≥ 1 axillary node metastases; or in > 3 axillary nodes with internal mammary node micrometastases; or supraclavicular node metastasis
a	Metastases in ≥ 10 axillary nodes with at least one tumor deposit of > 2 mm, or in infraclavicular nodes
b	Metastases in clinically apparent internal mammary nodes in the presence of ≥ 1 axillary node metastases; or in > 3 axillary nodes with internal mammary micrometastases that are clinically inapparent
c	Metastases in ipsilateral supraclavicular nodes
Mx	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases present

Note: regional lymph nodes include axillary and ipsilateral internal mammary nodes. The axillary nodes are divided into 3 groups: Level I nodes are lateral to pectoralis minor muscle, Level II nodes are between lateral and medial border of pectoralis minor (Rotter's nodes), and Level III nodes are medial to pectoralis minor including subclavicular, infraclavicular and apical nodes. Metastases to other nodes, including cervical, and contralateral internal mammary nodes are considered distant (M1).

VI. Treatment

Treatment for breast cancer is complex and rapidly evolving. Full discussion of this topic is beyond the scope of this monograph. Continually updated management guidelines can be accessed through the National Comprehensive Cancer Network at www.nccn.org

References

Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ. Cancer statistics, 2006.
CA Cancer J Clin 2006; 56: 106-30
Breast Cancer Guidelines. www.nccn.org

Cervical Cancer

I. Incidence: Second most common cancer of women, worldwide. 12th most common cancer of women and 3rd most common gyn malignancy in USA. 9,710 cases, and 3700 deaths in 2006 in USA (Jemal)

II. Epidemiology:

A. Falling incidence 1940 to 1986. Rising since 1986 for Caucasian women

B. Table of Relative Risks (Morrow, Wright in Hoskins) RR

Age at coitarche (years)	<16 vs >19	16
	16-19 vs >19	3
Menarche-coitarche interval (years)	<1 vs >10	26
	1-5 vs >10	7
	6-10 vs >10	3
Sexual partners (# before age 20)	>4 vs 0-1	4
Genital Warts		3
Smoker > .25 PPD, >20 years vs < 1 yr		4
HPV detectable on exam	Varies by HPV type	4-40
OCP, long term use		1.5-2
Deficient carotene, vitamin C (Verreault)		2-3

Increased risk: lack of screening or screening interval too long (Hartmann, Shy), immunosuppression (HIV, pharmacologic), black, poor, hi-risk male (multiple sexual partners, uncircumcised with poor hygiene)

Decreased risk: barrier contraceptives, religious social behavior

C. Etiology: cervical cancer is a sexually transmitted disease (Wright in Hoskins)

1. Human Papillomavirus (HPV) DNA detectable > 95% of squamous cervical cancers, and many adenocarcinomas (30-40%). Types 16, 18, 31, 45 (and less common types 33, 35, 39, 51, 52, 54, 55, 56, 58, 59, 66, 68) more frequently associated with malignancy than 6, 11 more often seen with condyloma. Possible co-carcinogens: nicotine, herpes
2. HPV is circular, double-strand DNA virus of about 8kb with eight open reading frames, when in its infectious state and in condyloma. Viral DNA inserts into host genome when progression to malignant phenotype occurs. HPV E6 gene codes for a protein that degrades p53 and HPV E7 gene codes for a protein which complexes with pRB, thereby releasing transcription factor E2F. The cell is immortalized.
3. Invasion is the endpoint of disease beginning as dysplasia, progressing through various stages of CIN. Incidence of progression: CIN-1 (16%), CIN-2 (30%), CIN-3 (70%). Average transit time from CIN-1 to CIN-3 is 7 years. Transit of CIN-3 to invasion ranges between 0 and 20 years.

III. Pathology, with subtypes Prevalence HPV Associated

Squamous carcinoma	65-85% (falling)	>95%
Verrucous	rare	
Adenocarcinoma	10-25% (rising) <u>Subset</u>	>30%
Endocervical	47-69%	
Endometrioid	1-17%	
Clear cell	<13%	
Adenoid cystic	<3%	
Adenosquamous	5%	±
Glassy cell	rare	
Small Cell Neuroendocrine	uncommon	unlikely
Sarcoma/lymphoma/serous	rare	unlikely

IV. Natural history

- A. Symptoms: Postmenopausal bleeding (46%), Metrorrhagia (20%), Postcoital bleeding (10%), vaginal discharge (9%), pain (6%).
- B. Spread via local invasion followed by lymphatic and vascular metastasis

V. Screening: ACS / NCCN / ASCCP consensus (Saslow)

A. When to Initiate Screening

1. Begin 3 years after coitarche or by age 21
2. Begin earlier if DES exposed, Hx of HPV or cervical CA, immunocompromised
3. Do not delay onset of gyn care if screening not yet needed

B. When to discontinue screening

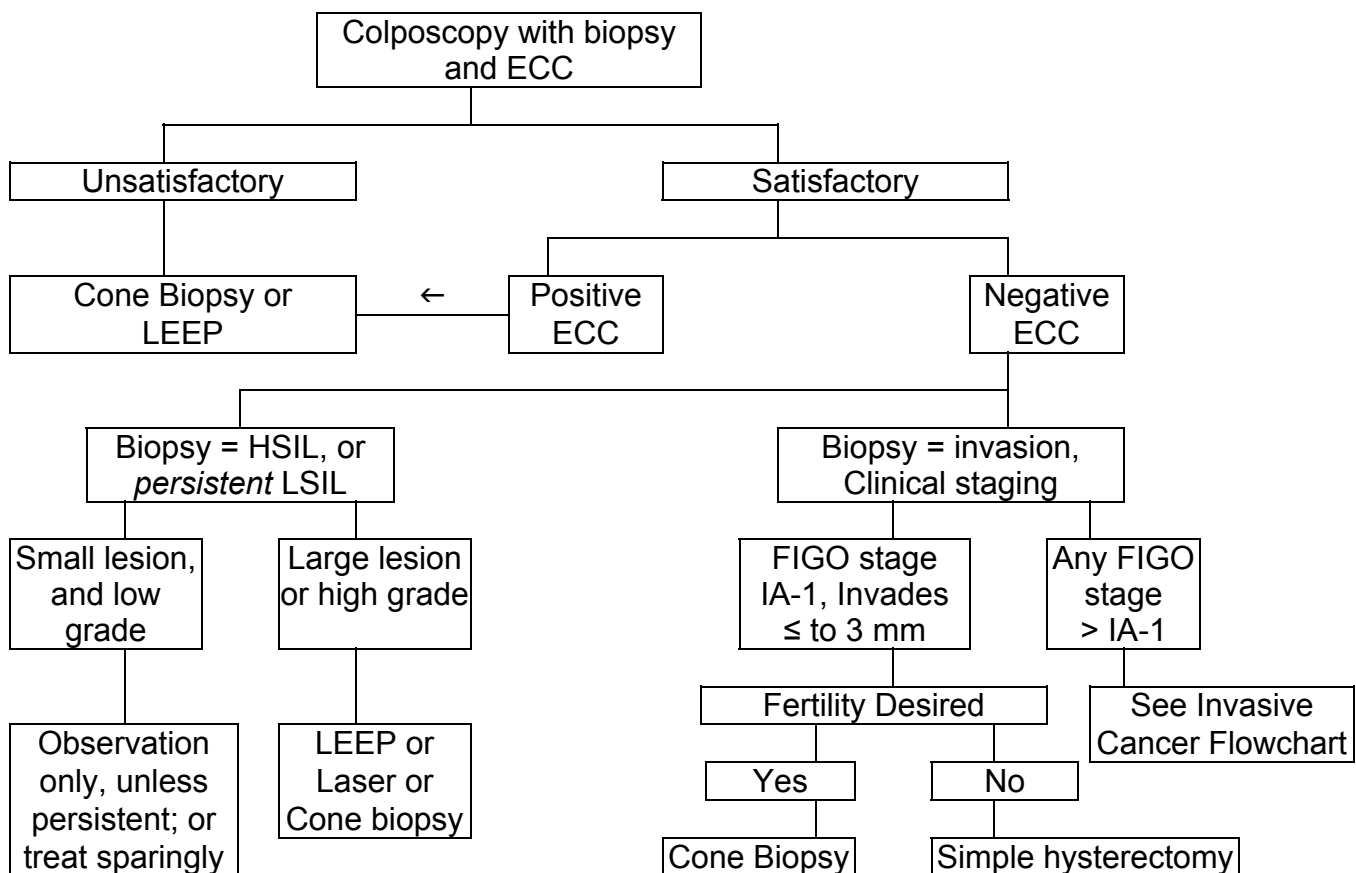
1. ≥ 70 y with 3 consecutive negative Paps & no CIN for 10y
2. Hysterectomy without CIN2-3 or cancer as indication
3. Co-morbid or life threatening illness

C. Screening interval

1. Initial interval
 - a. Every 1y conventional or
 - b. Every 2y liquid cytology. Higher sensitivity than glass-slide method
2. At ≥ 30 y age may increase to
 - a. Every 2-3y if 3 consecutive, satisfactory, negative Paps and no high risk factors such as CA, DES or immunocompromised
 - b. Every 3y using HPV test for hi risk types with either Pap method

VI. Diagnosis of dysplasia and invasive carcinoma

- A. Speculum and bimanual exam with biopsy of visible lesions
- B. Cytology: false negative rate 20% for squamous CA, 40% for adeno CA
- C. Colposcopy with biopsy and ECC.
 1. Flow Chart for Management of the Abnormal Pap



2. Pap Triage and Indications for Colposcopy (ALTS trial, ASCCP consensus guidelines [Wright], and www.NCCN.org)
 - a. ASC-US: reflex HPV test if liquid-based pap done. If HPV positive for high-risk types, then do colposcopy. If HPV negative, resume annual pap
 - b. HSIL, LSIL or ASC-H: colposcopy
3. Technique of colposcopy with directed biopsy and ECC.
 - a. Stain with acetic acid (3-5%). Frequently moisten mucosa.
 - b. Inspect with colposcope, 15X objective; with and without green filter.
 - c. Find squamocolumnar junction (SCJ). This defines "satisfactory" or "adequate" colposcopy. Most cervical cancers arise at the SCJ.
 - d. Look for acetowhite epithelium and vascular patterns. Biopsy atypical areas. Always do ECC unless patient pregnant.
 - e. Warning signs to safeguard against overlooking cancer
 - i. Yellowish color, especially areas that are friable
 - ii. Irregular contour (exophytic or ulcerative)
 - iii. Atypical vessels
 - iv. Extremely coarse mosaicism or punctation
 - v. Large, complex, multiquadrant lesions

3. Colposcopy scoring system (Reid)

Reid's scoring system to improve colposcopic accuracy:

	Score		
	0	1	2
Margin	Exophytic condylomata; areas showing a micropapillary contour Lesions with distinct edges Feathered, scalloped edges Lesions with angular, jagged shape Satellite areas and acetowhite staining distal to the original SCJ	Lesions with regular shape, showing smooth, straight edges	Rolled, peeling edges Any internal demarcation between areas of differing colposcopic appearance
Color	Shiny, snow-white color Areas of faint, semitransparent whitening	Intermediate shade (shiny, but gray-white)	Dull reflectance with oyster-white color
Vessels	Fine caliber vessels, poorly formed patterns	No surface vessels	Definite, coarse punctation or mosaic
Iodine	Any lesion staining mahogany brown, or mustard yellow staining by a minor lesion	Partial iodine staining, mottled pattern	Mustard yellow staining of significant lesion (score of ≥ 3 by first three criteria)

If Score 0-2: expect condyloma / CIN-I

If Score 3-5: expect CIN-II

If Score 6-8: expect CIN-III

VII. Treatment of Cervical Dysplasia. Guidelines supported by ASCCP and NCCN. In general, "treat lesions, not cytology"

A. Condyloma and CIN-I:

1. Observation with pap smears every 6 months x 2
2. If antecedent pap was HSIL, review cytology and consider LEEP or cone biopsy
3. If lesion regresses on both paps, resume annual pap
4. If lesion persists at one year or if high risk HPV types are present at one year, repeat colposcopy

B. CIN II and CIN III

1. LEEP, or laser, or cryocautery or cone biopsy
2. Followup with pap every 6 months x 2, then resume annual pap

3. Hysterectomy is acceptable if age, reproductive desire, and comorbidity are concordant

C. Unsatisfactory colposcopy

If colposcopy, ECC or cytology suggest endocervical lesion, then cone biopsy. LEEP may not suffice given the difficulty in obtaining an intact endocervical canal specimen

D. Management During Pregnancy

1. Speculum and bimanual exam with screening cytology. Biopsy visible lesions
2. If pap abnormal, then colposcopy with directed biopsy if HSIL or invasive carcinoma suspected. ECC contraindicated
 - a. Pap low grade SIL, colposcopic appearance concurs: pap q. 8-12 weeks and repeat colposcopy postpartum
 - b. Pap high grade SIL, and/or colposcopic appearance of high grade lesion: biopsy, then repeat colposcopy (\pm biopsy) q. 6-8 weeks until postpartum
 - c. Vaginal delivery indicated
3. Antepartum conization only for microinvasion on punch biopsy or for suspicion of invasion

E. Treatment of vaginal dysplasia or condyloma

1. Krebs regimen. 5% Efudex cream, 1.5 gm (one quarter applicator) intravaginally once per week for 10 weeks. Use Desitin ointment on vulva, water douche morning after Rx. Minor skin irritation common. Contraindicated during pregnancy. This is an Off Label use of the drug.
2. Laser photoablation. Requires an anesthetic, cost higher.
3. A few case reports support use of imiquimod cream 5% (Aldara) for treatment of vaginal or vulvar dysplasia (Diakomanolis)

VIII. General Principles of Laser Treatment for Pre-invasive Disease

- A. Clinical utility depends on use of appropriate wavelength. The CO₂ laser is most applicable to ablation of condyloma, dysplasia, and carcinoma-in-situ. It is also well suited for laser conization. The 10,600 nm wavelength is absorbed by water, resulting in tissue vaporization. Absorption occurs at the surface. Thermal damage to underlying tissue is minimized
- B. Power density must be adequate to prevent char
 $PD \text{ (Watts/cm}^2\text{)} = (\text{Watts} \times 100) / \pi r^2$, r = spot radius (not diameter)
- C. A colposcope is used to guide the laser. Low power Helium Neon (HeNe) laser (red beam) is used for aiming. Eye protection mandatory

IX. Laser Treatment for Cervical Pre-invasive Disease

A. Technique

1. Transformation zone (T-zone) outlined using acetic acid and colposcope
2. Set power density to 750-1000 W/cm²; 25-30 W with spot size of 2 mm
3. Anesthetize cervix with 1% Lidocaine with epinephrine (0.5 mL injections around circumference of portio)
4. Vaporize entire T-zone, one quadrant at a time, to a depth of 7 mm. This ablates gland crypts. If bleeding noted, defocus beam for hemostasis. Any char produced is removed immediately to prevent increased thermal injury
5. Apply Monsel's solution for hemostasis

B. Advantages of Laser Treatment

1. Precise control of tissue ablation/excision
2. Minimal damage to adjacent normal tissue
3. SCJ remains at external os
4. More effective than cryotherapy for large lesions

C. Disadvantages of Laser Treatment

1. Risk of bleeding 1-3%; risk of stenosis 1%

2. Expensive
 3. More training required than for cryocautery
 4. Small but real concern of airborne transmission of viral particles
 5. Destruction of large portion of cervix possible
- X. General Principles of Electrosurgery for Cervical Pre-invasive Disease
- A. Radio frequency current (350 KHz-3.3 MHz) results in kinetic energy transfer to intracellular ions which vaporizes intracellular water. Avoid Faradic Effect (50 Hz-200 KHz), which stimulates muscle and nerve causing pain by using proper equipment
 - B. Cutting: sine-wave RF current; coagulation: pulsed ("spark gap") RF current
- XI. Loop Electrosurgical Excision Procedure (LEEP)
- A. Technique
 1. Transformation zone outlined using acetic acid and colposcope
 2. Anesthetize with 1% Lidocaine with epinephrine
 3. Choose loop to excise entire T-zone (1.5 cm x 7 mm, or 2.0 cm x 8 mm)
 4. Excise tissue in single pass, using 40 W, blend mode (use insulated speculum)
 5. Obtain ECC
 6. Cauterize base with ball electrode at 50 W, coagulation mode
 7. Apply Monsel's solution
 - B. Advantages
 1. Diagnostic and therapeutic intervention, potentially with one clinic visit
 2. Histologic specimen improves diagnostic accuracy
 3. SCJ remains at external os
 4. Equipment less costly than laser
 - C. Disadvantages
 1. Risk of bleeding 1-3%; risk of stenosis 1%
 2. Greater cost to patient than cryocautery
 3. Small but real concern of airborne transmission of viral particles
 4. Destruction of large portion of cervix possible
- XII. General Principles of Cryosurgery for Cervical Pre-invasive Disease
- A. Rapid cooling with NO₂ forms intracellular ice which ruptures cell membranes
 - B. Freeze-thaw-freeze technique results in higher success rates than single freeze
- XIII. Cryocautery Procedure for Cervical Pre-invasive Disease
- A. Technique
 1. Transformation zone outlined using acetic acid and colposcope
 2. Select flat or dimpled cryo-probe (not cone tip) and apply lubricant to tip
 3. Freeze until ice ball extends 5 mm lateral to all sides of cryo-probe. Do not use time as a measure of adequacy of the freeze
 4. Allow tissue to thaw until pink and pliable
 5. Repeat step 3
 - B. Advantages
 1. Inexpensive
 2. Easy to learn
 - C. Disadvantages
 1. Risk of bleeding 1%; risk of stenosis 1%
 2. Heavy vaginal discharge during healing
- XIV. Treatment Results for Cervical Pre-invasive Disease. Successful elimination of CIN

Treatment	CIN 2	CIN 3 (≤ quadrants)	CIN 3 (> 2 quadrants)
Cryocautery	80-94%	85%	60-65%
Laser	80-94%	80-94%	80-94%
LEEP	90-95%	82-88%	82-88%
Cone Biopsy	90-97%	90-97%	90-97%

- A. If margin of LEEP or cone biopsy is involved with dysplasia, likelihood of successful eradication of CIN is 60%. Options include surveillance versus repeat excision.

XV. Followup for Cervical Pre-invasive Disease

- A. Repeat Pap smear (and colposcopy at discretion of physician) every 6 months x 1 year
B. Partner should be informed about HPV and role of "safe sex"
1. 70% will have lesions
2. Treatment of male has no proven effect on prevention of recurrence in the female

XVI. Treatment Failures for Cervical Pre-invasive Disease

- A. Reinfection of epithelium with existing latent HPV virus (not preventable)
B. Incomplete destruction of transformation zone (preventable)
C. Missed diagnosis of invasive lesion (preventable)
D. Prevention of treatment failures

Risk of preventable treatment failure minimized by use of triage rules:

Never ablate (cryocautery or laser) a cervical lesion unless:	
1.	All of the transformation zone is visible, <u>and</u>
2.	Biopsies and Pap smears are consistent, <u>and</u>
3.	Endocervical curettage is negative, <u>and</u>
4.	There is no colposcopic or cytologic suspicion of invasion
Otherwise, excise for diagnosis (LEEP or cone biopsy)	

XVII. Cervical Cancer Stage: determined by clinical examination.

FIGO Staging for Cervix, Revised 2009	
I	Carcinoma confined to the cervix (Disregard extension to corpus)
I A 1	Measurable invasion ≤ 3 mm in depth and ≤ 7 mm in diameter
I A 2	Measurable invasion > 3 and ≤ 5 mm in depth and ≤ 7 mm in diameter
I B 1	Lesion of > 5 mm depth and/or > 7 mm diameter, but ≤ 4 cm in diameter
I B 2	Lesion of > 4 cm diameter
II	Invades beyond uterus but not to pelvic wall or to the lower 1/3 of vagina
II A 1	Tumor size ≤ 4 cm
II A 2	Tumor size > 4 cm
II B	Parametrial invasion
III	Tumor extends to the pelvic wall, or may involve the lower 1/3 of vagina
III A	No extension to pelvic wall
III B	Extension to pelvic wall. Includes hydronephrosis or non-functioning kidney
IV	Spread beyond the true pelvis or involvement of bladder or rectal mucosa
IV A	Spread to adjacent organs (bowel or bladder)
IV B	Spread to distant organs

- A. Tests which may be used to stage include biopsy, colposcopy, IVP, CXR, cystoscopy, and sigmoidoscopy. Tests which may not be used to stage include surgery, CT or MRI scans, and lymphangiograms. All tests may be used for treatment planning
B. Cystoscopy and sigmoidoscopy usually indicated only in stage IIB, III, IV or if symptoms such as hematuria or narrowed fecal stream exist (Shingleton)

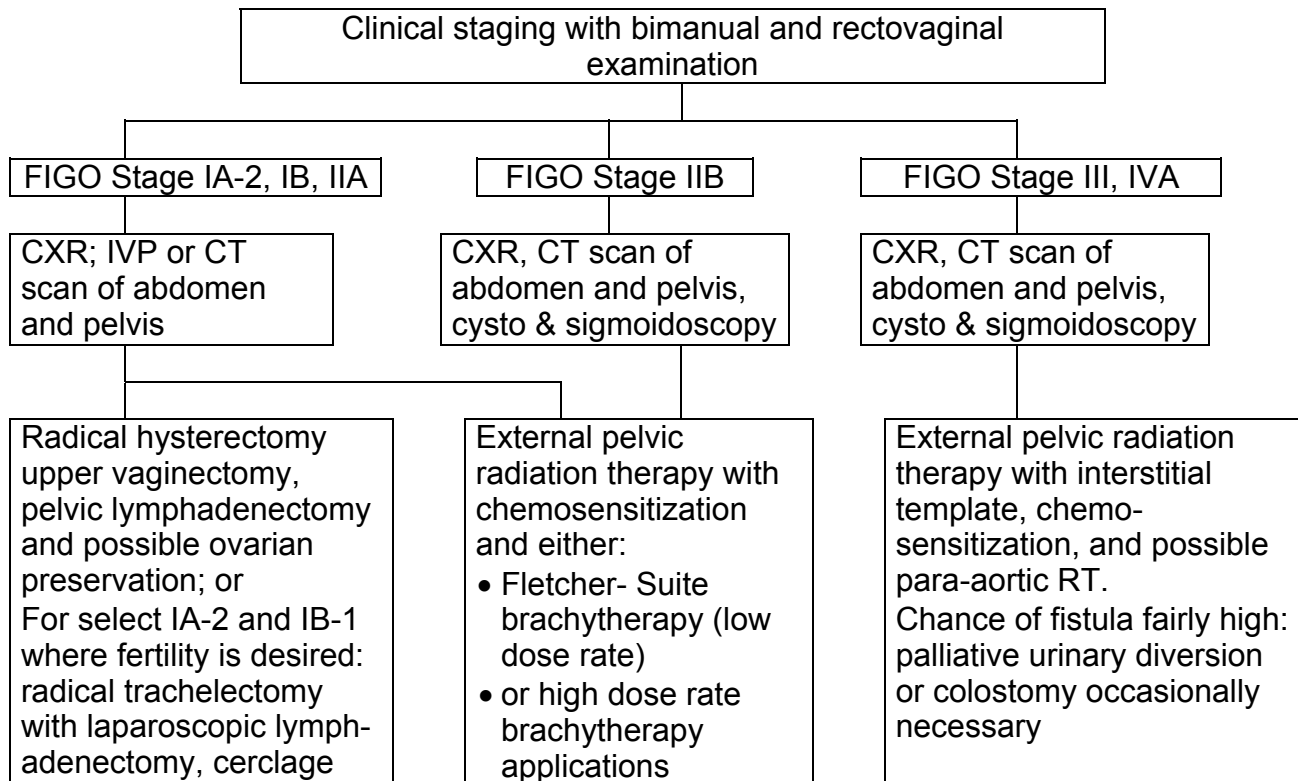
XVIII. Management of invasive cervical carcinoma

- A. Microinvasion: a subset of early cancers with minimal risk of local or node metastases. See Flow Chart VI.C.1 (above) for diagnosis and clinical management
1. Rationale for conservative treatment to preserve fertility

	SGO (FIGO IA-1)	FIGO IA-2
Histology	NO VSI or Confluence	-
Incidence of node mets	$< 1\%$	8%

2. Adenocarcinoma is not substaged into a microinvasive category although literature supports conservative treatment in selected cases (Schorge)

B. Flow Chart for Management of Invasive (> Stage IA-1) Cervical Cancer. For microinvasive cervical cancer, see VI.C.1. (above) for flowchart.



C. Conventional radical hysterectomy is via the laparotomy approach. Newer techniques include laparoscopic radical hysterectomy, laparoscopic lymphadenectomy with Schauta (vaginal) radical hysterectomy or radical trachelectomy (Dargent, Plante, Reynolds)

D. Chemosensitization has been shown to significantly improve outcome in 5 randomized trials. Most common regimen is cisplatin 40 mg/meter²/week (maximum dose of 70 mg/week) during RT. Other regimens include cisplatin and 5-FU. (Rose, Keys)

E. Comparison of Surgery vs Radiation (for Stage Ib/Ila tumors)

	Surgery	Radiation
Survival	91%	89%
Serious complications	Urologic Fistulae 1-2%	Intestinal and urinary strictures and fistulae 1.4-5.3%
Vaginal function	Initially shortened, lengthens with intercourse or dilator	Fibrosis and stenosis, especially in postmenopause. Dilator minimizes stenosis.
Ovarian function	Conserved	Destroyed
Chronic effects	Atonic bladder 3%	Radiation enteritis 6-8%

F. Special Cases

1. Pregnancy

a. Stage for stage, pregnancy does not worsen survival. Delayed diagnosis is common

- b. Timing of treatment controversial. Classical approach is to terminate pregnancy if gestation ≤ 24 weeks at diagnosis. If > 24 weeks, delay therapy until fetal viability. Newer studies suggest no decrease in survival with longer treatment delays (Takushi)
 - c. Cesarean delivery usually recommended for invasive lesions due to friability of tumor. Vaginal delivery does not worsen prognosis but tumor implants in episiotomy sites have been reported
2. Occult carcinoma: tumor not diagnosed prior to surgery
 - a. Treatment options include pelvic radiation, radical parametrectomy
 - b. If appropriate treatment not done, recurrence rate $> 75\%$
 - c. Prognosis is poor if gross tumor is cut through on margins of hysterectomy
3. Barrel shaped cervix: intact cervix of $\geq 4-6$ cm diameter (Keys, Maruyama, Paley)
 - a. High rate of central pelvic failure (25-40%) after RT
 - b. Some advocate combined RT followed by extrafascial TAH. Reported pelvic recurrence drops from 19% to 2%, and extrapelvic recurrences from 16% to 7%.
4. Positive lymph vascular space involvement, positive nodes or extracervical spread detected during or after completion of radical hysterectomy (Peters)
 - a. If node or parametrial involvement is documented, then pelvic radiation therapy with cisplatin chemosensitization is given. If VSI positive, consider RT + chemo
 - b. If para-aortic nodes involved, consider scalene node biopsy and offer extended field radiation, if scalene nodes negative
5. Central pelvic recurrence
 - a. Patient with prior radical hysterectomy: radiation therapy to pelvis with chemosensitization.
 - b. Patient with prior pelvic radiation with or without prior radical hysterectomy: total pelvic exenteration. Contraindicated with lymphatic metastases, extension of disease to pelvic sidewall or distant metastasis. Removes bladder, uterus, vagina and rectum. Requires extensive reconstruction including urinary conduit (continent or non-continent), low rectal anastomosis or end colostomy, and vaginoplasty with split thickness skin graft or myocutaneous flap. Salvage rate 60-70%, mortality rate 2%
 - c. In special circumstances, patients with recurrent disease extending to the pelvic sidewall may benefit from the laterally extended endopelvic resection (LEER) procedure or intra-operative radiation to the sidewall (Höckel)
6. Distant metastatic disease cannot be considered curable with chemotherapy. Progression free intervals are in the 9-15 month range. Regimens include:
 - a. Cisplatin, 50-75 mg/m², 23% response rate
 - b. Ifosfamide, 1.7gm/m²/day x 3days, with MESNA (uroprotector), 20% of ifosfamide dose given IV 15 minutes before, 4 and 8 hours after each dose. MESNA can be given 2 and 6 hours after ifosfamide at 40% of ifosfamide dose. Response rate 33%
 - c. Other single agents reported to be active: 5-fluorouracil (5-FU), paclitaxel, topotecan
 - d. Cisplatin and ifosfamide, 79% response rate for tumor in non-irradiated sites, 18% response rate for tumor in previously radiated sites. Other reported combinations include cisplatin (50 mg/m² on day 1) with topotecan (0.75 mg/m²/day on days 1-3); OR paclitaxel (135 mg/m² over 24 hours on day 1) with cisplatin (50 mg/m² on day 2)
 - e. Cisplatin and 5-FU, similar response rates to cisplatin and ifosfamide.
 - f. Participation in clinical trials is strongly encouraged

XIX. Prognostic Factors and Survival

A. Factors important to survival include: age, stage, size, VSI, grade, and node status

B. Incidence of Nodes by Stage

Stage	% Positive Pelvic Nodes	% Positive Para-aortic Nodes
Ia2	4.8	<1
Ib	15.9	2.2
IIa	24.5	11
IIb	31.4	19
III	44.8	30
IVa	55	40

C. Survival

Stage	Nodes	5 Yr Survival Squamous	Adenocarcinoma
I	Unknown	91%	60%
I	Negative	96%	82%
I	Positive	56%	28%
I	Positive ≤3 PLN	70%	
I	Positive >3 PLN	40%	
I	Positive PAN	37%	
II		65%	47%
III		45%	8%

XX. Prevention

A. Immunization (Blumenthal, Mao, Stanley)

1. Gardasil (Merck): FDA approved in 2006, quadrivalent for HPV 6, 11, 16, 18. Phase III randomized trial (n=12,150) with injection on day 1, month 2 and month 6 showed 100% prevention of CIN 2-3 at 17 months followup if no HPV infection occurred and 97% efficacy if HPV infection occurred after immunization with 24 months followup (Villa). May be commercially available by late 2006
2. Cervarix (Glaxo Smith Kline): FDA approval anticipated in 2007-08. Bivalent for HPV 16 and 18.

B. Sex education to alter high-risk behavior and age of first intercourse (Howard)

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Endometrial Carcinoma

I. Incidence: most common gyn tumor in U.S. Fourth most common cancer of women in U.S. In 2006, 41,200 new cases per year, resulting in 7,350 deaths (Jemal). Average age at onset is 58 years.

II. Epidemiology

A. Represents progression from normal to hyperplastic to atypical then invasive endometrial cells.

B. Risk factors RR

Overweight (age 50-59)	by 20-50 pounds	3
	by > 50 pounds	10
GO vs G> 5		5
Menopause after age 52		2
Diabetes		3
Unopposed estrogen replacement	(Includes tamoxifen)	6
Combination OCP		0.5

C. Etiology

1. Prolonged or non-cyclic estrogen stimulation (endogenous or exogenous) for Type I cancers
2. Risk of progression to cancer of endometrial hyperplasia without atypia (1-3%), with atypia (29%) (Kurman)
3. 5% of endometrial cancers arise as hereditary cancers in HNPCC families associated with mismatch repair genes MLH, MSH, PMS1, and PMS2 (Boyd)

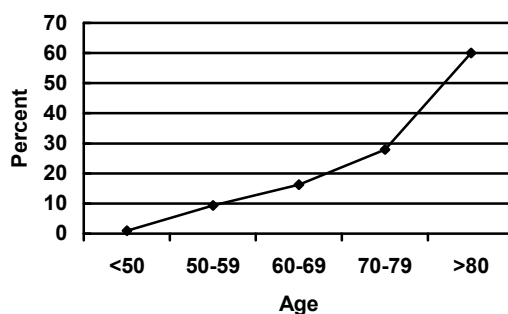
III. Screening

No test or procedure has been identified as a cost-effective method to screen for endometrial cancer. ACOG does not recommend screening

IV. Diagnosis

A. Symptoms: 90% present with postmenopausal bleeding (PMB) or abnormal discharge

1. Common etiologies of PMB: hormone replacement therapy (27%), endometrial carcinoma (13-16%), cervical carcinoma (1-4%), atrophy (10%), polyps (7-23%), cervicitis (6-14%). No pathology (20-23%).
2. Likelihood that PMB is associated with endometrial cancer is a function of age:



B. Pap test very low sensitivity, but necessary to rule out cervical cancer as a cause of postmenopausal bleeding

C. Endometrial biopsy 90-97.5% sensitive (Stovall)

D. Fractional curettage ± hysteroscopy is diagnostic gold standard

E. Vaginal U/S for endometrial thickness. Cancer rare if stripe <4 mm (Varner)

F. Preoperative CXR

G. Preop CA-125: accurate predictor of extra-uterine disease and survival (Sood)

V. Pathology

Endometrioid	75-85%
Squamous differentiation	common
Papillary (Villoglandular)	rare
Secretory	rare
Uterine Papillary Serous Tumor (UPST)	5-7%
Clear Cell Carcinoma	4%
Mucinous	Rare
Squamous	Rare

Type I refers to well differentiated tumors arising from estrogen stimulation

Type II refers to poorly differentiated or non-endometrioid histology and is associated with poorer prognosis (Boyd)

VI. Prognostic Factors

A. Recurrence rate without extrauterine mets (7%), with extrauterine mets (43%)

B. Incidence of adnexal metastases by grade and depth of invasion in clinical stage I:
Grade 1 (2.5%), 2 (3.5%), 3 (13%); Depth 0 (4%), $\leq 1/3$ (1.5%), $\leq 2/3$ (9%), $> 2/3$ (10%).

C. Histologic type: prognosis poor with papillary serous and clear cell types.

D. Estrogen/Progesterone receptors: present in 80% of grade 1, and 30% of grade 3 tumors.

E. Incidence of Node Metastases

1. When complete surgical staging has not been done (Boronow)

Risk Factor	Pelvic Node Mets	Paraortic Node Mets
Grade 1	3%	2%
Grade 2	9%	5%
Grade 3	18%	11%
No invasion	1%	1%
Invades inner third	5%	3%
Invades middle third	6%	1%
Invades outer third	25%	17%
Invades lower uterine segment	16%	14%
Vascular space involvement	27%	19%
Positive peritoneal cytology	25%	19%
Adnexal metastasis	32%	20%

Pelvic / Paraortic Node Mets by Depth of Invasion and Grade

	$\leq 1/3$	$\leq 2/3$	$> 2/3$
Grade 2	3/0%	33/17%	20/20%
Grade 3	24/33%	25/0%	42/25%

2. Incidence of positive pelvic nodes in Stage II 36%.

VII. Staging is surgical:

FIGO Staging for Endometrium (Revised 2009)		
I	Tumor confined to uterine corpus	
I A	No or < 1/2 myometrial invasion	
I B	≥ 1/2 myometrial invasion	
II	Tumor involves cervical stromal	
III	Disease outside of uterus confined to pelvis or retroperitoneum	
III A	Invades to serosa, or involves adnexa	
III B	Involves vagina, parametrium, or pelvic peritoneum	
III C	Retroperitoneal node involvement	
IV A	Invasion to surrounding organs i.e. bladder or bowel	
IV B	Distant metastases	
	Grade 1	≤5% of nonsquamous solid growth pattern
	Grade 2	6-50% of nonsquamous solid growth pattern
	Grade 3	>50% of nonsquamous solid growth pattern

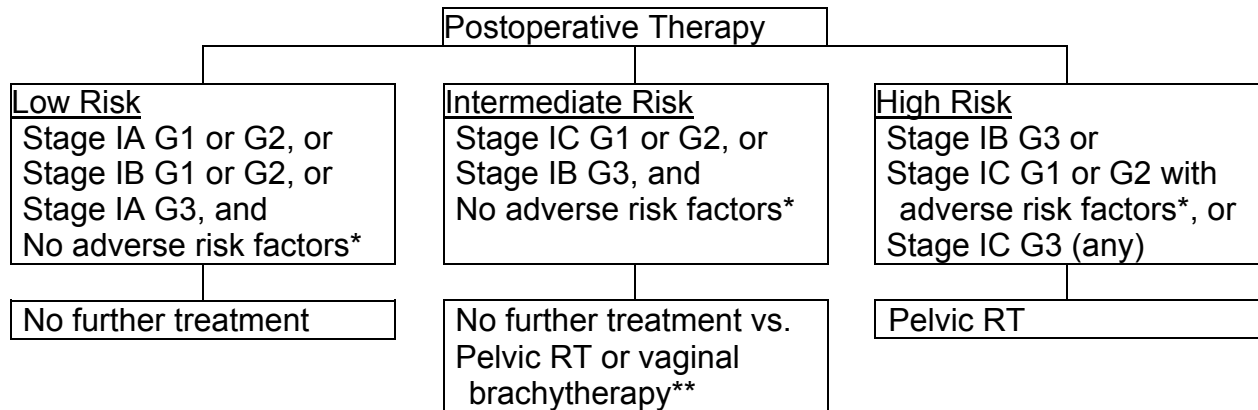
VIII. Treatment based on initial clinical presentation

- A. If medically operable, clinical stage I: total hysterectomy with bilateral salpingo-oophorectomy (TH/BSO), pelvic and para-aortic lymphadenectomy, peritoneal cytology
 1. Abdominal hysterectomy has historically been the standard approach for treatment of endometrial cancer
 2. Laparoscopic hysterectomy
 - a. A number of studies have shown similar staging efficacy and complication rates for laparoscopic vs. abdominal approach (review by Kueck).
 - b. Small prospective randomized trials show equivalent survival outcome (review by Kueck).
 - c. Definitive, large, randomized trial (GOG LAP-2) has not yet reported survival outcomes comparing laparoscopy vs laparotomy
 3. Role of lymphadenectomy
 - a. Surgery without lymphadenectomy will miss metastatic disease in 29% (Ben-Shachar, Yenen) and upstaging or upgrading occurs in 67% of fully staged patients compared to those in whom frozen section is relied upon to determine need for staging (Frumovitz)
 - b. Therapeutic value of lymphadenectomy is debated, with a number of studies suggesting survival benefit (Chan, Cragun, Creutzberg, Kilgore, Trimble) and a number of studies showing no benefit (Ceccaroni, Kitchener, Vizza). There have been no sizable, prospective, randomized trials to date.
 4. Panniculectomy: may improve exposure for the obese patient. Shown to increase number of nodes recovered and ability to complete surgical staging (Wright)
- B. If poor candidate for complete staging procedure, clinical Stage I, Grade 1-2: vaginal hysterectomy with bilateral salpingo-oophorectomy
- C. In young patients desiring to retain fertility with clinical stage I grade 1 disease: treat with curettage followed by progestin therapy (megestrol acetate 80 mg po bid for 3 months) followed by repeat biopsy or curettage. Small series show excellent outcomes, but careful informed consent necessary for non-standard therapy (Farhi)
- D. If medically inoperable: pelvic radiation therapy with brachytherapy application(s)
- E. Clinical Stage II: pelvic radiation therapy (Pelvic RT and brachytherapy) followed by TAH/BSO and para-aortic lymphadenectomy, or radical hysterectomy/BSO and nodes
- F. Suspected metastatic disease in peritoneal cavity or nodes: Pre-op imaging with CT or MRI, then TH/BSO, pelvic and para-aortic lymphadenectomy, peritoneal cytology, omentectomy, debulking (Bristow, Mariani)

- G. Suspected metastatic disease in vagina, parametrium, bladder or rectum: Pre-op imaging with CT or MRI, then RT +/- surgery or chemotherapy
- H. Suspected distant metastases: Pre-op imaging with CT or MRI, then multimodal therapy with chemotherapy +/- RT or surgery

IX. Adjuvant therapy for surgically staged disease

A. Stage I disease (Defined using FIGO 1989 staging system)



1. Adverse risk factors (*) defined as age >60, lymph vascular space involvement (LVSI), tumor size, lower uterine segment involvement
2. Randomized trials (**) show reduced pelvic recurrences with pelvic radiotherapy but no improvement in overall survival (Keys: GOG 99, Creutzberg: PORTEC-1).

B. Stage II

1. Stage IIA grade 1-2: observe or vaginal brachytherapy
2. Stage IIA grade 3 or all stage IIB: vaginal brachytherapy +/- pelvic RT
3. If initial Tx was radical hysterectomy without extrauterine spread, then no RT

C. Stage III:

1. Stage IIIA
 - a. Positive washings with no other evidence of metastatic disease. Prognostic significance debated with some studies showing no impact on survival (Grimshaw, Kasamatsu) and some showing poor outcome (Creasman)
 - b. Adnexal or uterine serosal involvement: treated with chemotherapy +/- tumor directed RT (NCCN)
2. Stage IIIB: tumor directed RT +/- chemotherapy
3. Stage IIIC: chemotherapy better (50% vs. 38% disease free survival at 5 years) based on randomized trial comparing whole abdominal RT vs. cisplatin and doxorubicin chemotherapy (Randall)
4. Treatment individualized. May include surgery, and/or tumor directed RT

D. Stage IV: Treatment individualized.

1. Chemotherapy
 - a. Cisplatin 50 mg/m² day 1, doxorubicin 45 mg/m² day 1 and paclitaxel 165 mg/m² day 2 with cytokine support days 3-12 repeated every 3 weeks. Regimen has highest response rates 57% vs. 34% for cisplatin 50 mg/m² and doxorubicin 60 mg/m². Average progression free survival is 5 to 8 months (Fleming)
 - b. Doxorubicin (Adriamycin), 60-75 mg/m² IV q3weeks (maximum cumulative dose 450 mg/m²), is the most active single-agent drug. Response rate is 37%
2. Tumor directed RT may be useful to palliate bleeding or pain.

3. For estrogen-progesterone receptor positive tumors, or metastatic grade 1-2 tumors, hormonal therapy with megestrol acetate, 80 mg po bid and / or tamoxifen 10-20 mg po bid, sometimes useful
- E. There is no demonstrated benefit of adjuvant chemotherapy or hormonal therapy (Morrow)
- F. Uterine papillary serous tumors (UPST)
 1. Clinical stage underestimates extent of disease in 50%.
 2. Patients with surgical stage I recur in 50-60%. Recur in upper abdomen 67%. Natural history resembles ovarian tumors.
 3. Adjuvant therapy using combination chemotherapy with or without pelvic RT favored in phase II trials. No sizable phase III studies available. Best regimens reported include carboplatin and paclitaxel alone (Dietrich) or in combination with RT (Bancher-Todesca, Kelly, Turner)
- G. Incompletely staged disease. If uterine disease is myoinvasive or grade is 2-3, then either complete staging surgically or image and base adjuvant therapy on best assessment of disease extent.

X. Survival

A. Endometrioid Histology

		5 Yr Survival
Stage I	Grade 1	94%
	Grade 2	87%
	Grade 3	75%
Stage II		57%
Stage III		36%
Stage IV		9%

B. Uterine Papillary Serous Histology

		5 Yr Survival
Stage I-II		45%
Stage III-IV		11%

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Gestational Trophoblastic Neoplasia

- I. Trophoblastic neoplasms are essentially tumors of the placenta. The disease can be divided into a non-invasive group of tumors consisting of complete and partial moles, and an invasive group of tumors including invasive mole, choriocarcinoma and placental site trophoblastic tumor.
- II. Incidence of hydatidiform molar pregnancies (Non-invasive disease)
 - A. Population based studies 1:522 (Japan) to 1:1560 (Sweden)
 - B. Hospital based studies 1:85 (Indonesia) to 1:1724 (USA)
 - C. In elective abortions in US 1:600 and 1:1500 pregnancies in US
- III. Epidemiology of hydatidiform moles

Table of Relative Risks	RR
Prior Molar Pregnancy	10-40
Maternal age <20	1.5
Maternal age >40	5.2
Prior Spontaneous Abortion	1.9-3.3
Vitamin A, above median	0.6
Parity >1	0.4

- IV. Pathology of hydatidiform moles
 - A. Complete: Arise from fertilization of an empty oocyte with 1 sperm that is then duplicated (more common) or 2 sperm (less common)
 - B. Partial: Arises from fertilization of an apparently normal oocyte with 2 sperm

Characteristic	Complete Mole	Partial Mole
Karyotype	46XX (90%) 46XY (10%) All paternal chromosomes	Triploid (90%) 69XXX or 69XXY Diploid (10%) 46 paternal chromosomes
Fetus	Absent	Often present
Villous edema	Prominent and diffuse	Focal if at all
Fetal RBC	None	Usually present
Proliferation of trophoblast	Prominent	Mild to moderate
Likelihood of local invasion	15%	3.5%
Likelihood of metastasis	4%	0.6%

V. Clinical Features

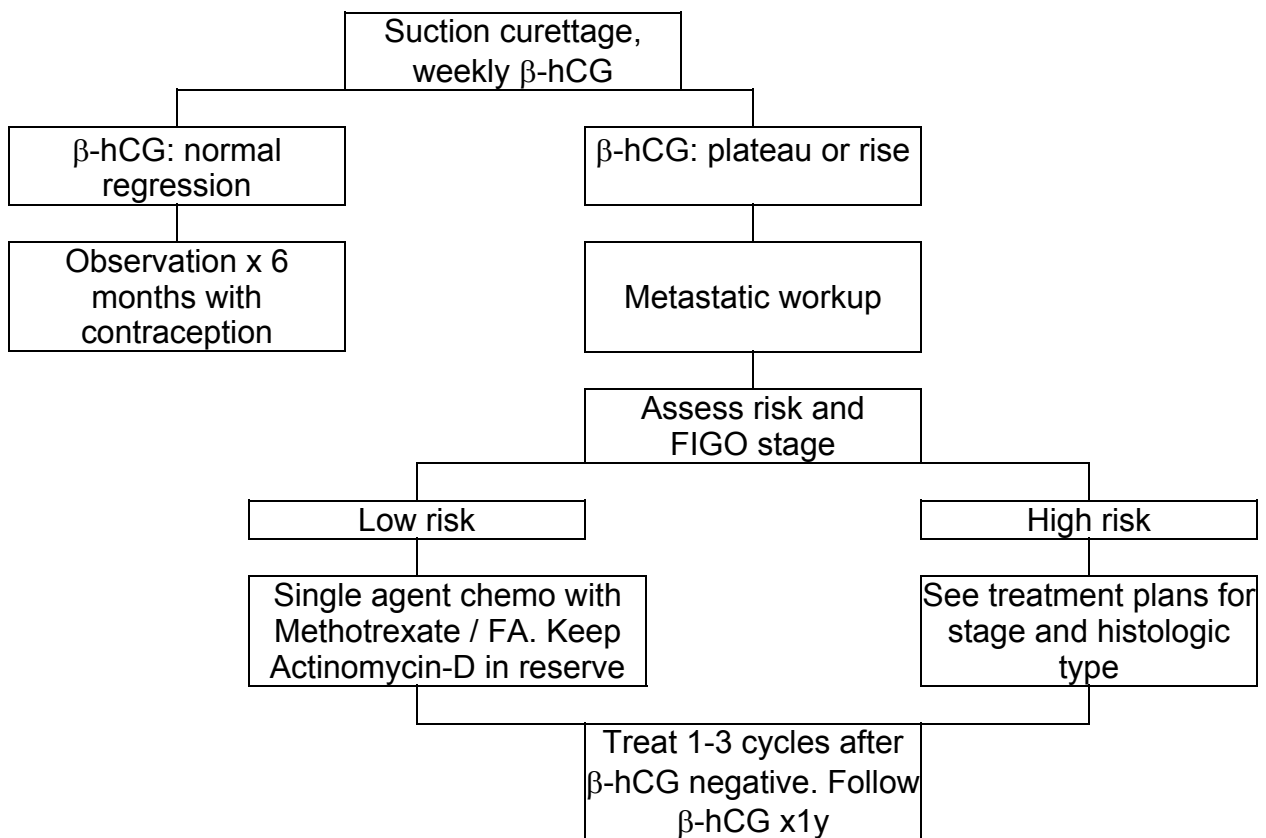
A. Presenting Symptoms of Moles	Complete	Partial
Vaginal Bleeding	97%	73%
Excessive Uterine Size	51%	8%
Theca Lutein Cysts (>6 cm)	50%	0%
Preeclampsia	27%	3%
Hyperemesis	26%	0%
Hyperthyroidism	7%	0%
Trophoblastic Emboli (over all)	2%	0%
If size of uterus is > 16 weeks	27%	

- B. Diagnosis of hydatidiform moles
 1. Usually diagnosed in first trimester. Workup often initiated because of symptoms (Section V.A.)
 2. Ultrasound:
 - a. Complete mole: vesicular pattern, "snowstorm pattern"

- b. Partial mole: focal cystic change in placenta and ratio of transverse to AP dimension of gestational sac of > 1.5 . A small for dates fetus with multiple anomalies may be present
3. β -hCG elevated, especially in complete moles. 46% of complete moles have β -hCG $> 100,000$ mU/mL. Only 6% of partial moles have β -hCG $> 100,000$ mU/mL. Partial moles may have higher percentage of α -hCG.

VI. Treatment of hydatidiform moles

- A. Pre-treatment workup: CBC and platelet count; clotting function studies; β -hCG; liver, renal and thyroid function tests; blood type with Rh and antibody screen; chest X-ray
- B. Curettage, suction and sharp, using oxytocin. Do not begin oxytocin until uterus evacuated to minimize intra-uterine tone and trophoblastic emboli. Hysterectomy acceptable, if fertility no longer desired
- C. Post-treatment follow-up: Follow β -hCG every week until normal for 3 weeks, then monthly for 6 months. Contraception to prevent confusion over interpretation of β -hCG values is important. OCPs do not increase the likelihood of persistent disease.
- D. If β -hCG levels plateau x3 weeks or rise x2 weeks, then metastatic workup and chemotherapy is initiated. Repeat curettage occasionally useful.
- E. Management Flow Diagram



- F. Two randomized trials show that high risk moles may be treated with prophylactic chemotherapy. High risk defined as β -hCG $> 100,000$ mU/mL, uterine size $>$ dates and ovary(s) > 6 cm. Results in reduced risk of post-molar invasion (47 vs. 14%). If persistence occurs, more cycles of chemo needed. Deaths have been reported with prophylactic chemo using methotrexate and folinic acid or dactinomycin regimens.

- G. Choriocarcinoma can arise from a normal pregnancy (1 : 22,000-100,000 pregnancies). Mother is at increased risk of medical complications of pregnancy. Karyotype of pregnancy may be required to confirm diagnosis. Genetics different than other GTN. Worse prognosis.
- H. Phantom hCG (false positive) can confuse diagnosis. Usually seen with low hCG levels. Caused by heterophilic antibodies in circulation. Should be suspected if clinical response to methotrexate does not occur. Should be ruled out before doing hysterectomy or multi-agent chemotherapy. Can be tested for by urine pregnancy test (negative) with positive blood test, or by doing serial dilution tests.

VII. Incidence of invasive gestational trophoblastic disease (GTD)

- A. Invasive mole noted after 15% of complete moles and 3.5% of partial moles
- B. Metastases occur following 4% of complete moles and 0.6% of partial moles
- C. Choriocarcinoma occurs following 3-7% of hydatidiform moles and 1:40,000 term pregnancies. Of all choriocarcinoma cases, 50% preceded by mole, 25% by SAb, 25% by term pregnancy
- D. Placental Site Trophoblast Tumor (PSTT) is a rare variant of GTD (55 cases by 1991)

VIII. Pathology of GTD

- A. Invasive mole: hyperplastic trophoblasts with villi invading myometrium
- B. Choriocarcinoma: trophoblasts without villi invading myometrium or other tissues. Necrosis and hemorrhage common
- C. PSTT comprised of intermediate cytotrophoblasts
- D. Tumor marker: β -hCG useful for all types except PSTT (hPL may be elevated in PSTT)
- E. Metastases, when present, occur in: lung (80%), vagina (30%), pelvis (20%), brain or liver (10%), bowel or kidney or spleen (<5%).

IX. Evaluation for metastatic disease

- A. Metastatic workup:
 1. Initial Labs: CBC; β -hCG; liver, thyroid, renal function tests; chest X-ray
 2. If chest X-ray positive or if choriocarcinoma is present or if vaginal mets present, then: CT of head, chest, abdomen and pelvis
 3. Lumbar puncture for β -hCG if CXR positive, but head CT negative. Serum/CSF β -hCG ratio <60 indicates CNS disease.
 4. Pelvic ultrasound with or without Doppler may be helpful to detect sites of persistent intra-uterine disease.
 5. Avoid biopsy of vaginal lesions due to tendency to hemorrhage
- B. FIGO Anatomic Staging for Gestational Trophoblastic Neoplasia (GTN)

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of uterus, but is limited to genital structures including adnexa, vagina, broad ligament
Stage III	GTN extends to lungs with or without genital tract involvement
Stage IV	All other metastatic sites

- C. Current staging combines anatomic staging with the modified WHO prognostic scoring system. For stage I disease, risk is usually low. For stage IV disease, risk is usually high. Stage II and III disease is best stratified with the modified WHO prognostic scoring system
- D. Stage is recorded as Anatomic Stage and FIGO modified WHO score, separated by colon. Example of format. Stage IV: 8

E. Modified WHO Prognostic Scoring System as adapted by FIGO

Factor	Score			
	0	1	2	4
Age (y)	< 40	≥ 40		
Antecedent pregnancy type	Mole	Ab	Term	
Preg. to Treatment interval (m)	< 4	4 - <7	7 - 13	≥ 13
Pretreatment β-hCG (IU/L)	< 10 ³	10 ³ - 10 ⁴	10 ⁴ - 10 ⁵	≥ 10 ⁵
Tumor size including uterus (cm)	-	3 - 5	≥ 5	-
Site of Metastases	Lung	Spleen Kidney	GI	Brain Liver
Number of Mets	0	1 - 4	5 - 8	> 8
Previous failed chemo regimens			Single	≥ 2

Total: If score is ≥ 7, then patient is high risk and requires intensive, multi-agent chemotherapy

X. Treatment of Invasive or Metastatic GTD

A. Stage I, Low Risk

- Fertility desired: Treat with single agent chemo. 87% will be complete responders (CR) with a single regimen. If a second single agent regimen is needed for persistent disease, the CR increases to 92%. Rarely, resistance may require hyst or multiagent chemotherapy regimens (EMA/CO). Results in CR of 100% remissions (2 reported failures in literature). First line regimen is methotrexate with folinic acid. Treatment conversion to dactinomycin is made if resistance or dose-limiting toxicity occurs.
 - Methotrexate (1.0 mg/kg IM days 1,3,5,7) and Leucovorin (0.1 mg/kg IM days 2,4,6,8). Repeated every 2 weeks.
 - Dactinomycin (1.25 mg/m² IV, Q14 days)
 - Other dose schedules for both drugs are published (Rubin)
 - 5 fluorouracil is widely used for treatment of GTN in other countries, with excellent results
- Fertility not desired: hysterectomy and adjuvant single agent chemotherapy as above.
- Treatment continues until the β-hCG is negative. Surveillance includes weekly β-hCG during treatment, then β-hCG every 2 weeks x 3, then monthly β-hCG for 12 months after completion of therapy.

B. Stages II and III, High Risk

- Multi agent chemotherapy with EMA/CO is the preferred regimen
 - Etoposide 100 mg/m² IV on day 1 and 2, dactinomycin (Actinomycin-D) 0.5 mg IV on day 1 and 2, methotrexate 100 mg/m² IV push on day 1 then 200 mg/m² IV over 12 hours on day 1 (alkalinize urine). Leucovorin 15 mg IM or PO q 6 hours x 4 doses beginning 12 hours after methotrexate is completed.
 - Cyclophosphamide 600 mg/m² IV on day 8, vincristine 1 mg/m² on day 8
 - Repeat cycle every 2 weeks
 - If resistance occurs, cisplatin 80 mg/m² IV on day 8 and etoposide 100 mg/m² IV on day 8 is administered in the EMA/EP regimen as a replacement of the cyclophosphamide and vincristine portion of the EMA/CO regimen. The EMA portion of the regimen is unchanged.

- e. If brain metastasis is present, high dose EMA/CO is used. EMA/CO doses are the same as above except the methotrexate dose: 1000 mg/m² by 24 hour infusion on day 1 (alkalinize urine), Leucovorin 15 mg IV, IM or PO q 8 hours x 9 doses after MTX infused. May also need to add intrathecal methotrexate 12.5 mg every 2 weeks.
2. Treatment continues for three full cycles after the β -hCG becomes negative. Surveillance includes weekly β -hCG during treatment, then β -hCG every 2 weeks x 3, then monthly β -hCG for 24 months after completion of therapy.
- C. Stage IV, High Risk
 1. Treatment is urgent and includes EMA/CO, selective surgery and selective radiation therapy depending on the sites of metastases. Liver lesions may hemorrhage and resection is occasionally needed.
 2. Brain metastasis is usually symptomatic and is considered an oncologic emergency. Treatment is either with radiation therapy (30 Gy in 10 fractions) or intrathecal methotrexate or high dose EMA/CO (see section X.B.1.e, above).
- D. If resistant disease develops, diagnosis may be aided by PET scan, angiography, or radiolabelled antibody to β -hCG. Surgical resection of resistant foci of disease in uterus, lung, brain, or liver may improve prognosis
- E. Placental site trophoblastic tumor (PSTT) is refractory to chemotherapy. When identified, surgical treatment including hysterectomy is indicated.

XI. Survival

	Rx	Survival
Low Risk	MTX-FA, Act-D	95-100%
High Risk	EMA/CO	83%
High Risk, CNS	EMA/CO, CNS RT	68%

Note that low risk disease includes lung metastases.

XII. Fertility is essentially unchanged once the disease has been cleared.

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Rev. 3/2005

Ovarian Cancer

I. Incidence:

- A. Second most common gyn malignancy in U.S. Largest number of gyn cancer deaths. In 2006, incidence 20,180 cases with 15,310 deaths (Jemal)
- B. Incidence rises with age, peak incidence age 54-64
- C. Individual lifetime risk of any ovarian neoplasm 5-7%. Individual lifetime risk of ovarian cancer 1.8%. Risk that adnexal mass is malignant 7-13% (premenopause), and 30-45% (postmenopause) (Koonings)
- D. Differential diagnosis for adnexal masses
 1. Ovary
 - a. functional cysts
 - b. endometriosis
 - c. benign neoplasm: epithelial, germ cell, stromal
 - d. malignant neoplasm: epithelial invasive, epithelial low malignant potential, germ cell, stromal
 2. Uterus (e.g. pedunculated fibroid, sarcoma, etc.)
 3. Fallopian tube (e.g. hydrosalpinx, paratubal cyst, Fallopian tube carcinoma, etc.)
 4. GI tract (e.g. diverticulosis, appendiceal abscess or tumor, rectal carcinoma, etc.)
 5. Urinary tract (e.g. neurogenic bladder, bladder carcinoma, etc.)
 6. Other: (e.g. aneurysm or A-V malformation, pelvic fracture, etc.)

II. Epidemiology

- A. Incidence increased 200% between 1930-2004

- B. Risk Factors, Epithelial Ovarian Carcinoma

	RR
Positive Family History	29
History breast cancer	2
Nulliparity (vs. P >5)	4-5
Age at 1st pregnancy (>25 vs < 20)	3
Talc (rare cause of cancer because exposure is low)	3
Obesity	2
OCP use	0.5

- C. Risk factors, germ cell: 50% risk of dysgerminoma in patients with dysgenetic gonads

- D. Proposed etiologies, epithelial carcinomas

1. "Incessant ovulation". Probably accounts for the majority of ovarian cancers.
 - a. Prolonged stimulation by pituitary gonadotropins
 - b. Repetitive surface trauma / healing due to ovulation or inflammation
2. Genetic: autosomal dominant gene with variable penetrance. Three known pedigrees for Familial Breast / Ovarian Cancer (FBOC): site specific, breast-ovary, "cancer family syndrome" (Lynch II). FBOC accounts for 5-10% of ovarian cancers
 - a. BRCA-1. Chromosome 17q21. Tumor suppressor gene. Over 500 mutations reported. Accounts for 70-80% of FBOC. Founder mutations in Ashkenazi Jews: 185delAG, 5382insC.
 - b. BRCA-2. Chromosome 13q12. Tumor suppressor gene. Over 300 mutations reported. Accounts for 10-30% of HBOC. Associated with male breast cancer. Founder mutation in Ashkenazi Jews: 6174delT.
 - c. Criteria to determine high risk individual for BRCA1 or BRCA2 testing:
 - i. Personal history of breast cancer < age 40, bilateral breast cancer, or breast and ovarian cancer.
 - ii. Family history predictive of >10% chance of mutation: breast cancer in ≥ 2 relatives at age < 50, or 1 breast cancer at age < 50 and any ovarian cancer,

or ≥ 2 ovarian cancers, or any male relative with breast cancer, or any Ashkenazi Jewish family with breast or ovarian cancer

- iii. If individual is high risk, then:
 - a. Genetic counseling should be recommended and gene testing offered.
 - b. High risk individuals may benefit from chemoprevention with OCP (literature with conflicting studies)
 - c. For BRCA mutation carriers, prophylactic oophorectomy results in 85-96% ovarian cancer risk reduction and 53-68% breast cancer risk reduction (Lalley: Kauff, Reebeck)
 - d. HNPCC (Lynch II). Mismatch repair genes: MLH1, MSH2, MSH6, PMS2. Identify high risk individual for HNPCC testing using Amsterdam criteria for risk assessment: (1) 3 or more relatives with colon cancer across 2 generations, (2) at least 1 colon cancer < 50 years of age, (3) exclude FAP, (4) any colon with either endometrial cancer < 50 years of age or ovarian cancer at any age.
 - e. Risk of cancer depends on specific mutation and age of patient and may be modified by environmental issues (e.g. chemoprevention).

Site	BRCA1	BRCA2	HNPCC
Female breast cancer	60-85%	60-85%	N / C
Ovarian cancer	20-40%	10-20%	12%
Endometrial cancer	N / C	N / C	42-60%
Colon cancer	Possible \uparrow	N / C	70-82%
Stomach / GI	N / C	Possible \uparrow	19%
Male breast cancer	N / C	6%	N/A
Prostate	25%	5-7.5%	N / C

- E. Presenting symptoms: Abd discomfort (50%), GI (20%), urinary (15%), vaginal bleeding (15%), weight loss (15%). 11% of stage I patients have symptoms and only 5% are asymptomatic (Goff). Symptoms may mimic pregnancy. Germ cell tumors may present with acute pain. Precocious pseudopuberty and virilization seen with some germ cell and sex cord/stromal tumors

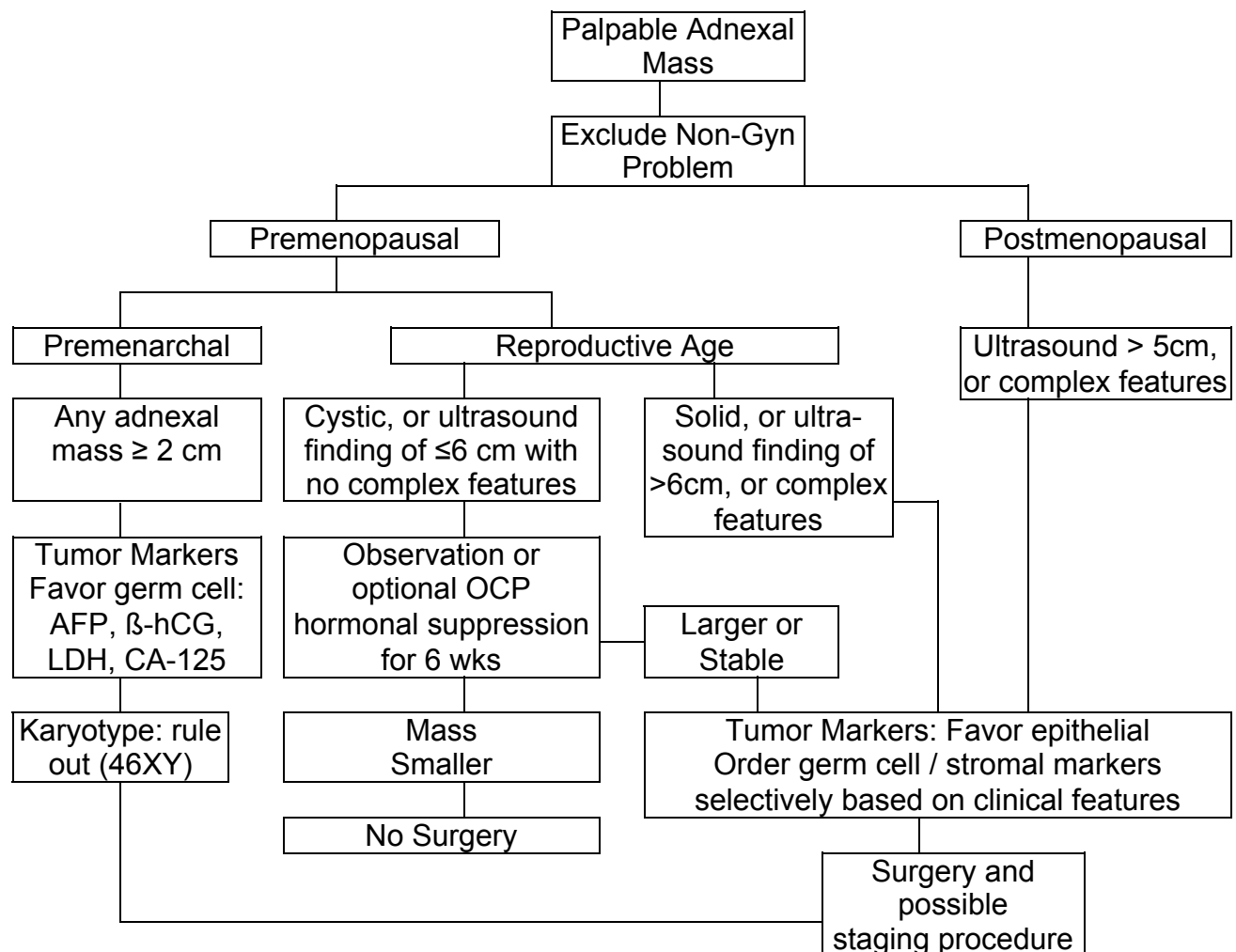
III. Diagnosis and Screening for Ovarian Mass

- A. Obtain family history and initiate genetic counseling and gene testing for high risk individual. (See Section II.D.2.a-e.)
- B. Regular pelvic exams per ACOG recommendation.
- C. Ultrasound for screening controversial due to cost and sensitivity/specificity (van Nagell). When used to triage a known mass 75-100% sensitive, 83-95% specific (Sassone, Kawai, Kurjak)
- D. Tumor Markers. Sensitivity and specificity too low for screening. CA-125 has 55% false negative rate for stage I epithelial ovarian cancer. See Pathology Section (VII.A-D.) for markers associated with each tumor type. New markers such as Ovachek (proteomics-based chip) and LPA are in development.
- E. Prospective, randomized trial does not show benefit to screening for ovarian cancer with combined CA-125 and ultrasound (Jacobs)

IV. Preoperative Testing and Preparation (Guidozzi, Ozols)

- A. Tumor marker(s) appropriate for patient's age
- B. Ultrasound helpful for triage of clinically palpable cystic masses
- C. Chest X-ray abnormal in 9% of new cases, to rule out metastases or effusions
- D. Liver function tests, important if ascites present to rule out primary liver disease
- E. Barium enema or colonoscopy abnormal in 39% of new cases with large or fixed masses. Order if > 45 years old or if GI symptoms present

- F. Abdominal and pelvic CT scan useful for some new cases with large or fixed masses.
Not necessary for all new cases
- G. Intravenous pyelogram abnormal in 45% of new cases. CT scan more useful particularly if large or fixed mass present
- H. Head CT or abd/pelvic MRI; liver, spleen, and bone scans NOT routinely indicated
- I. Patients with suspicious adnexal masses should be prepared for definitive staging procedure
1. Preoperative consultation with or referral to gynecologic oncologist
 2. Consent for primary staging and cytoreductive surgery
 3. Mechanical bowel preparation
 4. Pre-operative antibiotics
 5. Thromboembolic prophylaxis with SCDs and / or heparin or fractionated heparin
 6. Appropriate positioning of the patient
 - a. Low lithotomy for patients with cul de sac masses
 - b. Supine for all others
 7. Appropriate incision
 - a. Vertical incision preferred if malignancy is likely
 - b. Maylard incision is acceptable alternative
 - c. Pfannenstiel incision not desirable for high risk cases. Can be converted to Cherney incision for improved upper abdominal exposure
 - d. Laparoscopic approach requires careful triage (Reynolds)
- J. Adnexal mass decision tree:



V. FIGO Staging for Ovary, Revised 1989

<u>Stage I:</u>	Growth limited to the ovaries.
I a	Growth limited to one ovary; no ascites. No tumor on the external surface; capsule intact.
I b	Growth limited to both ovaries; no ascites. No tumor on the external surface; capsule intact.
I c	Tumor on the surface of one or both ovaries; or with capsule ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.
<u>Stage II:</u>	Growth involving one or both ovaries with pelvic extension.
II a	Extension and/or metastases to the uterus and/or tubes.
II b	Extension to other pelvic tissues.
II c	Tumor of stage II with tumor on surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.
<u>Stage III:</u>	Tumor involving one or both ovaries with peritoneal implants outside the pelvis and or positive retroperitoneal or inguinal lymph nodes. Superficial liver metastasis equals Stage III.
III a	Histologically confirmed microscopic seeding of abdominal peritoneal surfaces.
III b	Histologically confirmed implants of peritoneum, ≤ 2 cm in diameter. Nodes negative.
III c	Abdominal implants >2 cm and/or positive retroperitoneal or inguinal lymph nodes.
<u>Stage IV:</u>	Distant metastases. If pleural effusion is present, there must be positive cytologic test results to allot to a stage IV. Parenchymal liver metastasis equals stage IV.

VI. Surgical Procedures for Ovarian Cancer

A. Initial surgical procedure for diagnosis and staging:

1. Objective is to define stage and to remove as much of the tumor as possible.
2. Staging requires biopsy or removal of affected ovary, pelvic and para-aortic lymph nodes, omentum, peritoneal biopsies (pelvic sidewall, cul de sac, bladder serosa, pericolic gutters, and diaphragm), intraperitoneal cytology, and any suspicious lesions.
3. Debulking removes macroscopic disease. Residual disease is described in terms of diameter of largest remaining nodules and percentage of tumor removed.
4. Techniques and procedures for debulking include. Aggressiveness of resection depends on the likelihood of attaining optimal debulking. If a patient has non-resectable disease, radicality of debulking will be decreased to minimize morbidity.
 - a. TAH-BSO
 - b. Modified posterior exenteration
 - c. Small or large intestinal resection
 - d. Splenectomy
 - e. Peritoneal stripping
 - f. Ablation or resection of surface lesions with CUSA, LEEP, laser or excision
 - g. Resection of portions of affected organs such as ureter, liver, and stomach

B. Interval cytoreductive surgery

1. Debulking surgery following neoadjuvant ("induction") chemotherapy for patients who could not have an optimal primary cytoreductive surgery due to extent of disease
2. Significant survival benefit demonstrated in one prospective randomized clinical trial (van der Burg)

C. Second look surgery

1. Surgical reassessment for patients with complete response after primary surgery and chemotherapy
2. May be used as part of treatment protocols with informed consent but should not be used as routine clinical practice

D. Secondary cytoreductive surgery

1. Debulking surgery for patients with persistent disease after completion of planned therapy or with recurrent disease after a period of remission.
2. Best candidates for this surgery have localized recurrences.
3. Predictors of successful secondary cytoreduction include relapse 12 months or longer from completion of therapy, tumors that were responsive to primary chemotherapy, high performance status, and potential for complete resection based on preoperative evaluation (Eisenhauer)
4. Patients able to be debulked to microscopic residual disease have 51% survival at 5 years compared to 10% survival at 5 years if any residual disease remained. (Hoskins)

E. Palliative secondary surgery

1. Surgery to relieve symptoms associated with progression of ovarian carcinoma such as bowel obstruction.
2. Palliative surgery is kept to a minimum and is offered to patients likely to receive symptomatic relief
3. Selection of patients likely to benefit from palliative surgery for bowel obstruction associated with progression of ovarian cancer can be objectively scored (Krebs)
 - a. If score ≤ 6 , 84% chance of palliative benefit from surgery resulting in survival of at least 8 weeks.
 - b. If score > 6 , 20% chance of palliative benefit from surgery resulting in survival of at least 8 weeks.
 - c. Scoring system

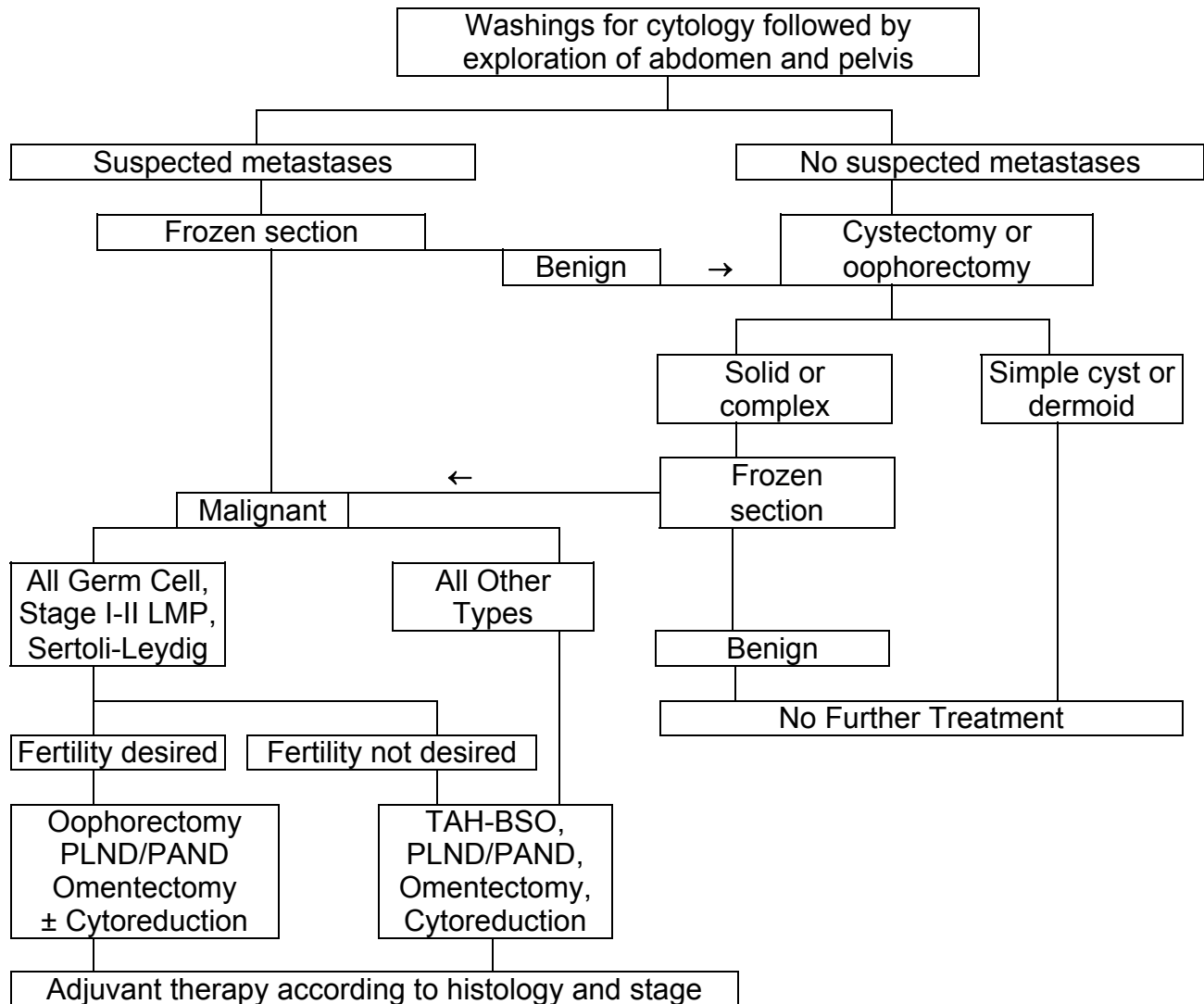
Parameter		Risk Score
Age (years)	< 45	0
	45-65	1
	>65	1
Nutritional Deprivation	None or minimal	0
	Moderate	1
	Severe	2
Tumor Status	No palpable intraabdominal masses	0
	Palpable intraabdominal masses	1
	Liver involvement or distant mets	2
Ascites	None or mild (asymptomatic, no distension)	0
	Moderate (abdominal distension)	1
	Severe (requiring frequent paracentesis)	2
Previous chemotherapy	None or no adequate trial	0
	Failed single drug therapy	1
	Failed combination therapy	2
Previous radiation therapy	None	0
	Pelvic radiotherapy	1
	Whole abdominal radiotherapy	2

- F. Prophylactic oophorectomy (Berchuck, NIH consensus)
 - 1. Candidates for prophylactic oophorectomy should have documented hereditary ovarian cancer pedigree (ovarian site specific, breast-ovary, or hereditary non-polyposis colorectal cancer) or proven gene mutation (BRCA-1, BRCA-2, MSH-2, MLH-1, PMS-1, PMS-2)
 - 2. Ovaries removed after age 35 or completion of childbearing
 - 3. Primary peritoneal carcinoma can occur in women who have undergone prophylactic oophorectomy in 2–10% of cases but risk of dying from ovarian cancer drops from RR 24 to RR13 in the surgically treated group
- G. Management of the pelvic mass in pregnancy (Carney)
 - 1. Surgical intervention usually deferred until second trimester, if possible, in order to minimize anesthetic risks to developing embryo.
 - 2. Staging may be abbreviated due to suboptimal exposure secondary to uterine enlargement
 - 3. If tumor is of advanced stage or high grade, chemotherapy during pregnancy may be needed. Literature supports use of chemotherapy but data on effects upon pregnancy are scant. Treatment for lower risk disease deferred until postpartum.
- H. Surgical pitfalls. Ovarian cancer outcome may be hampered by poor surgical technique, inadequate or incomplete staging, and absence of aggressive debulking. Adequacy of staging and survival is improved when treatment is performed by a gynecologic oncology specialist (Gershenson, Gostout, Carney, Earle, Elit, McGowan)
- I. Surgical controversies
 - 1. Rupture of ovarian cyst during surgery does not worsen prognosis (Sevelde)
 - 2. Delay of definitive surgery after initial diagnosis worsens prognosis (Lehner)
 - 3. Role of restaging after incomplete staging procedures (Soper)
 - 4. Role of laparoscopic surgery (Maiman, Reynolds)
 - 5. Attaining optimal debulking is the result of:
 - a. Favorable tumor biology (Covens)
 - b. Surgical expertise and subspecialty training (Eisenkop)
- J. When to refer to a subspecialist (ACOG / SGO Committee Opinion, Gostout)
 - 1. Postmenopausal women with pelvic mass and at least 1 of the following: CA-125 above normal, ascites, nodular or fixed mass, evidence of abdominal or distant mets, family history of 1 or more first degree relatives with ovarian / breast cancer
 - 2. Premenopausal women with pelvic mass and at least 1 of the following: CA-125 >200 U/mL, ascites, evidence of abdominal or distant mets, family history of 1 or more first degree relatives with ovarian / breast cancer
- VII. NIH consensus recommendations regarding management of ovarian cancer
 - A. Women with masses having a significant risk of malignancy should be given the opportunity to have surgery performed by a gynecologic oncologist
 - B. Aggressive cytoreductive surgery as primary management of ovarian cancer will improve chances for long term survival
 - C. Fully staged FIGO IA-1 and IB-1 ovarian cancers do not require postoperative adjuvant therapy
 - D. Second look laparotomy should only be done for patients enrolled in clinical trials or for those patients in whom surgery will affect clinical decision making
 - E. Platinum-based (carboplatin or cisplatin) and paclitaxel (Taxol) are optimal first line chemotherapy drugs following primary debulking surgery
 - F. There is no evidence to support screening of women with or without affected first degree relatives

G. Recommendations for prophylactic oophorectomy include

1. Confirmed pedigree
2. Annual U/S and CA-125 until 35y or completed childbearing
3. Oophorectomy after 35y or completed childbearing

VIII. Intra-operative steps for initial assessment and staging of adnexal masses regardless of laparotomy versus laparoscopy approach.



IX. Pathology

A. Epithelial Ovarian Tumors: 80-90% of ovarian cancers. Subdivided into low malignant potential (LMP, "borderline"), and malignant types. LMP tumors account for 15-20% of epithelial cancers, and 40-80% are detected while stage I. Malignant epithelial tumors present beyond Stage I in 60-80% of cases.

1. Serous: 50% of epithelial CA. Bilateral >33%. Marker: CA-125
2. Mucinous: 10-15% of epithelial CA. Bilateral 5-10%. Marker: CA 19-9, CEA
3. Endometrioid: 10-15% of epithelial CA. Bilateral 15%. Synchronous endometrial primary 15-30%. Marker: CA-125
4. Clear Cell: 5% of epithelial CA. Bilateral 5-10%. Marker: CA-125
5. Brenner: <1% of epithelial CA. Marker: CA-125

- B. Germ Cell Tumors: 3-5% of ovarian cancers (15% in oriental or black populations). 65-70% present Stage I. Almost always unilateral, except for dysgerminoma.
 - 1. Dysgerminoma: 50% of malignant germ cell tumors. 75% occur between age 10-30, rare after 35. 15% have mixed histology. 5% associated with dysgenetic gonad. 75% present Stage I; node mets \geq 25%. Bilateral 15-20%. Marker: LDH, PLAP
 - 2. Teratoma. Marker: none.
 - a. Immature: 20% of malignant germ cell tumors. 50% occur between ages 10-20.
 - b. Malignancy arises in 1-2% of mature teratomas (usually squamous carcinoma).
 - 3. Endodermal Sinus Tumor (yolk sac tumor): 20% of malignant germ cell tumors. Median age at incidence 17, 33% occur before menarche. 75% present with pain. Spontaneous rupture common. Marker: AFP
 - 4. Embryonal Carcinoma: 5% of malignant germ cell tumors. Median age at incidence 14. Markers: AFP, hCG
 - 5. Mixed germ cell tumors: 10-15% of malignant germ cell tumors, components: DG 80%, EST 70%, choriocarcinoma 70%, IT 53%. Marker: AFP, hCG
 - 6. Rare types: polyembryoma, choriocarcinoma, gonadoblastoma
- C. Sex Cord/Stromal Tumors: 5-6% of ovarian cancers. Usually diagnosed while Stage I
 - 1. Granulosa Cell Tumor
 - a. Adult type: 3% of all ovarian cancers. Average age at incidence 53. , Can recur after 5-30 years. Often rupture and hemorrhage. Bilateral <5%. Produce estrogen, causing endometrial adenocarcinoma in 10-15%, and hyperplasia in 25-50%. Virilization occurs rarely. Markers: inhibin A & B, estradiol
 - b. Juvenile type: rare tumor, 97% occur before 30y. Usually produces estrogen.
 - 2. Sertoli-Leydig Cell Tumor: <1% of ovarian cancers. Average age at incidence 25. 70-85% hormonally active, usually virilizing. Bilateral <1%. Marker: testosterone
 - 3. Thecoma-Fibroma: rare. Usually benign, 1-5% of all ovarian tumors. Bilateral 10%
 - 4. Rare types: Sertoli cell tumor (Pick's adenoma), Leydig cell tumor, hilus tumor, sex cord tumor with annular tubules, gynandroblastoma
- D. Tumors metastatic to ovary: 5-6% of ovarian cancers.
 - 1. Gyn sites: endometrial CA 5% metastasize to ovary, cervical adenocarcinoma 1%
 - 2. Breast: at autopsy, 24% with metastases to ovary
 - 3. GI: Krukenberg tumors account for 30-40% of ovarian metastatic lesions
 - 4. Lymphoma: 5% with advanced stages have ovarian metastases

X. Treatment Plans

Note that complete surgical staging and debulking is required even if uterus and contralateral ovary are to be preserved

A. Epithelial carcinomas

- 1. Low malignant potential
 - a. Stage I, II: unilateral salpingo-oophorectomy (USO) or TAH-BSO, depending on reproductive desires. Complete surgical staging and debulking is required. No adjuvant therapy if no residual disease.
 - b. Stage III-IV: TAH-BSO. Complete surgical staging and debulking is required. Then:
 - i. No adjuvant therapy if no residual disease
 - ii. If residual disease is present or for either invasive implants or micropapillary architecture, then carboplatin and paclitaxel (Taxol) IV chemo x 6 cycles. Consider intraperitoneal therapy if residual disease / adhesions minimal
 - iii. Consider clinical trial for primary, consolidation or recurrent disease therapy
 - iv. Second look laparotomy only if on clinical trial

2. Invasive epithelial carcinoma
 - a. Stage Ia grade 1, Ib grade 1: USO, BSO or TAH-BSO, depending on reproductive desires. Complete surgical staging and debulking is required. No adjuvant therapy.
 - b. Stage Ia grade 2, Ia grade 3, Ib grade 2, Ib grade 3, Ic; IIa, IIb, IIc: TAH-BSO Complete surgical staging and debulking is required. Then:
 - i. Carboplatin and paclitaxel (Taxol) IV chemotherapy x 3-6 cycles, or
 - ii. Consider clinical trial for primary, consolidation or recurrent disease therapy, or
 - iii. Consider intraperitoneal chemotherapy if residual disease and adhesions minimal
 - c. Stage III, IV: TAH-BSO. Complete surgical staging and debulking is required. Then:
 - i. Carboplatin and paclitaxel (Taxol) chemotherapy x 6 cycles, or
 - ii. Consider clinical trial for primary, consolidation or recurrent disease therapy, or
 - iii. Strongly consider intraperitoneal chemotherapy if, or
 - iv. Consider whole abdominal radiation therapy, if residual disease < 5 mm (not a standard therapy)
 - v. Second look laparotomy only if on clinical trial
 - vi. If unable to be debulked, consider neoadjuvant chemotherapy followed by secondary cytoreductive surgery
- B. Germ cell malignancies (carboplatin is NOT equivalent to cisplatin for these tumors)
 1. Dysgerminoma
 - a. Stage Ia: USO. Complete surgical staging and debulking is required. No adjuvant therapy.
 - b. All others: USO or TAH-BSO, depending on reproductive desires. Complete surgical staging and debulking is required. Then:
 - i. BEP regimen: cisplatin, etoposide, bleomycin repeated q 3-4 weeks x 3-6 cycles, or until markers negative x 3; or,
 - ii. VAC: vincristine, dactinomycin (Actinomycin-D), cyclophosphamide repeated q 3-4 weeks x 3-6 cycles, or until markers negative x 3; or
 - iii. Whole abdominal radiation therapy (not preferred therapy because chemotherapy has excellent chance of cure while preserving fertility whereas radiation will cause ovarian failure)
 2. Teratoma
 - a. Stage Ia grade 1: USO. Complete surgical staging and debulking is required. No adjuvant therapy.
 - b. All others: USO or TAH-BSO, depending on reproductive desires. Complete surgical staging and debulking is required. Then: BEP or VAC chemo x 3-6 cycles, or until markers negative x 3.
 3. All Other germ cell tumors, all stages: USO or TAH-BSO, depending on reproductive desires. Complete surgical staging and debulking is required. Then: BEP or VAC chemo x 3-6 cycles, or until markers negative x 3.
- C. Sex-cord stromal malignancies
 1. Stage Ia grade 1: USO. Complete surgical staging and debulking is required. No adjuvant therapy. D&C required to rule out synchronous endometrial tumor.
 2. All others: USO or TAH-BSO, depending on reproductive desires. Complete surgical staging and debulking is required. Then cisplatin, vinblastine, bleomycin (PVB); or BEP x 3-6 cycles or until markers negative x 3. D&C required if uterus not removed to rule out endometrial cancer or hyperplasia.
- D. Tumors metastatic to ovary: Treat based on site of primary disease.

E. Relapse after primary treatment

1. Epithelial tumors sensitive to platinum and with progression-free interval > 12-24 months: retreat with carboplatin + paclitaxel regimen.
2. Epithelial tumors with resistance to platinum or progression-free interval < 6 months:
 - a. Treat with sequential monotherapy using FDA approved chemotherapy. Active drugs include liposomal doxorubicin (Doxil), etoposide, gemcitabine, topotecan, and docetaxel (Taxotere). Also active but used less often are: irinotecan, cyclophosphamide (Cytosan), altretamine (Hexalen), melphalan, and vinorelbine (Navelbine)
 - b. Enroll on clinical trials. Active trials listed at www.NCI.NIH.gov in the PDQ database.

XI. Survival

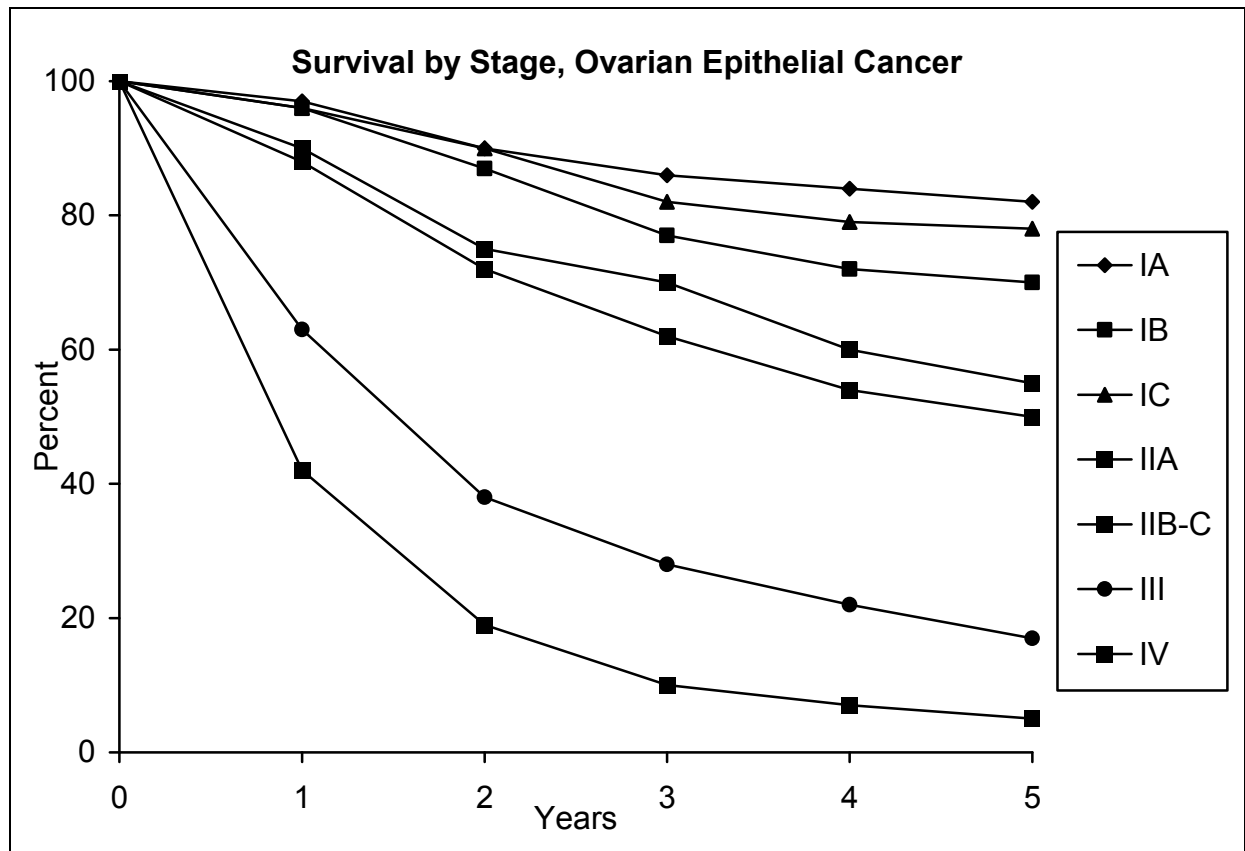
A. Epithelial Tumors

1. Grade effects survival. Stage I, grades 1, 2, 3 5y survival 96%, 81%, 58%, resp.
2. LMP tumors: excellent survival in all stages if tumor completely resected. Recurrences can be late (> 10 y.)
3. Advanced stage disease successfully debulked to microscopic residual (NED) vs. <2 cm, vs. >2 cm (Cohen)

Group	Survival	Status
NED	100% @ 45m.	NED
≤2 cm	100% @44m.	50%AWD
>2 cm	35% @15.9m.	100%AWD

4. Randomized clinical trials
 - a. ICON 2: demonstrated that carboplatin alone was equally efficacious to cisplatin, doxorubicin and cyclophosphamide. ICON 3 reconfirmed this finding when single agent carboplatin was compared to carboplatin and paclitaxel. ICON 4 shows weak, but statistically significant benefit to the combination of carboplatin with paclitaxel.
 - b. GOG #111: cisplatin with either cyclophosphamide or paclitaxel showed that paclitaxel-containing treatment arm had higher complete response (51 vs. 31%), higher overall response (73 vs. 60%), longer PFI (18 vs. 13 months), and longer median survival (38 vs. 24 months). (McGuire)
 - c. GOG #158: paclitaxel with either cisplatin or carboplatin was equally efficacious. Carboplatin arm had lower neurotoxicity and more severe thrombocytopenia. (Ozols)
 - d. Dose intensity trial tested single-agent carboplatin at escalating doses. Effectiveness was equivalent for all doses above AUC 4 using the Calvert formula. (Jakobsen)
 - e. Intraperitoneal versus intravenous therapy shows survival and progression-free interval advantages with IP therapy in 3 of 5 randomized trials (Markman). GOG # 172 randomized IV paclitaxel (135 mg/m² over 24 hours) and IV cisplatin (75 mg/m²) q 21 days for 6 cycles versus IV paclitaxel (135 mg/m² over 24 hours on day 1), IP cisplatin (100mg/m² on day 2), and IP paclitaxel (60 mg/m² on day 8) q 21 days for 6 cycles. Median progression-free survival was 18.3 and 23.8 months, and overall survival was 49.7 versus 65.6 months, respectively. Only 42% of patients could complete the IP therapy largely due to catheter complications. Quality of life was significantly worse in the IP group during and shortly after Tx but not at 1 year. Grade 3-4 toxicity was higher in the IP group by the following ratios: GI (2x), renal (3.5x), infection (2.5x), fatigue (4x), pain (7x), and metabolic events (3.5x) (Armstrong)

5. Ovarian epithelial cancer survival, by stage



Morrow, 1998

B. Germ Cell and Stromal Tumors

Histology	Stage	Therapy	Survival
DG	Ia	Surgery, VAC or RT if recurs	95%
	All others	Surgery plus VAC	85%
IT	Ia1	Surgery	90-95%
	All others	Surgery plus BEP	85%
EST	All stages	Surgery plus BEP or PVB	75-95%
Granulosa Cell	All stages	Surgery ± chemotherapy (VAC, BEP, PVB, RT or hormone tx.)	95%, 68% 5y, 10y
Sertoli-Leydig	All stages	Surgery ± VAC or BEP or PVB	70-90%

XII. Fertility

- If anatomic structures are preserved, fertility excellent
- Alkylating chemotherapy drugs cause ovarian failure as function of age and dose. If amenorrhea occurs, < 10% chance of resumed ovarian function
- Radiation therapy causes ovarian failure as function of age and dose. All women receiving > 800 cGy to pelvis develop ovarian failure

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Uterine Sarcomas

I. Incidence

- A. Uterine sarcoma accounts for about 4 - 6% of all uterine malignancies, resulting in about 1600-2300 cases per year in the US in 2007 (Jemal).
- B. Carcinosarcoma accounts for 4% of uterine cancers, with leiomyosarcoma accounting for 1.5% and stromal sarcoma accounting for about 0.5% (Sutton, 2009)
- C. Sarcoma rarely may arise in non-uterine sites such as ovary, cervix, vagina and vulva

II. Epidemiology

A. Mean age at diagnosis varies by sarcoma type Years

Carcinosarcoma	65-67
Adenosarcoma	57-58
Leiomyosarcoma	53-56
Endometrial stromal tumors	41-48

B. Racial disparity

1. African heritage increases age adjusted incidence 2-fold
 - a. Leiomyosarcoma incidence per 100,000 1.5 (Black) 0.9 (White)
 - b. Carcinosarcoma incidence per 100,000 4.3 (Black) 1.7 (White)
2. European-Jewish ancestry increases risk 2-fold compared to Asian-African Jews or non-Jewish females

C. Risk Factors (Schwartz)

	Relative Risk
Late menarche	1.8 (0.5 – 6.7)
Early menopause	1.2 (0.3 – 5.0)
Late first birth	3.6 (1.2 – 10.9)
Prior abortion	2.5 (0.8 – 7.4)

D. Etiology

1. Etiology for sarcoma is poorly understood. Most are felt to be sporadic in origin.
2. Prior radiation therapy or exposure has been implicated in up to a third of carcinosarcomas but is rarely associated with leiomyosarcoma
3. Carcinosarcoma is frequently associated with common endometrial carcinoma risk factors and presumably shares some etiologic pathways (D'Angelo)
4. Translocations causing fusion genes are found in a growing number of sarcoma types.
 - a. Low grade endometrial stromal sarcoma is associated with translocation t (7;17) (p 15-21; q 12-21) in more than 33% of cases. This fuses and affects function of zinc finger proteins JAZF1 and JJAZ1 (Nucci)
 - b. Clear cell sarcoma, myxoid liposarcoma, alveolar rhabdosarcoma, and alveolar soft-part sarcomas are also associated with fusion genes
5. Activation, over expression, or mutation of oncogenes or tumor suppressor gene pathways, offer possible insights into etiology, markers, and targeted therapies.
 - a. Some leiomyosarcomas (Range 0-83% depending on series) express *c-kit*, a receptor that activates tyrosine kinase signal transduction. This may respond to imatinib (Gleevec) targeted therapy as proven with GIST tumors
 - b. Other possible markers include *p53*, *mdm-2*, *PDGF-β*, *c-abl*, *HER2/neu*, *VEGF*, *IGF-II*
6. Immunocompromised patients with Epstein-Barr virus have increased incidence of leiomyosarcoma seen in at least 2 populations:
 - a. HIV in pediatric patients (Rogatsch)
 - b. Immunosuppressive drugs in transplant patients (Boman)

E. Presenting symptoms (Salazar)

Abnormal uterine bleeding	86%
Abdominal pain	19%
Abdominal mass	15%
Weight loss	7%
Vaginal discharge	4%

F. Natural History

1. Patterns of spread (Rose)

Metastatic sites	
Omentum – peritoneum	59%
Lung	52%
Pelvic nodes	41%
Para-aortic nodes	38%
Liver parenchyma	34%

2. Causes of Death (Rose)

Metastatic sites	
Omentum – peritoneum	59%
Lung	52%
Pelvic nodes	41%
Para-aortic nodes	38%
Liver parenchyma	34%

III. Pathology

A. World Health Organization Classification for Uterine Sarcomas (2003)

1. Mesenchymal Tumors

a. Endometrial stromal and related tumors

- i. Endometrial stromal sarcoma, low grade
- ii. Endometrial stromal nodule
- iii. Undifferentiated endometrial sarcoma

b. Smooth muscle tumors

i. Leiomyosarcoma

- A. Epithelioid variant
- B. Myxoid variant

ii. Smooth muscle tumor of uncertain malignant potential

iii. Leiomyoma, not otherwise specified

Histologic variants	Lipoleiomyoma variant
Mitotically active variant	Growth pattern variants
Cellular variant	Diffuse leiomyomatosis
Hemorrhagic cellular variant	Dissecting leiomyomatosis
Epithelioid variant	Intravenous leiomyomatosis
Myxoid	Metastasizing leiomyoma
Atypical variant	

c. Miscellaneous mesenchymal tumors

- i. Mixed endometrial and smooth muscle tumor
- ii. Perivascular epithelioid cell tumor
- iii. Adenomatoid tumor
- iv. Other malignant or benign mesenchymal tumors

2. Mixed epithelial and mesenchymal tumors

- a. Carcinosarcoma (Malignant Mixed Mullerian Tumor, metaplastic carcinoma)
- b. Adenosarcoma
- c. Carcinofibroma

- d. Adenofibroma
- e. Adenomyoma with or without Atypical polypoid variant

IV. Mesenchymal Tumors of Endometrial Stroma

- A. Endometrial Stromal Nodule. Rare. Median age 53. Solitary nodules, pushing margins without infiltration, LVSI absent, variable mitotic index.(usually $\leq 5/10$ HPF). Treatment: TAH; recurrences not reported.
- B. Endometrial Stromal Sarcoma (ESS) (Obsolete names: Endolymphatic stromal myosis, low grade endometrial stromal sarcoma)
 - 1. Epidemiology. Rare. Patients usually premenopausal.
 - 2. Natural History and Prognostic Factors. Rarely diagnosed pre-op. Stage $> I$ in 21% of cases. Indolent course despite 55% recurrence rate for stage I disease. Recurrence more likely if tumor > 5 cm. Long-term survival common, even with disease. Low estrogen receptor content is bad prognostic indicator.
 - 3. Pathology. Low mitotic index (usually $< 10/10$ HPF). Gross appearance of "worm-like" growth through myometrium.
 - 4. Treatment
 - a. Surgical resection. Radical hysterectomy preferred if diagnosed pre-op. Oophorectomy reduces recurrence risk. Measure hormone receptors in tumor
 - b. Adjuvant RT improves local control; 40% have distant recurrences.
 - c. Progestin therapy effective: 25% CR, 25% PR, 45% stable disease
 - d. Post surgical RT or progestins warranted if tumor > 5 cm, or if LVSI present.
 - e. Chemotherapy has limited effectiveness. Doxorubicin active, 25%
- C. Undifferentiated Endometrial Sarcoma (UES)
 - 1. Epidemiology. ESS accounts for 14% of uterine sarcomas. Patients usually postmenopausal.
 - 2. Natural History and Prognostic Factors. Patients present with PMB, menorrhagia, pain. Prognosis very poor.
 - 3. Pathology. High mitotic index, homologous cell type. Cytologic atypia to the extent that cells cannot be recognized as stromal in origin
 - 4. Treatment
 - a. TAH, BSO, consider node sampling
 - b. Adjuvant RT has little role due to high likelihood of distant recurrence

V. Mesenchymal Tumors of Smooth Muscle

- A. Benign and Borderline Types
 - 1. Atypical smooth muscle tumors: leiomyoblastoma, clear cell leiomyoma, epithelioid leiomyoma, plexiform tumorlet. Very rare. Treated by excision, $\leq 10\%$ recur.
 - 2. Intravenous leiomyomatosis. Rare. Usually premenopausal and hormonally sensitive. Treated by excision and hormone therapy, $\leq 13\%$ recur.
 - 3. Benign metastasizing leiomyoma. Rare. Histologically benign pulmonary mets. Disease progresses in premenopausal women, stable in postmenopausal women. Treated by estrogen ablation.
 - 4. Leiomyomatosis peritonealis disseminata. Rare. Risk factors: Black (67% of cases), pregnant (50% of cases), oral contraceptive users (30% of cases). May not require treatment.
- B. Leiomyosarcoma (LMS)
 - 1. Epidemiology. Mean age at diagnosis 53. Nulliparas account for 20% of LMS. LMS accounts for 35-40% of uterine sarcomas. Risk factors: poorly understood.
 - 2. Natural History and Prognostic Factors. Patients present with menometrorrhagia or post menopausal bleeding (75%), pain, awareness of mass, vaginal discharge. Only 15% detected preoperatively. Recurrences detected locally $<25\%$; lung mets common

3. Pathology.

- a. Smooth muscle tumors can be subdivided into prognostic categories ranging from bland (Stromal Tumor of Uncertain Malignant Potential – STUMP) to aggressive.
- b. LMS graded by mitotic index (mitoses/10 high power fields) and cytologic atypia. Mitotic Index of <5 benign, 5-9 borderline, ≥10 malignant; recurrence rate <10%, 33%, 67%, respectively
- c. Stanford classification (Mittal)

Necrosis	Atypia	Mitotic Index	Diagnosis	Survival
No	No	5 – 20	Mitotically active leiomyoma	128/128
		> 20	Same, limited experience	2/2
	Yes, Focal	< 20	Active leiomyoma	17/17
	Yes, Diffuse	< 10	Atypical leiomyoma with low recurrence rate	1/58 AWD
		> 10	Sarcoma	4/10 DOD
Yes	No	< 10	STUMP	1/4 AWD
		> 10	Sarcoma	3/4 DOD
	Yes	Regardless	Sarcoma	24/33 DOD or AWD

4. Diagnosis

MRI may be able to discriminate between fibroids and sarcoma using presence of > 50% T2 weighed image and any small high-signal T1 weighted image (Tanaka)

5. Treatment

- a. TAH, BSO. Lymph node sampling not helpful due to likelihood of distant mets
- b. Adjuvant radiation does not improve survival. Evidence is equivocal on benefit of local control (Sutton 2009)
- c. Adjuvant chemotherapy does not improve survival
GOG Trial (Omura) randomized no treatment to doxorubicin in adjuvant setting. Recurrence rate was 51% vs. 39%, respectively at 73 months (not significant)
- d. Chemotherapy for metastatic disease. Active regimens: doxorubicin (27% response rate), gemcitabine with docetaxel, ifosfamide, VAC or MAI.

VI. Mesenchymal Tumors of Miscellaneous Type

A. Rhabdosarcoma

1. Embryonal form: sarcoma botryoides, see Vaginal Cancer chapter.
2. Adult form: pleomorphic histology, poor survival.

B. Osteosarcoma

C. Chondrosarcoma

D. Hemangiopericytoma

E. Peripheral Primitive Neuroectodermal Tumor (pPNET) or Ewing's Sarcoma

VII. Mixed Epithelial and Mesenchymal Tumors

- A. Müllerian adenosarcoma. Rare. Benign glands, atypical stroma. Frequently present with bleeding and prolapsing polyp. Two series report prior radiation or tamoxifen as risk factors. Most express hormone receptors and respond to hormone therapy. Prognosis excellent if no sarcomatous overgrowth on histology.

- B. Carcinosarcoma (CS), also called malignant mixed Müllerian tumors (MMMT)
1. Epidemiology. Account for 3-6% of all uterine cancers; 51% of uterine sarcomas. Risk factors: nulliparity (25% of cases), obesity (40% of cases), diabetes (15% of cases), prior radiation (10%, range 0-30% of cases). Estrogen not implicated.
 2. Natural History and Prognostic Factors. Patients present with bleeding (82%), prolapsing cervical mass (33%), pain (25%), abdominal mass (10%). Distant mets found in 10-20%, at presentation. Clinical stage I patients have 50% chance of extra-pelvic mets when initially explored.
 3. Pathology. Glandular and stromal components both malignant.
 - a. Homologous. Stromal differentiation into native uterine cell types
 - b. Heterologous. Stromal cell types not normally found in uterus (e.g. striated muscle, cartilage, bone)
 4. Treatment
 - a. TAH, BSO, lymph node sampling
 - b. Adjuvant radiation therapy indicated postoperatively to control high local recurrence rate (54% without RT, 23% with RT). Survival may or may not be prolonged
 - c. Adjuvant chemotherapy may prolong survival if extrauterine disease present
 - d. Chemotherapy for metastatic disease. Active drugs: doxorubicin, ifosfamide, cisplatin

VIII. Staging

- A. Carcinosarcoma is staged according to Endometrial Cancer staging rules (FIGO, 2009)

B. Leiomyosarcoma, FIGO 2009	
I	Tumor confined to uterus
I A	< 5 cm
I B	> 5 cm
II	Tumor extends to the pelvis
II A	Adnexal involvement
II B	Extends to extrauterine pelvic tissue
III	Tumor invades abdominal tissues (not just protruding into abdomen)
III A	One site
III B	> 1 site
III C	Metastases to pelvic and / or para-aortic nodes
IV A	Invades bladder and / or rectum
IV B	Distant metastasis

C. Endometrial Stromal Sarcoma and Adenosarcoma, FIGO 2009	
I	Tumor limited to uterus
I A	Limited to endometrium or endocervix with no myometrial invasion
I B	Myometrial invasion of \leq 50%
I C	Myometrial invasion of > 50%
II	Tumor extension to pelvis
II A	Adnexal involvement
II B	Involvement of extrauterine pelvic tissue
III	Tumor invades abdominal tissues (not just protruding into abdomen)
III A	One site
III B	More than one site
III C	Metastasis to pelvic or para-aortic lymph nodes
IV A	Tumor invades bladder and / or rectum
IV B	Distant metastasis

IX. Treatment

A. Surgery

1. The general recommendation for primary sarcoma staging surgery is to perform total hysterectomy, bilateral salpingo-oophorectomy, lymphadenectomy and assessment of intra-abdominal structures including omentum (NCCN).
2. Some sarcomas may require more or less aggressive resection as noted above
3. Likelihood of nodal mets ranges from 17% for carcinosarcoma to 3.5% for LMS (Silverburg, Sutton)
4. Neither debulking nor lymphadenectomy improves survival

B. Radiation

1. One randomized trial or observation vs. post-op RT (EORTC) shows reduction of pelvic recurrence with RT from 46.7% to 23.9% with RT for carcinosarcoma but not for LMS or Endometrial Sarcoma. Survival was not changed (Reed)
2. Retrospective data (SEER) shows survival benefit for carcinosarcoma treated with RT regardless of stage (33.2% vs. 41.5%, $p < 0.001$) (Smith)

C. Chemotherapy

1. Clinical trials have been difficult to perform due to rarity of the disease and lack of active agents, particularly for LMS
2. LMS: Active single agents include doxorubicin, ifosfamide. The most active combination therapy is gemcitabine with docetaxel (53% response rate).
3. Carcinosarcoma: Active single agents include ifosfamide, cisplatin, and paclitaxel. Active combination therapy includes ifosfamide with cisplatin (54% response rate, survival not improved) and ifosfamide with paclitaxel (45% with survival improved compared to ifosfamide alone) (Sutton, 2009)

D. Hormonal Therapy

1. Endometrial stromal sarcoma (low grade), adenosarcoma, and low grade leiomyosarcoma may respond to hormonal therapy.
2. Agents reported include progestins (Megace, Provera), tamoxifen, aromatase inhibitors, and GnRH analogues.

X. Survival

Prognosis generally poor due to > 50% recurrence rate even in stage I disease.

Stage	LMS	ESS	UES	CS
I	48%	89%	78%	36%
II	67%	75%	0%	22%
III	0%	67%	14%	10%
IV	0%		0%	6%

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Rev 2/2010

Vaginal Cancer

I. Incidence: 1-2% of all gyn cancers.

II. Epidemiology and Natural History: Etiology and cell types stratified by patient age

A. Childhood tumors

1. Sarcoma botryoides: embryonal rhabdomyosarcoma. 90% occur before 5y of age. Appearance of red-tan grape clusters protruding from vagina. Frequent lymphatic mets to groin and pelvis. Hematogenous mets occur as well.
2. Endodermal sinus tumor: germ cell origin (see ovary chapter). Occurs in infants. Can be mistaken for sarcoma botryoides.

B. Tumors of adolescence and young adulthood: Clear cell carcinoma (CCC) associated with *in-utero* diethylstilbestrol (**DES**) exposure.

1. Features of *in-utero* DES exposure: Risk of CCC (Vagina >> cervix) is 1:1000. History of *in-utero* DES exposure present in 67% of vaginal CCC, 33% of cervical CCC. Mean age of DES associated CCC 19y (range 7-42). Three histologic subtypes: tubulocystic, papillary, solid. Tubulocystic has better prognosis (88% vs 73% 5y survival) and usually occurs after age 19. Adenosis present in 33%. Squamous metaplasia in adenosis makes colposcopic evaluation of dysplasia difficult, but causes eventual regression of adenosis. Lifetime risk of vaginal dysplasia increased. Probably no significant increased risk of breast cancer (controversial). DES associated uterine anomalies (80%) and infertility widely reported.
2. Recommended routine DES exam: Initial colposcopy, pap smear, and palpation of vagina. Take separate pap from vagina and cervix. If adenosis present, re-examine q6 months with colposcopy at least every 4th visit.

C. Tumors of adults

1. Squamous carcinoma: Mean age 60-65y. Most common in upper 1/3 of vagina, and on posterior wall. Lymphatic drainage mimics cervix for upper vaginal lesions, and vulva for lower vaginal lesions. Frequently associated with HPV (usually HPV 16, see cervix chapter).
2. Malignant melanoma: Average age 55y (range 22-83). Usually in lower 1/3 of vagina, and on anterior wall. Pigmented in 95%, amelanotic in 5%.
3. Rarely, tumors develop in Gartner's duct cysts (Wolffian system) and Müllerian duct cysts. They tend to be located anterolaterally, and anteriorly, respectively. Lymphoma and sarcoma (adult type) also occur rarely.

D. Presenting symptoms: vaginal bleeding and foul discharge in 50-70%

III. Pathology

Squamous Carcinoma	80%
Adenocarcinoma	14%
Melanoma/Sarcoma	6%
Germ Cell Tumors	Rare

IV. Diagnosis

- A. Biopsy and pelvic exam. Must rule out cervical, vulvar, and rectal lesions. By convention, tumor extension to cervix or vulva reclassifies tumor as cervical or vulvar.
- B. Cystoscopy for anterior lesions
- C. Sigmoidoscopy for posterior lesions
- D. CXR and IVP, or CT of abdomen and pelvis

- E. Consider tumor markers: SCC (TA-4) and CEA for squamous lesions; CA-125 for adenocarcinoma

V. Staging

FIGO Staging for Vaginal Cancer is determined by clinical examination

I	Limited to vaginal wall
II	Involvement of subvaginal tissue
III	Extension to pelvic wall
IV	Spread beyond the true pelvis or involvement of bladder or rectal mucosa
IVa	Spread to adjacent organs
IVb	Spread to distant organs

Melanoma is staged using Breslow's system (see vulva chapter).

VI. Treatment

A. Carcinoma

1. Radiation therapy. Four field pelvic port (40-50 Gy) followed by interstitial implant (25-40 Gy to tumor volume). If lower 1/3 of vagina involved, inguinal nodes also treated. Patients with large or high stage lesions may benefit from addition of radiation sensitizers (cisplatin and/or 5-fluorouracil). Small stage I lesions can be treated with brachytherapy alone.
2. Surgery. Upper vaginal lesions treated with radical hysterectomy and vaginectomy. Better suited for superficial, posterior fornix lesions, or for patients who cannot be radiated. Recurrent tumors (after radiation) may be treatable by pelvic exenteration.
3. DES-associated CCC in young women. Treatment customized to include resection +/- radiation therapy. Possible to preserve fertility in some cases.

- B. Melanoma. No standard therapy. Treatment includes excision +/- radiation therapy, radical surgery, and radiation therapy alone. Local excisions recur locally 80%. Radical excision impacts little on survival.

- C. Sarcoma botryoides. Treatment individualized. Vincristine, dactinomycin (Actinomycin-D), cyclophosphamide (VAC) chemotherapy is crucial. Surgical resection ± radiation is suggested for the tumor site and positive margins, respectively. Local control with chemotherapy alone is 15%.

VII. Survival

A. Carcinoma

Stage	Percent in Stage	5y Survival
I	17	77%
II	25	45%
III	40	31%
IV	18	18%

- B. Melanoma, all stages 15-20% at 5y

- C. Sarcoma botryoides, all stages 75% at 5y

Vulvar Cancer

I. Incidence: 4.4% of all gyn malignancies, 0.5% of all malignancies in women. 3740 new cases and 880 deaths in the USA in 2006 (Jemal). Mean age 65

II. Epidemiology:

- A. Bimodal age distribution. In young women HPV linked to development of cancer. In older women, lichen sclerosis more common.
- B. HPV types associated with gynecologic neoplasia (Hoskins). Underlined lesions are predominant.

Lesion	HPV Association
Condyloma	<u>6</u> , <u>11</u> , 16, 30, 40, 41, 42, 44, 45, 54, 55, 61
VIN, VAIN	6, 11, <u>16</u> , <u>18</u> , 30, <u>31</u> , <u>33</u> , 35, 39, 40, 42, 45, 51, 52, 55, 59, 61, 62, 64, 66-70
Cervical Cancer	<u>16</u> , <u>18</u> , <u>31</u> , 33, 35, 39, <u>45</u> , 51, 52, 54, 55, 56, 58, 59, 66, 68

C. VIN and vulvar cancer etiology. N=235 with VIN and CA, from 24 N.Y. hospitals, case control study, 30 months duration (Trimble).

	HPV Positive	Mean Age
VIN, n=54	88.9%	49
Basaloid / Warty CA, n=21	85.7%	61
Keratinizing SCC, n=48	6.3%	65

D. Association of vulvar cancer with prior vulvar dystrophy and VIN. (Trimble).

	LS&A	Hyperplastic	VIN
KSCC, n=48	19%	33%	4%
B-W, n=21	5%	19%	81%

KSCC=keratinizing squamous cell carcinoma

B-W=basaloid-warty carcinoma

E. Comparison of relative risk for HPV and Non-HPV associated vulvar cancer (Trimble)

	Overall	B-W	KSC
Sex Partners, ≥2 (vs 1)	2.9	8.1	2.2
Coitarche, <20y	1.5	7.4	2.5
Abnl Pap	2.3	4.7	NC
Condyloma	5.9	10	NC
Smoker, ever	4.9	12.3	NC

F. Progression of untreated VIN to cancer

- Age of women with VIN 3 fell from 52.7y to 35.8y between 1961 and 1992 (Jones)
- Incidence of VIN rose exponentially between 1961 and 1992 (Jones)
- Untreated VIN more likely to progress to cancer. (Jones)

Status	Cancer
Treated VIN (n=105)	3.8%
Untreated VIN, ≤ 8 years (n=8)	87.5%

G. Relative Risks in Non-HPV Associated Vulvar Cancer RR

Coffee (>2 cups/day vs. none)	2.8
Occupation (laundry, dry cleaning)	3.8
Hx vulvitis (granulomatous STD)	8.5
Hx leukoplakia	13.0

H. Association with cervical malignancy in 15% of all vulvar cancers.

III. Pathology: (Dunton)

Squamous carcinoma	85-90%
Melanoma	5-10%
Bartholin's Adenocarcinoma	4%
Basal Cell carcinoma	<2%
Sarcoma	<2%
Paget's Disease	<1%

A. Melanoma occurs most often in 6th and 7th decades in Caucasian. One third occur in women younger than 50 (Wilkinson). Incidence 360 per year in USA in 2001 (Greenlee)

B. Melanoma Types

1. Superficial Spreading Melanoma. Accounts for 4% of vulvar lesions (Ragnarsson). Radial spread 4 or more rete lateral to the vertical or infiltrative growth (Wilkinson)
2. Nodular Melanoma. Accounts for 22% of vulvar lesions. Vertical growth pattern. (Ragnarsson).
3. Lentiginous types account for 57% of vulvar lesions (Ragnarsson).
 - a. Acral Lentiginous Melanoma, more common subtype on vulva.
 - b. Lentigo Maligna Melanoma
4. Amelanotic melanoma, containing no melanin, occurs in up to 27% of vulvar lesions (Ragnarsson)

IV. Natural History

A. Symptoms

1. Mass (45%)
2. Pruritus (45%). More commonly associated with LS&A and dysplasia.
3. Pain (23%)
4. Ulcer (13%)

B. Spread

1. Indolent local invasion, followed by
2. Lymphatic spread: superficial inguinal to femoral to pelvic nodes. Spread is usually ipsilateral, but 0.4% positive contralateral nodes with ipsilateral negative nodes reported

V. Diagnosis

A. Differential Diagnosis

1. Benign solid neoplasms including leiomyoma, lipoma, syringoma, trichoepithelioma, granular cell tumor, neurofibroma, schwannoma
2. Glandular neoplasms including papillary hidradenoma, nodular hidradenoma, ectopic breast or nipple, endometriosis
3. Cysts including Bartholin's cyst, epithelial inclusion cyst (sebaceous cyst), Wolfian cyst (mesonephric cyst), cyst of canal of Nuck (mesothelial cyst)
4. Vascular lesions including angiokeratoma, capillary hemangioma, cavernous hemangioma, cherry angioma, varicose veins
5. Nevi and pigmented lesions including vitiligo, fibroepithelial polyp (skin tag, acrochordon), seborrheic keratosis, vulvar melanosis, nevus, dysplastic nevus
6. Infectious diseases including HPV, HSV, condyloma lata, molluscum, chancroid, lymphogranuloma venereum, granuloma inguinale
7. Vulvar dystrophy

B. Biopsy indicated for obtaining diagnosis. Complete excision not required.

C. Punch biopsy technique: use Keys punch or Kevorkian forceps with local anesthetic. No suture required. Apply silver nitrate or Monsel's solution for hemostasis (Reid). Excision of small lesion: make elliptical incision following lines of tension in skin. Incise, undermine and remove lesion with minimal margin, if benign in appearance. Undermine surrounding skin to mobilize for closure. Use mattress or subcuticular stitch with fine absorbable suture (Jenison, Karlen).

- D. Shave biopsy technique contraindicated for possible melanoma lesions
- E. Colposcopy of the Vulva
 - 1. Indications
 - a. Persistent condyloma or visible lesion
 - b. Chronic pruritus or pain
 - 2. Colposcopy technique
 - a. Soak vulva with gauze moistened with acetic acid. Let soak for several minutes
 - b. Inspect methodically
 - c. Lesions may appear white, red, or pigmented. Mosaic and punctation uncommon
 - d. Biopsy anything which does not appear normal

VI. Treatment of Pre-Invasive Disease

- A. Condyloma
 - 1. TCA ($\geq 85\%$): apply topically 1-3x per week. Safe during pregnancy
 - 2. Laser (CO_2): requires anesthesia. See technique below.
 - 3. LEEP: requires local anesthetic. Best method for debulking large condylomata
 - FDA Approved Topicals
 - 4. Imiquimod (Aldara): FDA approved. Apply to skin 3 times per week for up to 16 weeks. Apply at h.s. and leave on 6-10 hours, then wash off
 - 5. Podofilox 0.5% topical gel (Condylox): FDA approved. Apply BID for 3 days x 4 weeks. No more than 10 cm^2 area.
 - 6. Veregen ointment (15%): FDA approved. From sinecatechins in green tea. Apply TID to external warts for up to 16 weeks. May cause local irritation.
 - Non-FDA Approved topicals or local therapies
 - 7. α -Interferon: 1,000,000 units s.c. 3x per week for 4-6 weeks
 - 8. Efudex cream (5 FU, 5%): massage small amount into skin 2 nights per week for 10 weeks. Cleanse skin next AM. Alert patient to expected symptoms (burning). Contraindicated in pregnancy
- B. Ablative techniques indicated for condyloma and vulvar intraepithelial neoplasia
 - 1. Laser (CO_2) or ultrasonic surgical aspiration: best cosmetic result on mucosal surfaces
 - 2. Wide local excision: best results on hair-bearing surfaces (Wright VC)
- C. Laser ablation
 - 1. Clinical utility depends on use of appropriate wavelength. The CO_2 laser is most applicable to ablation of condyloma, dysplasia, and carcinoma-in-situ. The 10,600 nM wavelength is absorbed by water, resulting in tissue vaporization. Absorption occurs at the surface. Thermal damage to underlying tissue is minimized
 - 2. Power density must be adequate to prevent char
 - a. $\text{PD (Watts/cm}^2\text{)} = (\text{Watts} \times 100) / \pi r^2$, r = spot radius (not diameter).
 - b. Use of a motorized handpiece (Silk Touch) will result in a smoother and more uniform depth of ablation
 - c. A colposcope may be used to guide the laser. Low power Helium Neon laser (red beam) is used for aiming. Eye protection mandatory
 - 3. Depth of laser ablation must be below the basement membrane for dysplasia treatment
 - a. Ablate to a depth of 1-2 or 2.5 mm in non-hairbearing skin and hairbearing skin, respectively (Morrow, Baggish)

b. Surgical Planes defined by Reid use visual landmarks to determine depth

Plane	Tissue vaporized	Healing	Landmark	Technique
1 Condy	Proliferating epithelium	No scar	"Opalescent debris"	Single brush, wipe with moist gauze
2	Superficial papillary dermis	No scar	"Chamois"	Plane 1, then rapid brush
3 VIN	Superficial reticular dermis	Mild scar	"Water-logged cotton"	Plane 1, then slow brush
4	Deep reticular dermis	Scar	"Sand grains"	Plane 3, then slow brush

4. Operative Technique

- Requires anesthesia
- Ice vulvar skin and drape surrounding area with wet towels
- Stain epithelium with 5% acetic acid and mark lesions
- Set power density to 600-750 W/cm²; 15-20 W with spot size of 2 mm
- Frequently wipe char from area during ablation

5. Post Operative Care

- Sitz bath b.i.d. until re-epithelialized
- Blow dry on low setting, then apply neomycin-bacitracin ointment
- Separate labia b.i.d. to prevent coaptation. Foley if periurethral tissues ablated
- For discomfort, moist tea bag compresses b.i.d. after sitz baths
- Follow weekly until re-epithelialization complete

6. Treatment Results

- Condyloma and VIN: 70-90% success at 2 years

D. Ultrasonic Surgical Aspiration (Rader)

- Uses mechanical vibration to cavitate tissue allowing aspiration of the disease
- Unlike laser, specimen can be submitted for histology
- Operative Technique
 - Stain epithelium with 5% acetic acid and mark lesions
 - Set power to 5-6 on CUSA and ablate to a depth of 2-2.5 mm
- Post Operative Care as for laser ablation, although pain less severe
- Treatment Results: Condyloma and VIN 78% success at 50 weeks

E. General Principles of Electrosurgery

- Radio frequency current (350 KHz-3.3 MHz) results in kinetic energy transfer to intracellular ions which vaporizes intracellular water. Avoid Faradic Effect (50 Hz-200 KHz), which stimulates muscle and nerve causing pain by using proper equipment
- Cutting: sine-wave RF current; coagulation: pulsed ("spark gap") RF current

F. Loop Electrosurgical Excision Procedure

1. Technique

- Lesion outlined using acetic acid and colposcope
- Anesthetize with 1% Lidocaine with epinephrine
- Choose loop to excise lesion
- Excise tissue in single pass, using 34 - 40 W, blend mode
- Cauterize base with ball electrode at 50 W, coagulation mode
- Apply Monsel's solution

2. Advantages

- Diagnostic and therapeutic intervention, potentially with one clinic visit
- Histologic specimen improves diagnostic accuracy
- Equipment less costly than laser

VII. Staging of Invasive Disease.

- A. Vulvar cancer staging is surgical. AJCC and FIGO staging systems are identical. This system applies for all tumor types other than melanoma
- B. Staging assessment may require cystoscopy, sigmoidoscopy, and chest X-ray for locally advanced lesions.

FIGO revised 2009, replaces 1995 and 1988	
I	Tumor confined to vulva or perineum
I A	Lesion \leq 2 cm in size, <u>and</u> stromal invasion of \leq 1 mm, nodes negative
I B	Lesion $>$ 2 cm in size, <u>or</u> stromal invasion of $>$ 1 mm, nodes negative
II	Tumor of any size extending to adjacent perineal structures: (anus, lower 1/3 of urethra, lower 1/3 of vagina); nodes negative
III	Tumor of any size with or without extension to adjacent perineal structures: (anus, lower 1/3 of urethra, lower 1/3 of vagina); nodes positive
III A i	With 1 lymph node metastasis of \geq 5 mm
III A ii	1-2 lymph node metastases of $<$ 5 mm
III B i	With 2 or more lymph node metastases of \geq 5 mm
III B ii	3 or more lymph node metastases of $<$ 5 mm
III C	Positive nodes with extracapsular spread
IV A i	Invades upper 2/3 urethra or vagina; bladder or rectal mucosa; or fixed to pelvic bone
IV A ii	Fixed or ulcerated inguino-femoral nodes
IV B	Any distant mets including pelvic nodes

Depth of invasion measured from epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion

- C. Melanoma staging is separate from the above and is based primarily on lesion thickness.
 1. Microstaging systems for melanoma (Breslow, Chung, Clark)

Stage	Breslow	Chung	Clark
I	<0.76 mm	Intraepithelial	Intraepithelial
II	0.76-1.5 mm	\leq 1 mm	Into papillary dermis
III	1.51-2.25 mm	1-2 mm	Filling dermal papillae
IV	2.26-3.0 mm	$>$ 2 mm	Into reticular dermis
V	$>$ 3 mm	Into subcutaneous fat	Into subcutaneous fat

2. American Joint Commission on Cancer (AJCC) TNM system for melanoma, 2001

Primary Tumor	
Tis	Melanoma <i>in situ</i>
T1a	Tumor \leq 1.0 mm in thickness, without ulceration and level II/III
T1b	Tumor \leq 1.0 mm in thickness, with ulceration or level IV/V
T2a	Tumor 1.01-2.0 mm in thickness without ulceration
T2b	Tumor 1.01-2.0 mm in thickness with ulceration
T3a	Tumor 2.01-4.0 mm in thickness without ulceration
T3b	Tumor 2.01-4.0 mm in thickness with ulceration
T4a	Tumor $>$ 4.0 mm in thickness without ulceration
T4b	Tumor $>$ 4.0 mm in thickness with ulceration

<u>Regional Lymph Nodes</u>	
N0	No regional node metastasis
N1a	1 lymph node metastasis, microscopic
N1b	1 lymph node metastasis, macroscopic
N2a	2-3 lymph node metastases, microscopic
N2b	2-3 lymph node metastases, macroscopic
N3	≥ 4 lymph node metastases, or matted nodes, or in-transit / satellite metastases
<u>Distant Metastasis</u>	
M0	No distant metastasis
M1a	Distant skin, subcutaneous or nodal metastasis and normal serum lactate dehydrogenase
M1b	Lung metastasis and normal serum lactate dehydrogenase
M1c	All other visceral metastases or any distant metastasis with elevated serum LDH

<u>Stage Grouping</u>		
	<u>Clinical</u>	<u>Surgical</u>
Stage 0	Tis N0 M0	Tis N0 M0
Stage IA	T1a N0 M0	T1a N0 M0
Stage IB	T(1b or 2a) N0 M0	T(1b or 2a) N0 M0
Stage IIA	T(2b or 3a) N0 M0	T(2b or 3a) N0 M0
Stage IIB	T(3b or 4a) N0 M0	T(3b or 4a) N0 M0
Stage IIC	T4b N0 M0	T4b N0 M0
Stage III	T(any) N1-3 M0	
Stage IIIA		T(1-4a) N(1a or 2a) M0
Stage IIIB		T(1-4b) N(1a or 2a) M0
		T(1-4a) N(1b or 2b) M0
		T(1a or 1b) N2c M0
Stage IIIC		T(1-4b) N(1b or 2b) M0
		T(Any) N3 M0
Stage IV	T(Any) N(Any) M1	T(Any) N(Any) M1

VII. Treatment

- A. Stage I A: Microinvasion defined by International Society for the Study of Vulvar Diseases (ISSVD) in 1984, and adopted by FIGO in 1995. Incidence of inguinal node metastases is < 1%. Conservative surgical therapy without inguinal-femoral lymphadenectomy indicated.
- B. Stage I and II squamous carcinoma: Hemivulvectomy with unilateral inguinal lymphadenectomy. Bilateral lymphadenectomy if lesion within 1-2 cm of midline (Moore).
 1. Margin adequacy. At UCLA, 135 patients were retrospectively assessed for risk of recurrence based on margin of resection. If margin was > 1 cm, 0% recurred locally (0/91) and if margin was < 8 mm, 47% (21/44) developed local recurrence. Of the 23 who did not recur locally, 39% (9/23) developed distant metastases. (Heaps)
 2. Depth of resection is the superficial fascia of the urogenital diaphragm
 3. If < 2 positive groin nodes: dissect contralateral groin, no adjuvant therapy
 4. If ≥ 2 positive nodes, then radiation therapy to pelvis and groin increases survival from 30% to 60% by GOG randomized trial (Homesley).

C. Stage III-IV

Treatment is individualized according to size and location of the lesion. Options include:

1. Radical vulvectomy with unilateral or bilateral groin node dissection. For lesions involving anal mucosa or urethra, treatment options are:
2. Exenteration for locally advanced disease in an individual who has been radiated previously or who is not a candidate for chemoradiation.
3. Neoadjuvant radiation therapy and chemotherapy with 5-fluorouracil (and optional mitomycin), followed by standard surgical therapy if any residual disease is detected (Burke). 70% chance of local control with chemoradiation alone (Boronow)

D. Lymphadenectomy is both therapeutic and diagnostic. Conventional approach is superficial and deep lymphadenectomy. Superficial node dissection without removal of deep nodes may have an 8% local recurrence rate representing a significant false negative rate.

E. Sentinel node mapping is the standard of care for melanoma cases and is being tested prospectively by the GOG for squamous vulvar carcinoma. Both radiolymphoscintigraphy and blue dye are used to localize the sentinel node. The radiocolloid used is technetium 99 (450 μ Ci ^{99}Tc) sulfur colloid (filtered to 0.2 μm) is injected intradermally in 4 sites at the periphery of the tumor 2-4 hours pre-op. Gamma scan is performed and sentinel node(s) is marked. Films are brought with the patient to the OR. At beginning of surgical procedure, 8 ml of 1% isosulfan blue dye is injected intradermally at 4 sites around the periphery of the tumor. Incision is made over the sentinel node determined by lymphoscintigraphy and blue dye is located. Hand held gamma probe assists in localization of node(s). Specimen is submitted for frozen section. If negative, no further nodes are removed unless hand held probe identifies a second node(s) with > 10% of the sentinel node activity or > 150% of background activity. If the frozen section is positive, full lymphadenectomy may be warranted depending on the clinical protocol. The specimens are held for 2-6 t_{1/2} before processing. (Fiorica, Moore, Levenback).

Accuracy (Ross, Albertini)

Blue dye alone	69-89%
Lymphoscintigraphy	83%
Both	96-99%

Histologic evaluation of sentinel nodes requires 10-15 serial sections. Immunohistochemistry staining for S-100 and HMB-45 may improve sensitivity and specificity. (Johnson 1998)

F. Special cases

1. Verrucous and basal cell carcinoma rarely spreads to nodes. Wide local excision or hemivulvectomy is sufficient therapy.
2. Paget's Disease is rarely invasive and rarely metastasizes. Wide excision is indicated.
3. Melanoma
 - a. Older approach included radical vulvectomy with lymphadenectomy.
 - b. Newer approach is to perform wide local excision (WLE) with sentinel node dissection on selected cases based on lesion thickness. (Johnson 1995-1998, Look, Piura, Rose)

c. Surgical margin guidelines

NIH Consensus Conference on Melanoma (NIH)

<u>Lesion Thickness</u>	<u>Surgical Margin</u>
≤ 1 mm	1 cm
1.1-2.0 mm	1-2 cm (latter preferred)
2.1-4.0 mm	2 cm
> 4 mm	3 cm

d. University of Michigan Treatment Guidelines for AJCC Stage I-II Melanoma. (Johnson 1995)

<u>Breslow Depth</u>	<u>Margin & Treatment</u>
≤ 0.75 mm	1 cm margin
0.76-1.49 mm	1-2 cm (1 cm for depth ≤ 1mm)
1.50-4.0 mm	1-2 cm margin (2 cm for depth > 2 mm) Sentinel node dissection +/- Adjuvant therapy with Interferon or clinical trial
> 4.0 mm	3 cm margin +/- Adjuvant therapy with Interferon or clinical trial

VIII. Surgical Complications, and Reconstruction

A. Wound breakdown

1. Acute breakdown following radical vulvectomy 50% and following radical hemivulvectomy 14% (Burrell)
2. Use of flaps for closure of large defects increases primary intention rate of healing to 89% (Reid 1997)
3. Chronic defects include 5-25% incidence of rectocoele, cystocoele, and uterine prolapse (Morrow)

B. Infections

1. Vulvar surgery is "Clean Contaminated" by American College of Surgeons classification
2. Risks for postoperative infection (Snyder)

<u>Increased risk of post-op infection</u>	<u>Decreased risk of post-op infection</u>
Age > 66 or < 14 years	Age 15-65 years
Lengthy procedure	Short procedure
Shaving skin pre-op	Clipping skin pre-op
Excessive electrosurgery	Irrigation
Foreign bodies	Inert or absorbable suture material

3. Most common organisms identified: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus A & B*, *Enterococcus*, *Streptococcus viridans*, gram negative enterobacteriaceae and mixed anaerobes. (Snyder)
4. Antibiotic prophylaxis to cover likely organisms warranted

C. Lymphocysts (Morrow)

1. Occur following 7-28% of inguinal lymphadenectomy
2. Prevent with closed suction drainage and minimization of resection
3. Treat with frequent aspiration
4. If aspiration unsuccessful, instill absolute ethanol or betadine to sclerose

D. Lymphedema (Morrow)

1. Occurs following 7-19% of cases.
2. Treat with elevation and compression.
3. Diuretics sometimes helpful.
4. Lymphedema clinic referral for pneumatic compression and massage.
5. Chronic lymphedema increases risk for life threatening cellulitis and DVT. These problems may be chronic.

E. Incontinence of urine or feces

F. Sexual dysfunction

G. Psychological problems

H. Reconstruction techniques

1. Split thickness skin graft (Morrow)

- a. Indicated for coverage of superficial resections too wide for primary closure and with preservation of subcutaneous fat pad. Typical case is resection for dysplasia, or Paget's disease.
- b. Dermatome used to harvest epithelium (0.016-0.018 inch thick) from anterior thigh or superior border of buttocks. Graft may need to be meshed to increase coverage. Non-meshed grafts require drainage incisions.
- c. Graft is sutured in place, Foley and rectal tubes are placed and a bolus (pressure dressing) is applied for 5 days

2. Cutaneous flaps for closure of small to intermediate sized defects

a. Rhomboid (Gallup Figs. 15-6, 15-8, 15-9).

- i. Indicated for closure of intermediate size defects, particularly on perineal body and posterior perineum.
- ii. Measure flap length to equal size of defect. Undermine surrounding skin to allow mobility of the flap. Close with modified mattress suture, keeping knots away from the flap side of the incision.
- iii. Apply pressure dressing for 24 hours and keep patient at bedrest for 5 days. Delay defecation for 2-3 days for posterior flaps.

b. Lateral transposition (Knapstein Fig. 13)

- i. Indicated for closure of intermediate size defects, particularly on perineal body and posterior perineum.
- ii. Measure flap length to equal size of defect. Flap length to width ratio should be 2 or less. Undermine surrounding skin to allow mobility of the flap.

3. Myocutaneous flaps for closure of large defects or defects in a previously radiated field

a. Gracilis (Knapstein, Morrow Figs. 8-29, 8-31, Reynolds Figs. 5B, 5C).

- i. Muscle origin is the anterior portion of the inferior pubic arch and insertion is to the medial tibial condyle. Blood supply is the medial femoral circumflex artery, entering the muscle 8-10 cm inferior to the pubic tubercle between the adductor longus and adductor magnus muscles. The saphenous vein is preserved anterior to the flap.
- ii. The flap design can be either an island or rotational flap. During dissection the skin should be sutured to the muscle and tissue handling should be gentle.
- iii. The flap is carefully rotated posteriorly and is sutured in place with closed suction drains in place.

b. Tensor fascia lata (Knapstein, Hacker Fig. 10-13)

- i. Muscle origin is the anterior superior iliac spine and insertion is the fibrous portion of the fascia lata. Blood supply is the lateral femoral circumflex artery.

- ii. The flap design is a rotational flap. During dissection the blood supply should be carefully preserved and tissue handling should be gentle. The flap can be up to 6 x 30 cm in size.
- c. Gluteus maximus (Knapstein, Hacker Fig. 10-14)
 - i. The muscle origin is the dorsal pubic ramus, posterior sacrum and sacrotuberal ligament. Insertion is the posterior upper femur and fascia lata. Blood supply is the inferior gluteal artery.
 - ii. The flap design can be either an island or rotational flap. The muscle is partially transected to the posterior skin incision to allow rotation. The flap can be up to 8 x 20 cm in size.
- d. Rectus abdominis (Knapstein, Morrow, Figs. 8-21, 8-23)
 - i. Indicated for closure of large vulvar defects only if the bladder or rectum has also been removed as in the case of an exenteration.
 - ii. Muscle origin is the symphysis pubis and insertion is the thorax into the fascia of the intercostal muscles and cartilage of the rib cage. Blood supply for pelvic flaps is the inferior epigastric artery.
 - iii. The flap design is an island flap.

IX. Prognostic Factors and Survival

A. Incidence of node metastases in squamous carcinoma of vulva

By lesion diameter (cm)		By depth (mm)	
≤1	5%	≤1	0%
1-2	16%	1.1-2	6.6%
2-4	33%		8.2%
>4	53%		22%
			25%
		>5	37%

Pelvic nodes positive 5% overall, but 44% if ≥ 3 positive groin nodes

B. Survival for Squamous Cancers

Stage	5 yr Survival
I	91.1%
I (negative nodes)	95.0%
II	80.9%
III	48.4%
IV	15.3%

If nodes positive but ≤2 on one side, survival 75%. If nodes positive but >2, or any number bilateral, survival 25%

C. Survival for Malignant Melanoma

Breslow's Depth	5 yr Survival
<0.76 mm	100%
0.76-1.5 mm	89%
1.51-3.0 mm	72%
>3.0 mm	22%

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Rev. 2/2010

Nutrition, Fluids and Electrolytes

I. Types of Malnutrition

	Protein Stores	Adipose Stores
Kwashiorkor	Loss	Stable
Marasmus	Stable	Loss
Cachexia	Loss	Loss

II. Risk Factors for Malnutrition

A. Body weight $\leq 20\%$ below ideal

(Ideal = 100 lbs for 60" height + 5 lbs for each additional inch)

B. Recent weight loss $\geq 10\%$ of usual weight

C. Alcohol abuse

D. Chronic diseases or cancer

E. NPO for ≥ 7 days with only IV hydration

F. Increased nutritional needs: burns, trauma, surgery, fever, sepsis, wounds, pregnancy

G. Nutritional losses: malabsorption, short bowel syndrome, dialysis, effusions, chronic bleeding or diarrhea

H. Catabolic drugs: steroids, immunosuppressants, chemotherapy agents

I. Protracted emesis

III. Nutritional Assessment

A. Anthropomorphic Measurement. e.g. triceps skin fold thickness.

B. Protein Store Assessment

	Normal	Mild	Moderate	Severe
Weight loss, 1 month, %	-	3 - 4	5	> 5
3 months, %	-	6 - 7	7.5	> 7.5
6 months, %	-	8 - 9.5	10	> 10
Transferrin, mg/dL	200 - 350	180 - 200	160 - 180	< 160
Albumin, mg/dL	≥ 3.5	3 - 3.5	2.5 - 3	< 2.5
Pre-albumin, mg/dL	> 13	10 - 13	6.5 - 10	< 6.5
Tot Lymphocyte Count	> 1800	1500 - 1800	900 - 1500	< 900
Skin test antigens, mm	> 15	10 - 15	5 - 10	< 5

Half-life of: albumin (20 days), transferrin (8-10 days), Pre-albumin (2 days).

Lymphocyte count is inaccurate for patients undergoing RT or chemotherapy.

C. Nitrogen Balance Estimate. Not accurate with fistulas, diarrhea, burns, dialysis

$$\mathbf{N\ Bal = [(P\ I / 6.25) - (UUN + 3)]}$$

Where UUN=24 hour urine urea nitrogen in grams, PI=24 hour protein intake in grams

IV. Estimation of Nutritional Requirements

A. Caloric Intake

1. Harris-Benedict Basal Energy Expenditure (BEE) equation:

$$\mathbf{BEE(kcal) = 655 + 9.6(wt, kg) + 1.7(ht, cm) - 4.7(age, yr)}$$

Coefficient of Adjustment	
Bed rest	1.2x(BEE)
Ambulatory	1.3x(BEE)
Sepsis	1.3x(BEE)
Anabolic/Burns	1.5x(BEE)

Increase BEE 12% for each degree of fever $> 37^{\circ}\text{C}$.

2. Respiratory Energy Expenditure (REE). Using measured O₂ consumption or difference in arterial and venous O₂ saturation. Accuracy $\pm 15\%$.

REE=(VO₂)x(5 kcal/L)x(60 min/hour)x(24 hours/day), where: **VO₂=(aO₂-vO₂)/CO**, and VO₂=O₂ consumption in L/min; (aO₂-vO₂)=difference in a-vO₂ content=(Hb)x(O₂ sat)x(1.36); CO=cardiac output in L/min

3. Respiratory Quotient: ratio of CO₂ produced for oxygen consumed **RQ=VCO₂/VO₂**

Fat	0.7
Protein	0.8
Carbohydrate	1.0

- B. Protein Requirement (usually 10-20% total caloric intake) **4Kcal/g** Take into account the patient's renal function, hepatic function and nutritional status (see section III)

Maintenance	0.8 - 1 g/kg-day	Use Adjusted Ideal Body Weight = [(Actual BW – IBW) x 25%] + IBW
Repletion	1.3 - 1.5 g/kg-day	

- C. Carbohydrate Requirements: usually 50-60% of total caloric intake. **3.4 Kcal/g**. Keep infusion less than 4 mg/kg-min in stressed individuals (surgery, trauma, burns, steroids)
- D. Lipid Requirements: Usually 20-30% of total calories. Should not exceed 60% of total. **9 Kcal/g**. Lower respiratory quotient than CHO helpful with borderline respiratory failure). Emulsion is isotonic. Essential fatty acids are linoleic and linolenic acids: absolute requirements for essential fatty acids is 3-5% of total caloric intake.
- E. Fluid Requirements. Add 10% for fever $>38^{\circ}$ C.

Wt ≤ 10 kg	100 mL/kg-day
10 kg < Wt ≤ 20 kg	(+)50 mL/kg-day
Wt > 20 kg	(+)20 mL/kg-day

- F. Electrolytes, Recommended Daily Supplements. Combined Calcium and phosphorous must be ≤ 30 mEq / L

Na ⁺	60-150 mEq	Cl ⁻	60-150 mEq	Mg ²⁺	8-24 mEq
K ⁺	60-120 mEq	PO ₄ ²⁻	20-40 mM	Ca ²⁺	10-15 mEq

- G. Vitamins, AMA daily therapeutic recommendations, and metabolic function

A (fat soluble)	3300 IU	Vision (rhodopsin), growth, reproduction
D (fat soluble)	200 IU	Calcium and phosphorous homeostasis
E (fat soluble)	10 IU	Antioxidant
K (fat soluble)	150 mcg	Synthesis of blood clotting factors II, VII, IX, X
B ₁ Thiamine	6 mg	Coenzyme: oxidative decarboxylation, transketolase
B ₂ Riboflavin	3.6 mg	Coenzyme: electron transport
B ₃ Niacinamide	40 mg	Component of NAD, NADP: red-ox reactions
B ₅ Dexpanthenol	15 mg	Part of coenzyme A: acyl transfers, essential for energy production from protein, fat, carbohydrates
B ₆ Pyridoxine	4 mg	Coenzyme in amino acid metabolism. Essential for neurotransmitter & heme synthesis
B ₁₂ Cyanocobalamin	5 mcg	Coenzyme for DNA synthesis, conversion of homocysteine to methionine, general metabolism
Biotin	60 mcg	Cofactor for carboxylation for protein, carbohydrate, fatty acid and nucleic acid metabolism
C Ascorbic Acid	100 mg	Antioxidant, hydroxylation cofactor, regulation of intracellular oxidation-reduction, role in synthesis of neurotransmitters, collagen, and vasoactive amines
Folic Acid	400 mcg	Transport of single carbon units, nucleic acid synthesis, metabolism of amino acids

H. Trace Elements

1. Replace if deficient or on parenteral alimentation
2. Metabolic function

Zinc	Metabolism of protein, carbohydrates, lipids, nucleic acids
Copper	Cofactor for oxidative enzymes, collagen synthesis, iron interactions
Manganese	Muccopolysaccharide metabolism, oxidative phosphorylation
Chromium	Potential of insulin effects via glucose tolerance factor
Selenium	Cofactor for glutathione peroxidase

Also: Iron, Molybdenum, Iodine, Fluoride

Patients with high output fistulas are usually deficient in zinc and copper.

I. Nutrient deficiency syndromes

B ₁	Beriberi (Wernicke's encephalopathy), paresthesia, cardiac failure, cerebellar signs, anorexia, weakness
B ₂	Sore lips and tongue, stomatitis, desquamation, anemia
B ₆	Seborrhea facies, cheilosis, glossitis, anemia, peripheral neuritis
B ₁₂	Weakness, fatigue, sore tongue, paresthesia, anorexia, diarrhea, alopecia, depression, pernicious anemia
Biotin	Alopecia, dermatitis
Folic acid	Fatigue, sore tongue, anemia, stomatitis, nausea
Niacin	Dermatitis, painful tongue, stomatitis, diarrhea, headache, pellagra (neuropsychiatric symptoms)
Dexpanthenol	Fatigue, paresthesia, weakness, burning feet
C	Weakness, irritability, gingivitis, joint pain, loose teeth, easy bleeding, scurvy, heart failure, poor wound healing
A	Night blindness
D	Tetany, muscle weakness, rickets, osteopenia
E	Areflexia, gait disturbance, paresis of gaze, hemolytic anemia
K	Bruising or bleeding
Iron	Anemia, stomatitis
Manganese	Ataxia, retarded skeletal growth, decreased reproductive function
Chromium	Neuropathy, ↑ free fatty acids, insulin resistant glucose intolerance
Copper	Neutropenia, anemia, diarrhea, scurvy symptoms
Zinc	Facial and extremity rash, skin ulcers, alopecia, confusion, apathy, hypogonadism, night blindness
Selenium	Muscle weakness, cardiac failure
Fatty acids	Scaling dermatitis, coarse hair, alopecia, diarrhea, numbness, paresthesia, weakness, blurred vision, poor wound healing

J. Sites of nutrient absorption

1. Stomach: intrinsic factor secretion
2. Duodenum: vitamins A & B, iron, calcium, glycerol and fatty acids, monoglycerides, amino acids, mono and disaccharides
3. Jejunum:
 - a. Entire: glucose, galactose, vitamin C, amino acids, glycerol and fatty acids, monoglycerides, folic acid, biotin, copper, zinc, potassium, pantothenic acid
 - b. Proximal: vitamins A & B, folic acid, iron, lactose
 - c. Distal: isomaltase, maltose, trehalose, sucrose
4. Jejunum and ileum: vitamins D, E, K, B₁, B₂, B₃, B₆, iodine, calcium, magnesium, phosphorus

5. Ileum:
 - a. Entire: chloride, sodium
 - b. Proximal: isomaltase, maltose, trehalose, sucrose
 - c. Distal: B₁₂ and intrinsic factor
6. Colon: water, synthesis of biotin

V. Hyperalimentation

A. Parenteral

1. Indications: pre-op and post-op support where malnutrition exists, or patient anticipated to be NPO>5-7 days, or patient with protracted emesis. Enteral feeding preferred if GI tract is functional
2. Access: must be infused through a large caliber, high flow vein
3. Formulations (in most hospitals): standard, peripheral, and custom ordered.

University of Michigan Standard Formulation:

Amino Acids (5%)	50 g	Total Volume	1050 mL
Dextrose (20%)	200 g		
Ca ²⁺	4.5 mEq	Osmolarity	Hi mOsm/L
Mg ²⁺	5 mEq		
K ⁺	40 mEq	Total Calories	880 kcal
Na ⁺	45 mEq		
Acetate	41 mEq		
Cl ⁻	45 mEq		
PO ₄ ²⁻	15 mM		
Heparin	1000 Units		
Multivitamins	Daily		
Trace Elements	Daily		
Vitamin K	Daily		

4. Lipids: Liposyn 20%, contains soybean and safflower oil, egg phospholipids, and glycerin in 500 mL bottles. Must not pass through IV line filter. Provides 2 Kcal/mL at 260 mOsm/L. Minimum essential fatty acid requirements met with two 300 mL bottles of Liposyn weekly.
5. Initiation of Total Parenteral Nutrition (TPN). Begin infusion at 40 mL/hour and taper up to calculated full infusion rate. Tapering of TPN must be done in a similar fashion to prevent hypoglycemia. Rule out hypoglycemia 1 hour after stopping
6. Recommended lab monitoring for TPN

Test	Initial	During Taper-Up	Stable TPN
Glucose, finger stick	x	q6h	2x weekly
CBC, Plts, Diff	x		weekly
Electrolytes	x	daily	2x weekly
BUN, Creatinine	x		2x weekly
Ca ²⁺ , PO ₄ ²⁻	x	daily	2x weekly
Liver enzymes	x		2x weekly
Bilirubin	x		weekly
Triglycerides	x		prn
Mg ²⁺	x	daily	weekly
PT, PTT	x		prn
Albumin, Prealbumin	x		weekly

7. TPN can be cycled in home administration setting to improve quality of life.

8. Complications of TPN
 - a. IV access: pneumothorax, hemothorax, infection, nerve injury, air embolism
 - b. Metabolic
 - i. Hyperglycemia/hypoglycemia, affected by infusion rates, stress, infection
 - ii. Hypophosphatemia: "Refeeding Syndrome" results in respiratory failure, cardiomyopathy. Requires slow advancement of TPN, careful monitoring of PO_4^{2-} , Mg^{2+} , and K^+
 - iii. Hypertriglyceridemia, associated with lipid and carbohydrate infusion
 - iv. Vitamin/Trace Element deficiencies
 - v. Hypercapnea: CO_2 production associated with carbohydrate infusion in excess of patient needs
 - c. Hepatobiliary complications
 - i. Cholestasis: most common hepatotoxicity. Associated with long term TPN, lack of gut stimulation, recurrent sepsis, short bowel syndrome,
 - ii. Overfeeding
 - d. Electrolyte disturbances
- B. Enteral
 1. Indications: nutrition for patients with functional GI tract
 2. Access: Dobhoff feeding tubes are more suitable than Salem sump NG tubes. Metoclopramide and/or fluoroscopy aids in tube placement
 3. Formulations
 - a. Nutritionally complete, lactose free, 1 kcal/mL. Standard protein (<20% kcal as protein): (This list is not comprehensive and formulations change frequently.)
Oral: Boost, Carnation Instant Breakfast, Ensure
Tube Feeding: Isocal, Osmolite HN, Vivonex.
Fiber containing: Jevity, Enrich
Low fat, oligomeric: Criticare HN
High Protein (>20% kcal as protein): Isotein HN
 - b. Specialized formulas: Travasorb Renal, Amin-Aid, Pulmocare
 4. Initiation
 - a. Start with half strength formula at 40-60 mL/h. Advance rate by 60-100 mL/h every 12-24 hours. When planned infusion rate reached, advance concentration to 3/4 strength formula for 24 hours, then to full strength
 - b. If gastric residual is >100 mL, hold feeding for 2 hours, then remeasure
 - c. Dobhoff tubes should be irrigated after each bolus feeding, or q6h if on continuous infusion
 - d. Head should be elevated $\geq 30^\circ$ during feeding to prevent aspiration
 5. Monitoring

Weights	daily
Accurate I&O's	q8h
Confirmation of correct tube placement	every feeding
Glucose, finger stick	q8h, 2x weekly when stable
Electrolytes, hepatic enzymes, BUN, creatinine	prn
 6. Complications: diarrhea, nausea/vomiting, constipation, dehydration, aspiration, electrolyte disturbance, lactose intolerance

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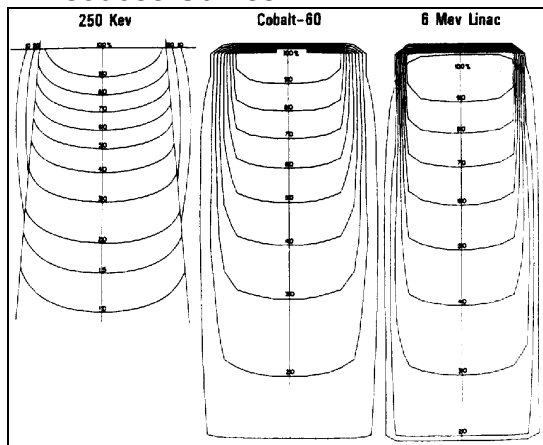
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Rev. 12/2006

Radiation Therapy

- I. Ionizing radiation: >10 eV, the binding energy of electrons. UV light does not ionize.
- II. Energy, $E=h\nu$; where h =Planck's constant, ν =frequency. Energy attenuates proportional to the inverse square of the distance from the source.
- III. Absorption=energy loss.
 - A. Types of energy absorption
 1. Photoelectric Effect: energy absorbed by inner shell electrons. Absorption proportional to cube of atomic number, a useful property for diagnostic X-rays. Energy range: 10-100 keV
 2. Compton Effect: portion of energy absorbed by outer shell electron. Residual energy transmitted. Energy range: 100 keV-3 MeV
 3. Pair Production: photon ($E > 1.02$ MeV) interacts with nucleus to produce electron + positron pair
 - B. Linear Energy Transfer (LET): energy absorption over distance, a function of particle charge squared, particle velocity squared, and electron density of the target.
 $-dE/dX = Z^2 \rho / v^2$, where x =distance, Z =charge, ρ =electron density, v =velocity
 - C. Absorbed Dose. Current unit: **Gray = (Joules/kg)**; Old unit: rad = (100 ergs/g); 1 Gy = 100 rads.

D. Isodose Curves



Penumbra: lateral spread, a function of source size as well as beam energy.

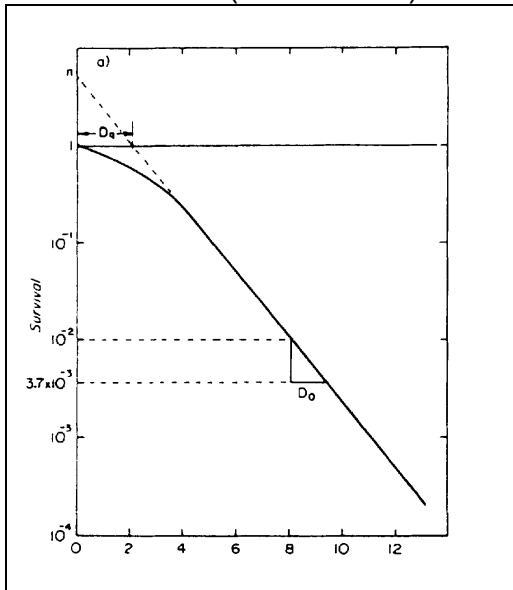
Depth-Dose Curves: function of beam energy and treatment fields.

Skin Sparing: high energy beams transfer maximum energy 0.5-1.5 cm or more below skin surface.

IV. Biological Effect of Radiation

- A. Cells are most radio-resistant in S and early G2 phases of cell cycle. Radiation causes delay of cell cycle by blocking progression from $G1 \rightarrow S$ and $G2 \rightarrow M$.
- B. $h\nu$ causes direct base damage and strand breaks. Oxygen free radicals indirectly cause DNA damage and formation requires presence of O_2
- C. Cell Survival
 1. Three theoretical models
 - a. Single hit kinetics: $N=N_0 \exp(-D/D_0)$, N =surviving cell number, D =radiation dose.
High LET $h\nu$ kills cells with single hit kinetics
 - b. Multiple hit kinetics: $N=N_0 \{1-[1-\exp(-D/D_0)]^n\}$, n =number of targets per cell
 - c. Linear quadratic kinetics: $N=N_0 \exp(-\alpha D - \beta D^2)$, α and β describe probability of interacting lesions caused by single and double tracks, respectively. Low LET $h\nu$ (i.e. therapeutic megavoltage radiation therapy) effects best approximated by linear quadratic model
 2. DNA repair mechanisms: endonuclease, exonuclease, DNA polymerase, DNA ligase, and photolyase enzymes. The more time a cell has before entering S phase, the more likely it is that successful repair will occur. 4-6h after radiation is sufficient for sub lethal damage repairs

3. Survival Curve (Low LET hv)



D_0 =dose defined by slope of log-linear region. Represents dose to reduce survival: $N \rightarrow 0.37N$

D_q =indication of capacity of cells to repair damaged DNA. Varies by cell type.

$D_q=0$ Gy for marrow

$D_q=3$ Gy for skin

4. Oxygen Enhancement Ratio: oxygenated cells are about 3x more sensitive to radiation than hypoxic cells. Hypoxia slows cell cycle, which increases time for repair, and hypoxia inhibits fixation of damage to DNA caused by free radicals
5. Principles of Fractionation (the "4 R's"): Repair, Repopulation, Redistribution, Reoxygenation

V. Radiation Sources

A. Types of radiation

1. Gamma rays (γ): arise naturally in atomic nucleus, no mass, no charge
2. X-rays: manufactured by electron beam striking tungsten target, no mass or charge
3. Beta particles (β): free electrons, negative charge, small mass
4. Alpha particles (α): Helium nucleus, positive charge, large mass

B. Useful Isotopes

Isotope	Energy (MeV)	Half Life	RCM
^{60}Co	γ 1.17, 1.32	5.26y	13.1
^{198}Au	γ 0.41-1.1 β 0.96	2.7d	2.4
^{192}Ir	γ 0.32-0.61	74d	4.7
^{226}Ra	γ 0.83 ave	1620y	8.25
^{137}Cs	γ 0.662	30y	3.3
^{32}P	β 1.7, 0.698 ave	14.3d	

RCM=roentgen/milliCurie/hour (dose rate).

Beta particles from ^{32}P penetrate 5-8 mm; those from ^{198}Au penetrate 3 mm

VI. Gynecologic Applications

- A. Cervix: Indicated for primary treatment of Stage I, II, III, and IVa disease. Also indicated for localized recurrences, and emergent control of bleeding. Treatment technique:

1. External Beam: 4-field technique to pelvis using megavoltage photons. Dose: 45-50 Gy \pm midline block. Fraction size: 180-200 cGy / day
2. Implants
 - a. Low dose rate (LDR) brachytherapy technique: Fletcher Suite applicator with ^{137}Cs sources. Two implants, spaced 1-2 weeks apart near conclusion of teletherapy, and removed after 24-48h. Dose rate: 50 cGy / hour to Point A.

- b. High dose rate (HDR) brachytherapy technique: Teflon sleeve sutured into cervix. Five weekly implants provide about 1000 cGy in outpatient setting
- c. Desired total dose to Point A=75-85 Gy, and to Point B=55-60 Gy. Bladder and rectal doses \leq 65, 70 Gy, respectively
- 3. Chemosensitization administered concurrently with radiation using cisplatin, 5-fluorouracil, or both. Supported by 5 randomized clinical trials (see cervical cancer chapter)

B. Endometrium

- 1. Adjuvant for Stage I disease
 - a. Pre-op: Out of favor
 - b. Post-op: Benefit of adjuvant therapy after surgical staging with negative nodes not yet demonstrated (See endometrial cancer chapter). Technique: external beam, 4-fields to pelvis using megavoltage photons. Dose: 45-50 Gy, followed by optional vaginal brachytherapy if vaginal apex recurrence risk is significant. In some settings (lower uterine segment disease or stage II A), vaginal brachytherapy alone may be adequate
- 2. Primary therapy for medically inoperable patients with Stage I – II disease
- 3. Advanced or recurrent disease: Pre-op therapy indicated for clinical Stage II lesions, followed by TAH/BSO. Localized recurrences amenable to radiotherapy for local control

C. Ovary

- 1. Whole Abdomen Radiation Therapy (WART). Historically reported for Stage IC- IIA epithelial tumors successfully debulked to minimal residual disease (\leq 5 mm) as either primary or salvage therapy, as well as for Stage I-II-III dysgerminoma. Technique: open field AP-PA, to dose of 30 Gy with blocks to liver (22 Gy) and kidney (18 Gy). Fraction size of 100-150 cGy/d (Dembo)
- 2. Intraperitoneal ^{32}P . Historically reported for Stage Ib-Ic epithelial tumors with no residual disease and no significant adhesions. Dose 15 mCi

D. Vulva

- 1. Post-operative therapy: Indicated for >1 positive inguinofemoral node, any positive pelvic nodes, and for residual disease of the vulva. Treatment ports customized, electrons commonly used for vulva/groins to maximize surface dose
- 2. Pre-operative therapy: Indicated for bulky T3-4 lesions to reduce tumor size, allowing less radical surgery. Concurrent chemotherapy using 5-fluorouracil, cisplatin, and/or mitomycin C improves likelihood of remission
- 3. Primary treatment: High failure rate if RT utilized without resection of primary site. Radiation of verrucous carcinoma contraindicated

E. Radiosensitizers: 5-fluorouracil and cisplatin used most often for radiosensitization outside of clinical trials

VII. Clinical Complications (Reynolds):

- A. Acute: diarrhea, nausea, vomiting, myelosuppression, ovarian failure, skin burns
- B. Chronic: radiation enteritis, vaginal stenosis, bowel obstruction, GI/GU fistulas, ureteral strictures, hepatic and renal injury, radiation carcinogenesis (after 10-20 years).

VIII. Common Questions

- A. What is the relationship of anemia to cervical cancer treatment? A: Tumor hypoxia decreases efficacy of radiation by reducing oxygen free radical mediated cell damage.
- B. What is the difference when using electrons instead of photons for treatment? A: Electrons have mass and charge causing them to slow when they encounter tissue. This results in clinically useful control of treatment depth

- C. What is Point A? A: A point 2 cm above and 2 cm lateral to the tandem flange (external os) and represents the crossover point of the uterine artery over the ureter. Point B is 3 cm lateral to Point A and represents the location of the obturator nodes.

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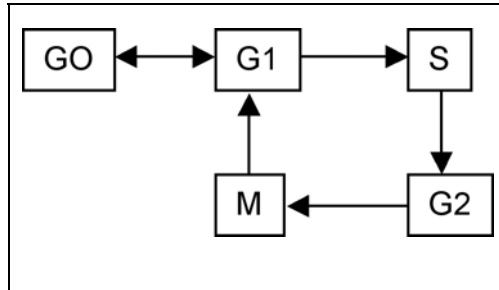
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Rev. 1/2007

Chemotherapy

I. Cancer Cell Kinetics

A. Cell cycle:



Cell Population Types:

1. Static: (e.g. muscle, nerve) well differentiated, rarely undergo mitosis in adults
 2. Expanding: (e.g. liver) proliferate in response to stress or injury
- These 2 population types are resistant to chemo as are G0 cells

3. Renewing: (e.g. marrow, GI mucosa) constant proliferation. Renewing cells are sensitive to chemotherapy.
4. Tumor growth rate is a function of cell cycle time, growth fraction, and death rate.
5. Cancer cells do not divide more rapidly than normal cells.

B. Gompertzian growth: as tumor mass increases, growth fraction decreases and doubling time increases. Doubling times usually range between 20-150 days

C. Mechanisms of resistance

1. Goldie-Coldman hypothesis: a mathematical model predicting the likelihood of somatic mutations capable of leading to drug resistance. Spontaneous mutation occurs every 10,000 to 1,000,000 cell divisions. Hypothesis correctly predicts that multi-drug regimens minimize likelihood of developing resistant clones

2. General Mechanisms of Resistance	Drugs (Cole)
Decreased uptake	Methotrexate, nitrogen mustard, antimetabolites, cisplatin
Increased efflux	Anthracyclines, vinca alkyloids, etoposide, taxanes, methotrexate
Decrease in drug activation	Antimetabolites
Increase in drug catabolism	
Altered level of target enzyme	Methotrexate, topoisomerase inhibitors, 5FU, imatinib
Altered structure of target enzyme	Methotrexate, antimetabolites, topoisomerase inhibitors, imatinib
Inactivation by binding to sulfhydryls (e.g. glutathione, metallothionein)	Alkylating agents, platinum analogs
Increased DNA repair	Alkylating agents, platinum analogs, anthracyclines, etoposide
Decreased apoptosis	

3. Mechanisms of resistance may include: defective drug transport into the cell, altered drug activation, reduced hormone receptor number or affinity, enhanced DNA repair, gene amplification, altered target proteins, and increased drug metabolism.
4. Multi-drug resistance gene (MDR-1): codes for P-glycoprotein P-170, an energy dependent efflux pump that reduces intracellular drug levels. Once induced, cross resistance to multiple unrelated drugs occurs (e.g. vinca alkaloids, dactinomycin, doxorubicin, and paclitaxel)
5. Sulfhydryl mechanisms (glutathione, metallothionein, and glutathione S-transferase): involved in conjugation of toxic molecules, and inactivation of free radicals and peroxides. (e.g. cisplatin and radiation therapy). Future medications may block this mechanism

II. Pharmacokinetics

- A. Log kill hypothesis (Skipper): chemotherapy drugs act via first order kinetics, whereby a constant fraction of cells are killed with each treatment
- B. Therapeutic index (TI): ratio of therapeutic dose to toxic dose of a drug. Reflects differential sensitivity of normal and neoplastic cells to chemotherapy drugs. Chemotherapy drugs typically have low TI
- C. Dose Intensity (DI): $DI = \text{Drug, mg/m}^2/\text{week}$. Especially important for cure of germ cell tumors.
- D. Cell cycle specificity, schedule dependency, drug distribution, drug metabolism and excretion, and drug interactions are all important in designing a treatment protocol

III. Drug Development

- A. Phases of drug development
 1. Phase I: determination of maximum tolerable dose, optimal schedule and dose limiting toxicity of a new drug
 2. Phase II: testing for responses of various tumors to a new drug
 3. Phase III: randomized study comparing efficacy of different treatment regimens
- B. Evaluation of responses: Response Evaluation Criteria in Solid Tumors **RECIST** (Eisenhauer). Defines how tumors are measured, which methods are most reproducible and how responses should be reported. Evaluation of target lesions:
 1. Complete Response (CR): Disappearance of all target lesions. Any pathologic nodes (whether target or non-target) must have reduction in short axis to <10 mm.
 2. Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
 3. Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
 4. Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study

IV. Cytotoxic chemotherapy Drugs (Note: doses may vary widely from protocol to protocol. Doses listed below are for general information only)

Altretamine (Hexalen). Class: miscellaneous alkylator

Use: epithelial ovarian cancer

Mechanism: possible DNA cross-linker or antimetabolite

Cell Cycle Specificity: nonspecific

Metabolism: $T^{1/2}$ 4-10 hours. Requires metabolism in liver to active form. Metabolites excreted in urine (60% in 24 hours, $<1\%$ in native form).

Toxicity: 1°: myelosuppression (nadir 21-28 d), N/V, peripheral sensory neuropathy, renal toxicity; 2°: mood disorders, seizures, ataxia.

Dose: $260 \text{ mg/m}^2\text{-day PO}$ for 14 d, cycle repeated q 28 d. Reduce dose for prior myelosuppression, severe neuropathy. Cimetidine prolongs half-life (P-450 enzyme)

Bleomycin. Class: antibiotic

Use: germ cell tumors, squamous cell carcinoma

Mechanism: scission of single strand DNA, inhibits DNA repair (DNA ligase). Requires presence of metal ion cofactor, primarily copper and to lesser degree nickel, manganese, cobalt.

Cell Cycle Specificity: G2 phase specific

Metabolism: $T^{1/2}$ 3-5 hours. Rapidly inactivated by aminopeptidase in all tissues except lung, skin. Excreted unaltered in urine (25-50% in 24 hours).

Toxicity: 1°: fever, stomatitis, interstitial pneumonitis (10%, especially in elderly) / pulmonary fibrosis (1%; limit total dose to $\leq 400\text{U}$), dermatologic (hyperpigmentation, desquamation), alopecia; 2°: N/V (mild), allergy (hypotension), myelosuppression.

Toxicity increased in presence of high oxygen concentration.

Dose: varies; usually $30\text{ U/m}^2 \times \text{IV weekly}$ as part of BEP regimen. CXR and PFT's before each treatment. Discontinue for decreased DLCO (decrease of $\geq 15\%$ from baseline) or abnormal CXR. Dose reduce for creat. clearance $30\text{-}50\text{ mL/min}$ by 25%.

Capecitabine (Xeloda). Class: antimetabolite

Use: epithelial ovarian cancer, cervical cancer

Mechanism: oral prodrug that is converted in-vivo to 5-FU, conversion in tumor is more efficient than normal cells. Same mechanism as 5-FU.

Cell Cycle Specificity: Cell Cycle Specificity: S phase specific

Metabolism: Excreted in urine with $T^{1/2}$ of 45 minutes. Dose reduce for creatinine clearance $< 50\text{ mL/min}$. Do not use for clearance of $< 30\text{ mL/min}$.

Toxicity: Similar to 5-FU. Skin: palmar-plantar erythrodysesthesia.

Dose: $2,500\text{ mg/m}^2$ total per day (range $1500\text{-}2500$) divided PO q12 hours ($1250\text{ mg/m}^2/\text{dose}$) 30 minutes after meals for 14 days out of each 21 day cycle. Reduce dose based on creatinine clearance: $30\text{-}50\text{ ml/min}$ reduce by 25%, hold for creat. clearance $< 30\text{ ml/min}$. Reduce dose if drug used in combination or for toxicities including: diarrhea, emesis, PPE, abdominal pain, lymphopenia.

Carboplatin (Paraplatin). Class: non-classical alkylator

Use: most gyn tumors

Mechanism: covalent platinum adducts to DNA resulting in intra-strand DNA cross-links and 40° angulation of DNA strands (60%: adjacent G-G bases at N-7, 30%: adjacent A-G bases at N-7). Also forms platinum adducts to RNA and proteins; Inhibits DNA, RNA, protein synthesis

Cell Cycle Specificity: nonspecific

Metabolism: Requires intracellular conversion to di-hydroxy form. $T^{1/2}$ triphasic: 15-30 minutes, 80-100 minutes, and 22-40 hours. Excreted in urine (70% in 24 hours).

Toxicity: In general: more myelotoxicity and less nephrotoxicity/neurotoxicity than cisplatin. 1°: thrombocytopenia (nadir 14-21 d), leukopenia (nadir 18-25 d), anemia, N/V; 2°: allergy, peripheral neuropathy, renal toxicity, hepatotoxicity. Rare: optic neuritis

Dose: $360\text{-}400\text{ mg/m}^2 \text{ IV q } 28\text{ d}$. Reduce dose for prior myelosuppression, decreased creatinine clearance.

Calvert Formula: Total dose = $C \times (\text{GFR} + 25)$, where $\text{GFR} = \text{Cr Cl}$ using Cockcroft-Gault equation. $C=7$ (previously untreated), 5 (heavily pretreated), 5 (combination chemotherapy). Alternative dose algorithm: Jeliffe formula (used for all GOG trials).

Cisplatin (Platinol). Class: non-classical alkylator

Use: most gyn tumors

Mechanism: covalent platinum adducts to DNA resulting in intra-strand DNA cross-links and 40° angulation of DNA strands (60%: adjacent G-G bases at N-7, 30%: adjacent A-G bases at N-7). Also forms platinum adducts to RNA and proteins; Inhibits DNA, RNA, protein synthesis

Cell Cycle Specificity: nonspecific

Metabolism: Requires intracellular conversion to di-hydroxy form. $T^{1/2}$ triphasic, 20-30 min, 50-70 minutes, and 24 hours. Highly protein bound, excreted in urine (25% in 24 hours). Detectable in tissue 4 months after administration.

Toxicity: 1°: N/V, anemia, renal toxicity, ototoxicity, peripheral neuropathy ($>300 \text{ mg/m}^2$), hypomagnesemia, hypokalemia; 2°: leukopenia, allergy, alopecia (uncommon), optic neuritis (rare), Reynaud's, agitation or seizures.

Dose: 50-100 mg/m^2 IV q 21-28 d. with vigorous hydration. Requires intensive antiemetic therapy. Avoid NSAIDs and nephrotoxic drugs (e.g. aminoglycosides). Reduce dose for peripheral neuropathy, decreased creatinine clearance, hearing loss. Avoid NSAIDs, aminoglycosides, and IV contrast proximate to administration.

Cyclophosphamide (Cytosan). Class: alkylator

Use: epithelial ovarian cancer, GTN

Mechanism: inter-strand DNA cross-links, usually at guanine N-7

Cell Cycle Specificity: nonspecific

Metabolism: $T^{1/2}$ 3-10 hours. Requires activation by hepatic cytochrome p450 enzymes to 4-hydroxy-cyclophosphamide. Subsequent metabolism in liver, excretion by kidney (50-70% in 48 hours, 12% as active drug)

Toxicity: 1°: leukopenia (nadir 8-14 d), N/V, alopecia; 2°: hemorrhagic cystitis (high doses), SIADH, pulmonary fibrosis, cardiac necrosis or myopericarditis (rare, high doses), dermatitis, chemical hepatitis. Increased toxicity with phenobarbital, chloral hydrate, phenytoin (increased activation), and cimetidine (decreased clearance).

Secondary malignancy: leukemia

Dose: varies; usually 500-1000 mg/m^2 IV q 21-28 d. Vigorous hydration decreases chance of hemorrhagic cystitis. Reduce dose for prior myelosuppression and in multi-drug regimens.

Dactinomycin (Actinomycin-D). Class: antibiotic

Use: germ cell tumors, GTN

Mechanism: DNA intercalation inhibiting DNA dependent RNA synthesis

Cell Cycle Specificity: nonspecific, but most active in G1

Metabolism: $T^{1/2}$: 36 hours. Drug not metabolized. Excreted in bile (50% in 24 hours) and urine (10% in 24 hours).

Toxicity: 1°: VESICANT, stomatitis, N/V, myelosuppression (nadir 1-7 d), alopecia; 2°: radiation recall dermatitis, hepatotoxicity.

Dose: varies. 1.25 mg/m^2 IV, repeat q 14 days. Reduce dose for prior myelosuppression, hepatotoxicity.

Docetaxel (Taxotere). Class: Taxane (*Taxus baccata*)

Use: epithelial ovarian cancer

Mechanism: promotes and stabilizes microtubule polymer formation, thus preventing cell division.

Cell Cycle Specificity: M phase specific

Metabolism: 95% protein bound. $T^{1/2}$ linear, between 5-52 hours. Metabolized in liver.

Primary route of elimination is hepatic (P-450 enzymes), excreted in bile, and unchanged in urine (5%).

Toxicity: 1°: myelosuppression, hypersensitivity (flushing, hypotension, urticaria), fluid retention, alopecia, irritant; 2°: mucositis, cough, dyspnea

Dose: Requires premedication: dexamethasone 8 mg bid x 3 days beginning 1 day prior to chemo.

100 mg/m^2 (range 60-100) IV over 1 hour, repeated every 3 weeks.

Doxorubicin (Adriamycin). Class: antibiotic

Use: endometrial adenocarcinoma, sarcoma, epithelial ovarian cancer

Mechanism: DNA intercalation inhibiting DNA dependent RNA and DNA synthesis.

Topoisomerase II-dependent DNA fragmentation. Produces O_2 free radicals (hydrogen peroxide) that cause DNA strand breaks, inhibit DNA repair, and disrupt membrane function. Requires iron to catalyze reaction. Peroxide is detoxified by intracellular enzyme catalase, present in very low levels in myocardium. Chelation of iron with Dexrazoxane reduces cardiomyopathy risk.

Cell Cycle Specificity: nonspecific

Metabolism: 70% protein bound. $T^{1/2}$ biphasic, 1.1 hours, 18-28 hours. Metabolized by liver, primary excretion in bile (50% as unchanged drug), 5-10% in urine.

Toxicity: 1°: myelosuppression (nadir 10-15 d), VESICANT, N/V, arrhythmia, cardiomyopathy (risk 3% if dose < 450 mg/m², 7% at 550 mg/m², 15% at 600 mg/m² and 40% at 700 mg/m²; cardiac toxicity more likely with pre-existing heart disease or prior mediastinal radiation), alopecia; 2°: radiation recall dermatitis, red urine.

Dose: varies. 60-75 mg/m² IV q 21-28 days. MUGA scan before first dose. Reduce dose for prior myelosuppression, hepatotoxicity. Discontinue for cardiac toxicity including 10% reduction from baseline ejection fraction or any ejection fraction < 50%. Dose reduce 50-70% if bilirubin ≥ 1.5. Limit total dose to ≤ 450 mg/m²

Doxorubicin, Liposomal (Doxil). Class: antibiotic

Use: endometrial adenocarcinoma, sarcoma, epithelial ovarian cancer

Mechanism: DNA intercalation inhibiting DNA dependent RNA and DNA synthesis.

Topoisomerase II-dependent DNA fragmentation. Produces O_2 free radicals (hydrogen peroxide) that cause DNA strand breaks, inhibit DNA repair, and disrupt membrane function. Peroxide is detoxified by intracellular enzyme catalase, present in very low levels in myocardium.

Cell Cycle Specificity: nonspecific

Metabolism: Small volume of distribution and longer $T^{1/2}$ than doxorubicin. Metabolized by liver, primary excretion in bile.

Toxicity: 1°: myelosuppression (nadir 10-15 days, milder than for doxorubicin), irritant, N/V (mild), palmar-plantar erythrodysesthesia (PPE), cardiomyopathy (less common than doxorubicin), alopecia; 2°: infusion reaction (7%) including pain, flushing, hypotension, dyspnea (slow down the infusion); radiation recall dermatitis.

Dose: varies. 40 mg/m² IV q 28 days. Measure ejection fraction (MUGA scan) before first dose. Reduce dose for prior myelosuppression, hepatotoxicity. Discontinue for cardiac toxicity including 10% reduction from baseline ejection fraction or any ejection fraction < 50%. Dose reduce 50-70% if bilirubin ≥ 1.5. Limit total dose to ≤ 450 mg/m²

Etoposide (VP-16). Class: epidophyllotoxin (Mandrake plant)

Use: small cell carcinoma, GTN, epithelial ovarian cancer, germ cell tumor

Mechanism: activates endonucleases (DNA strand breaks), inhibits topoisomerase II. Also binds tubulin.

Cell Cycle Specificity: S-G2 specific

Metabolism: Extensively protein bound. $T^{1/2}$ biphasic, 1.5 hours, 11 hours. Predominant elimination in the urine as unmetabolized drug. Metabolized by liver, excreted in urine (60% in 24 hours) and bile (16% in 24 hours).

Toxicity: 1°: myelosuppression (nadir 7-16 d), N/V, alopecia; 2°: allergy, hypotension or hypertension (with rapid IV infusion), peripheral neuropathy, irritant. Secondary malignancy: leukemia

Dose: Varies, often incorporated in multidrug regimens (see BEP, EMA-CO, VCPBAE), given IV.

Ovarian cancer salvage regimen: 50 mg/m² PO per day on days q 1-21. Cycle repeats every 28 days. Reduce dose for myelosuppression or prior radiation.

5-Fluorouracil (5-FU, Efudex cream). Class: antimetabolite

Use: squamous cell carcinoma of cervix or vulva, ovarian carcinoma, GTN

Mechanism: pyrimidine antagonist inhibits DNA synthesis by inhibition of thymidylate synthetase. Also inhibits RNA synthesis by blocking uracil incorporation.

Cell Cycle Specificity: S phase specific

Metabolism: Inactive until converted to active metabolites 5-FdUMP(DNA) and 5-FUTP(RNA). T_{1/2} 10-30 min. Catabolized by reduction in liver (80% excreted as inactive metabolite in urine, 10-15% un-metabolized in urine in 6 hours). Crosses BBB (2%).

Toxicity: 1°: myelosuppression (nadir 7-14 d), N/V, mucositis/diarrhea, alopecia, rashes and hyperpigmentation; 2°: cerebellar ataxia, photosensitivity, coronary vasospasm.

Dose: varies. 1000 mg/m² (range 750-1000) IV per day for 4-5 days as 24 hour infusion, q 28 d. Reduce dose for prior myelosuppression. Activity enhanced by administration with folinic acid or pre-administration of MTX. Discontinue for diarrhea, rashes.

Gemcitabine (Gemzar). Class: antimetabolite

Use: epithelial ovarian cancer, sarcoma

Mechanism: active transport into cells, phosphorylated to triphosphate form (active) by deoxycytidine kinase. Inhibits ribonucleotide reductase that inhibits DNA precursor production and is incorporated into DNA causing strand termination. Also inhibits DNA polymerase.

Cell Cycle Specificity: Not limited to S phase (mechanism unknown)

Metabolism: T_{1/2} 1 hour (prodrug) 24 hours (active metabolite). Primarily excreted in urine.

Toxicity: 1°: myelosuppression, N/V, stomatitis, infusion allergic reaction including hypotension (5%), flu-like symptoms, asthenia; 2°: maculopapular rash, radiation recall, hemolytic-uremic syndrome (rare), chemical hepatitis, acute respiratory distress syndrome (rare), somnolence, headache, peripheral edema.

Dose: 1000 mg/m² (range 750-1000) IV on day 1, 8, 15 out of each 28 day cycle. Infuse at 10 mg/m²/min.

Ifosfamide (Ifex). Class: alkylator

Use: cervical cancer, epithelial ovarian cancer, sarcoma

Mechanism: inter-strand DNA cross-links, usually at guanine N-7

Cell Cycle Specificity: nonspecific

Metabolism: Requires activation by hepatic enzymes to 4-hydroxy-ifosfamide. Subsequent metabolism in liver, excretion by kidney.

Toxicity: 1°: leukopenia (nadir 7-10 d), hemorrhagic cystitis, N/V, alopecia; 2°: lethargy, confusion, coma, SIADH, renal tubular acidosis, hypophosphatemia, elevated transaminases.

Dose: varies; usually 1.4-1.8 g/m²-d IV for 3-5 d, q 21-28 d. Must be given with uro-protector Mesna. Reduce dose for decreased albumin, creatinine clearance, prior myelosuppression

Methotrexate. Class: antimetabolite

Use: GTN

Mechanism: dihydrofolate reductase inhibitor, causes thymidine depletion.

Cell Cycle Specificity: S phase specific

Metabolism: $T^{1/2}$ 2-4 hours. 50-90% excreted unchanged in urine in 24 hours. Dose reduce if creatinine < 60 mL/min.

Toxicity: 1°: myelosuppression, mucositis/diarrhea, hepatic dysfunction (chronic doses), renal toxicity (high doses); 2°: interstitial pneumonitis, alopecia.

Dose: IM, IV or IT, regimens vary widely. High doses (>80 mg/m²) administered with Leucovorin rescue and alkalization of urine. Reduce dose for prior myelosuppression, hepatotoxicity. Beware of effusions (reservoir). Avoid NSAID's.

- Usual dose for low risk GTN is 1 mg/kg IM or IV on days 1, 3, 5, and 7 alternating with leukovorin 0.1 mg/kg IV, IM or PO on days 2, 4, 6, and 8. Cycle repeats every 2 weeks until markers normalized. See GTN Chapter for more detail.

Paclitaxel (Taxol). Class: Taxane (*Taxus brevifolia*)

Use: epithelial ovarian cancer, endometrial cancer

Mechanism: promotes and stabilizes microtubule polymer formation, thus preventing cell division.

Cell Cycle Specificity: M phase specific

Metabolism: 95% protein bound. $T^{1/2}$ nonlinear, between 5-52 hours. Metabolized in liver. Primary route of elimination is hepatic (P-450 enzymes), excreted in bile (40% in 24 hours), and unchanged in urine (10% in 24 hours).

Toxicity: 1°: myelosuppression (nadir 8-11 days, increased with 24h infusion vs 3h infusion), hypersensitivity (related to vehicle, Cremophor), bradycardia, alopecia, paresthesia (increased with 3h infusion vs 24h infusion); 2°: N/V, mucositis, myalgia, ventricular arrhythmia

Dose: Varies, usually administered in multidrug regimens. Requires premedication, non-PVC IV tubing, and in-line filter. Common doses include:

175 mg/m² IV by 3 hour infusion, repeated every 3 weeks.

135 mg/m² IV by 24 hour infusion, repeated every 3 weeks.

65-80 mg/m² IV by 1 hour infusion, repeated weekly

Topotecan (Hycamtin). Class: camptothecin (*Camptotheca acuminata*)

Use: epithelial ovarian cancer

Mechanism: binds topoisomerase I, causing covalent DNA-topoisomerase bond and single strand DNA breaks.

Cell Cycle Specificity: M phase specific

Metabolism: Eliminated by active biliary transport and renal excretion (50% in urine over 24 hours. $T^{1/2}$ 1.7-4.9 hours.

Toxicity: 1°: leucopenia, thrombocytopenia, alopecia; 2°: N/V, rash, mucositis, diarrhea

Dose: Varies, given either singly or in multidrug regimens. Common doses include:

1-1.25 mg/m² over 30 minutes, daily x 5 days, repeated every 21 days

4 mg/m² IV on days 1, 8, and 15 repeated every 28 days (Check)

Vincristine (Oncovin). Class: vinca alkaloid

Use: GTN, germ cell tumors

Mechanism: inhibits microtubular polymerization of tubulin causing reversible mitotic arrest.

Cell Cycle Specificity: M phase specific

Metabolism: Extensive protein binding. $T^{1/2}$ triphasic, 5 min, 50-150 min, and 24-90 hours. Clearance is predominantly hepatic. Partially metabolized in liver, excreted in bile (70%), and urine (5-16%).

Toxicity: 1°: leukopenia, neurotoxicity (paresthesia, ataxia, foot drop, muscle wasting), VESICANT, constipation, alopecia; 2°: SIADH, ARDS, cortical blindness (rare), elevated transaminases (mild), bronchospasm (rare), joint pain

Dose: Varies, usually given in multidrug regimens (see EMA-CO). 1 mg/m² IV q 14 days, dose not to exceed 2 mg. Reduce dose for prior myelosuppression, neurotoxicity. Do not give if liver function is abnormal.

Vinorelbine (Navelbine). Class: vinca alkaloid (semi-synthetic, from Madagascar periwinkle: vinca rosea)

Use: ovarian epithelial cancer

Mechanism: inhibits polymerization of tubulin causing reversible mitotic arrest.

Cell Cycle Specificity: M phase specific

Metabolism: Extensive protein binding. T¹/₂ triphasic, 5 min, 50-150 min, and 24-90 hours. Clearance is predominantly hepatic. Partially metabolized in liver, excreted in bile (70%), and urine (5-16%).

Toxicity: 1°: leukopenia, neurotoxicity (paresthesia, ataxia, foot drop, muscle wasting), VESICANT, constipation, alopecia; 2°: SIADH, ARDS, seizures (rare), elevated transaminases (mild), bronchospasm (rare), joint pain

Dose: 30 mg/m² IV weekly. If heavily pretreated, regimen will require periodic "off" week

Other chemotherapy agents occasionally used for gynecologic tumors include: chlorambucil (Leukeran), irinotecan (CPT-11), melphalan (Alkeran), mitomycin, mitoxantrone, oxaliplatin, vinblastine (Velban)

V. Targeted Therapy Drugs

Bevacizumab (Avastin)

Use: ovarian epithelial cancer (Not FDA approved for this indication)

Mechanism: monoclonal antibody binds and inhibits VEGF, decreasing angiogenesis.

May increase chemo delivery to tumor by reducing interstitial pressure

Metabolism: T¹/₂ 20 days. Route of elimination: unknown.

Toxicity: Common: Hypertension, headache, abdominal pain, diarrhea, constipation, stomatitis, DVT, neutropenia, bleeding, dermatitis, proteinuria. Rare GI perforation, impaired wound healing, CHF, nephrotic syndrome, MI, hypertensive crisis, stroke

Dose: 5-10 mg/kg IV q 14 days. Do not administer until > 28 days after surgery and wound fully healed. Hold for proteinuria.

Bortezomib (Velcade)

Use: ovarian epithelial cancer (Not FDA approved for this indication)

Mechanism: small molecule inhibitor 26S proteasome resulting in inhibition of NF-κB thereby promoting apoptosis.

Metabolism: 80% protein bound. Route of elimination: hepatic via CYP-450 2C19 & 3A4

Toxicity: peripheral neuropathy (frequent), myelosuppression (thrombocytopenia 39%, anemia 26%, neutropenia 19%), N/V, diarrhea, rash, elevated transaminases, dyspnea, hypotension, fever, myalgia, sudden cardiac death

Dose: 1 to 1.3 mg/m² IV twice a week for 2 weeks

Cetuximab (IMC-C225)

Use: ovarian epithelial cancer (Not FDA approved for this indication)

Mechanism: Chimeric monoclonal antibody to extracellular EGF receptor, blocking tyrosine kinase activity.

Toxicity: nausea, rash, allergic reaction (fever, chills, erythema), elevated transaminases

Dose: 200-250 mg/m² IV weekly.

Erlotinib (Tarceva)

Use: ovarian epithelial cancer (Not FDA approved for this indication)

Mechanism: small molecule inhibitor of EGF receptor tyrosine kinase resulting in cell cycle arrest and inhibition of angiogenesis. May be synergistic with chemotherapy.

Metabolism: $T^{1/2}$ 36 hours. Route of elimination hepatic CYP-450 enzymes with 83% unchanged excretion in feces.

Toxicity: diarrhea (severe), rash (severe), interstitial lung disease, elevated transaminases, corneal ulcer

Dose: 150 mg PO q day.

Gefitinib (Iressa, Investigational: currently available only for lung cancer protocols)

Use: ovarian epithelial cancer

Mechanism: small molecule inhibitor of EGF receptor tyrosine kinase resulting in cell cycle arrest and inhibition of angiogenesis. May be synergistic with chemotherapy.

Metabolism: $T^{1/2}$ 28 hours. Hepatic route of elimination.

Toxicity: diarrhea, rash, interstitial lung disease, dyspnea, corneal ulcer, elevate transaminases, amblyopia, asthenia, anorexia

Dose: 250 mg PO q day.

VI. Medications Used in Conjunction with Chemotherapy

A. Management of Nausea and vomiting

1. Chemotherapy induced emesis mechanisms: Stimulation of the chemoreceptor trigger zone in the area postrema causes CNS secretion of dopamine, serotonin and histamine that activate adjacent vomiting center in brain. Other mechanisms include stimulation of GI serotonin receptors and psychological effects.
2. There are 3 different forms of chemotherapy associated emesis: acute (first 24 hours after chemo), delayed (24-96 hours after chemo), and anticipatory.

B. Anti-emetics

1. 5-HT₃ receptor antagonist. These drugs are very effective but expensive. They are used to prevent nausea and vomiting for the first 3-4 days after chemo and are not appropriate for long-term continuous use or to treat pre-existing emesis. If Emend is used in the anti-emetic regimen, 5-HT₃ receptor antagonists are used only prior to chemotherapy. See below for table regarding use

Ondansetron (Zofran)

Mechanism: Serotonin (5-HT₃) receptor blockade

Metabolism: hepatic via CYP450 enzymes. Excreted in urine.

Toxicity: Headache, elevated transaminases, constipation, diarrhea, potential prolongation of Q-T interval

Dose: 8-16 mg IV or 8-24 mg PO 30 min before chemo. Given only on day 1 if combined with aprepitant. May also be given 8 mg PO or orally dissolving tabs tid first 3 days after chemo if no aprepitant given

Granisetron (Kytrel)

Mechanism: Serotonin (5-HT₃) receptor blockade

Metabolism: hepatic via CYP450 enzymes. Excreted in urine.

Toxicity: Headache, elevated transaminases, constipation, diarrhea, potential prolongation of Q-T interval

Dose: 1 mg IV < 30 min before chemo, or 1-2 mg PO 1 hour before chemo.

Given only on day 1 if combined with aprepitant. May follow with 1 mg po bid first 3 days after chemo if no aprepitant given

Dolasetron (Anzemet)

Mechanism: Serotonin (5-HT₃) receptor blockade

Metabolism: hepatic via CYP450 enzymes. Excreted in urine (70% and feces (30%), $T^{1/2}$ < 10 min.

Toxicity: Headache, elevated transaminases, constipation, diarrhea, potential prolongation of Q-T interval

Dose: 100 mg IV 30 min before chemo or PO 1 hour before chemo. Given only on day 1 if combined with aprepitant. May follow with 100 mg PO q day x 3 days if no aprepitant given

Palonosetron (Aloxi)

Mechanism: Serotonin (5-HT₃) receptor blockade. 100 x higher binding affinity than other 5-HT₃ antagonists

Metabolism: hepatic via CYP450 enzymes. Excreted in urine (70% and feces (30%), T_{1/2} 40 hours vs. 4-9 hours for other 5-HT₃ antagonists.

Toxicity: Pruritus, Q-T prolongation, headache, elevated transaminases, constipation, diarrhea. Caution if cardiac conduction problem, hypocalcemia, hypomagnesemia, erythromycins, prior anthracyclines. Use with phenothiazines may cause synergistic Q-T prolongation.

Dose: 0.25 mg IV 30 min before chemo. Single dose provides 3 or more days of antiemetic effect.

2. Substance P / NK1 receptor antagonist. See table below regarding use.

Aprepitant (Emend)

Mechanism: selective antagonism of human substance P-Neurokinin 1 receptors

Metabolism: hepatic CYP3A4 enzymes with excretion in feces and urine

Toxicity: fatigue, hiccups, constipation, diarrhea, anorexia, headache, abdominal pain, mucositis, neutropenia. May alter metabolism and effectiveness of many drugs including chemotherapy agents. Check with pharmacist.

Dose: 125 mg PO 1 hour before chemo, then 80 mg PO qAM on day 2-3.

Administer with dexamethasone 12-20 mg PO or IV pre-chemo and 8-12 mg PO daily on days 2-3

3. Motility agent

Metoclopramide (Reglan)

Mechanism: Dopamine blockade; Serotonin (5-HT₃) blockade at high doses.

Stimulates gastric motility and emptying.

Toxicity: Sedation (60%), diarrhea (15%), Extrapyramidal symptoms (EPS) (20%) if younger than 30. EPS usually treated with Benadryl, 25-50 mg IV.

Dose: 5-10 mg PO or IV q 6 hours prn, or 20-40 mg PO for more severe nausea, or 25 -50 mg IV for more severe nausea

4. Phenothiazine

Prochlorperazine (Compazine)

Mechanism: Dopamine D₂ receptor blockade

Toxicity: Sedation, dry mouth, EPS, orthostatic hypotension

Dose: 25 mg suppository PR q 12 hours or 10 mg PO or IV or IM q 6 hours prn

5. Benzodiazepine

Lorazepam (Ativan)

Mechanism: Sedative, anxiolytic via GABA neurotransmitter pathways

Side Effects: Drowsiness, confusion, ataxia, amnesia (desirable)

Dose: 0.5-2 mg IV, PO or sublingual, q 6 hours prn. Use lowest dose for elderly patients or if renal impairment.

6. Steroid

Dexamethasone (Decadron)

Mechanism: Unknown; possibly prostaglandin synthesis inhibitor

Toxicity: Euphoria, fluid retention, insomnia

Dose: Regimens vary widely (See table below). 20 mg IV 30 min before each chemo cycle. May also be given 2-8 mg PO bid for 2-4 days after chemo cycle. Reduce dose if giving with aprepitant due to decreased clearance of the steroid

C. Emetogenicity of chemotherapy drugs (Hesketh, NCCN) Drugs in parentheses rarely used for Gyn Oncology

Agent and Dose	Frequency of Emesis	Regimen
Altretamine Cisplatin ($> 50 \text{ mg/m}^2$) Cyclophosphamide ($> 1500 \text{ mg/m}^2$) Doxorubicin + cyclophosphamide (Carmustine, dacarbazine, mechlorethamine, oral procarbazine, streptozocin)	$> 90 \%$	High
Carboplatin Cisplatin ($< 50 \text{ mg/m}^2$) Cyclophosphamide ($\leq 1500 \text{ mg/m}^2$) Dactinomycin Doxorubicin ($> 60 \text{ mg/m}^2$) Etoposide (oral) Ifosfamide Methotrexate ($250 - 1000 \text{ mg/m}^2$) (Amifostine, azacitidine, busulfan, cytarabine, daunorubicin, epirubicin, oral imatinib, irinotecan, lomustine, melphalan $> 50 \text{ mg/m}^2$, oxaliplatin $> 75 \text{ mg/m}^2$, oral temozolomide, oral vinorelbine)	30-90 %	Moderate
Capecitabine Docetaxel Doxorubicin ($< 20 \text{ mg/m}^2$) Doxorubicin (liposomal) Etoposide (IV) 5-Fluorouracil Gemcitabine Methotrexate ($50 - 250 \text{ mg/m}^2$) Paclitaxel Topotecan (Amifostine $\leq 300 \text{ mg/m}^2$, cetuximab, cytarabine $100-200 \text{ mg/m}^2$, oral fludarabine, mitomycin, mitoxantrone, pemetrexed)	10-30 %	Low
Bleomycin Methotrexate ($< 50 \text{ mg/m}^2$) Vincristine Vinorelbine (Bevacizumab, bortezomib, busulfan, oral chlorambucil, dexrazoxane, erlotinib, fludarabine, gefitinib, oral melphalan, rituximib, vinblastine)	$< 10 \%$	Minimal

D. Anti-emetic regimens based on emetogenicity of the chemotherapy regimen

Severity, (Route)	Anti-emetic Regimen
Severe (PO)	<ul style="list-style-type: none"> • Aprepitant, as described above, <u>and</u> • Dexamethasone 12 mg PO then 4 mg PO bid x 3 days, <u>and</u> • 5-HT3 inhibitor PO (granisetron, ondansetron, dolasetron or palonosetron pre-chemo, day 1 only. Doses noted above, VI.B.1), <u>and</u> • Lorazepam (Dose noted above, VI.B.5) x 4 days (optional)
(unable to take PO)	<ul style="list-style-type: none"> • Dexamethasone 20 mg IV then 8 mg PO or IV x 3 days, <u>and</u> • 5-HT3 inhibitor IV (Using multi-day regimens noted above, VI.B.1), <u>and</u> • Lorazepam (Dose noted above, VI.B.5) x 4 days (optional)
Moderate	<ul style="list-style-type: none"> • Aprepitant, if receiving carboplatin, doxorubicin, ifosfamide, cyclophosphamide, or methotrexate, <u>and</u> • Dexamethasone 12 mg PO then 4 mg PO bid x 3 days, <u>and</u> • 5-HT3 inhibitor PO (granisetron, ondansetron, dolasetron or palonosetron pre-chemo, day 1 only. Doses noted above, VI.B.1), <u>or</u> • Metoclopramide (Dose noted above, VI.B.3) x 3 days, <u>and</u> • Lorazepam (Dose noted above, VI.B.5) x 4 days (optional)
Severe to moderate (delayed nausea)	<ul style="list-style-type: none"> • Prochlorperazine 25 mg suppository PR q 12 hours or 10 mg PO q 6 hours, <u>and / or</u> • Metoclopramide (Dose noted above, VI.B.3) with diphenhydramine as needed for extrapyramidal symptoms (EPS), <u>and / or</u> • Lorazepam (Dose noted above, VI.B.5), <u>or</u> • Haloperidol 1-2 mg PO or IV q 6 hours, <u>or</u> • Dronabinol 5-10 mg PO or IV q 8-12 hours. Maximum 15 mg/m²/day, <u>or</u> • Olanzapine 5 mg po bid-tid
Low	<ul style="list-style-type: none"> • Dexamethasone (Dose noted above, VI.B.3), <u>or</u> • Prochlorperazine (Dose noted above, VI.B.4), <u>or</u> • Metoclopramide (Dose noted above, VI.B.3), <u>or</u> • Lorazepam (Dose noted above, VI.B.5)
Minimal	<ul style="list-style-type: none"> • Treat nausea only if it occurs. No prophylaxis or compazine 10 mg po prior to treatment

D. Cytokines. These drugs are very effective for treatment of chemotherapy-associated neutropenia and anemia, and somewhat less effective for treatment of thrombocytopenia. All are expensive and should only be ordered for appropriate indications.

1. Cytokines for treating neutropenia

Filgrastim (Neupogen)

Mechanism: colony stimulator factor (G-CSF)

Toxicity: medullary bone pain (24%, may treat with NSAIDs), splenomegaly, elevated transaminases, abdominal pain, headache, thrombocytopenia, ARDS (rare), allergic reaction to *E. coli* proteins including anaphylaxis, splenic rupture (rare)

Indications: ASCO Guidelines 1996

Myelosuppression with > 40% expected incidence of febrile neutropenia, prior radiation, extensive prior chemotherapy, high dose intensity regimen, history of febrile neutropenia with prior chemo cycle, history of prior chemo dose reduction due to prolonged neutropenia

Dose: 5 mcg/kg per day SC (usually 300 mcg/day). Not to be given <24 hours before or after chemotherapy. Continue until absolute neutrophil count (ANC) > 1000 x 3 days and after expected nadir

Pegfilgrastim (Neulasta)

Mechanism: liposomal colony stimulator factor (GCSF), much longer half-life than filgrastim

Toxicity: medullary bone pain (24%), splenomegaly, elevated transaminases, abdominal pain, headache, thrombocytopenia, ARDS (rare), allergic reaction to *E. coli* proteins including anaphylaxis, splenic rupture (rare)

Indications: Same as for filgrastim

Dose: 6 mg SC x 1 dose. Not to be given <24 hours after chemotherapy or < 14 days before next chemo cycle. Safe use on day of chemo with chemo regimens requiring treatment q14 days has been reported in a small series.

2. Cytokines for treating anemia:

Black Box Warning by the FDA indicating possible increase of cancer recurrences and thrombo-embolic events has limited use of this class of medications

Epoetin alpha (Procrit, Epogen)

Mechanism: erythropoietin, a cytokine that stimulates erythroid progenitor cells

Toxicity: HTN, headache, arthralgia, nausea, fever, tachycardia, edema, dyspnea, dizziness, fatigue, cough, congestion, red cell aplasia. Rare toxicities include: seizures, MI, stroke, CHF, thromboembolism, allergic reaction

Indications: chemotherapy-associated anemia with starting hemoglobin (Hb) of <10-12 gm/dL

Dose: 40,000 units SC q week until target Hb > 12 g/dL reached. Reevaluate Hb after 4-8 weeks: dose may be escalated to 60,000 units SC q week prn

Darbepoetin alpha (Aranesp)

Mechanism: erythropoietin-like cytokine that stimulates erythroid progenitor cells

Toxicity: HTN, headache, arthralgia, nausea, fever, tachycardia, edema, dyspnea, dizziness, fatigue, cough, congestion, red cell aplasia. Rare toxicities include: seizures, MI, stroke, CHF, thromboembolism, allergic reaction

Indications: chemotherapy-associated anemia with starting hemoglobin (Hb) of <10-12 gm/dL

Dose: 200 mcg SC q 2 weeks until target Hb > 12 g/dL reached. Reevaluate Hb after 4-8 weeks: dose may be escalated to 400 mcg SC q 2 weeks prn.

Alternate dosing is 300 mcg SC q 3 weeks.

3. Cytokine for treating thrombocytopenia

Oprelvekin (Neumega)

Mechanism: IL-11, a cytokine that stimulates megakaryocytes

Toxicity: dilutional anemia, edema, tachycardia and palpitations or arrhythmia, pulmonary edema, pleural effusion, ocular bleeding, stroke

Indications: Thrombocytopenia with anticipation of nadir lasting at least one week

Dose: 50 mcg/kg SC q day beginning 24 hours after chemo for a maximum of 21 days. Not to be given < 48 hours before or < 24 hours after chemotherapy.

Continue until platelets are > 50,000 and past anticipated nadir

E. Protectors

Amifostine (Ethyol)

Mechanism: Binds to cisplatin metabolites. Used to treat platinum-associated renal toxicity (ovarian and lung cancer) and xerostomia associated with head and neck radiation. May reduce platinum-associated neuropathy (off label use)

Toxicity: severe nausea and vomiting, hypotension (stop anti hypertensive meds 24 hours before and pre-hydrate), hypocalcemia, flushing, fever. Rarely: apnea, dyspnea, seizures, syncope, allergic reaction, cardiac arrest, A-fib, Stevens-Johnson syndrome

Dose: 740 mg/m² IV over 15 minutes, administered 30 minutes before chemo (dose range 200 mg/m² for RT to 910 mg/m² for chemo).

Leucovorin (Citrovorum factor)

Mechanism: folinic acid, a tetrahydrofolate derivative, is a cofactor in the synthesis of pyrimidines and purines. Its presence bypasses enzymatic block caused by methotrexate. Leucovorin may be preferentially taken up by normal cells and not by cancer cells.

Toxicity: non-toxic. Rare allergic reactions

Dose: varies based on methotrexate regimen and methotrexate levels.

Mesna

Mechanism: a sulfhydryl compound that inactivates toxic metabolites of ifosfamide and cyclophosphamide (acrolein) within the urinary tract.

Toxicity: N/V and diarrhea (at high doses), allergic reaction (rare)

Dose: varies. 20% of Ifosfamide dose infused IV 15 min before, 4 h and 8 h after each dose. Alternate oral dosing: give usual pre-chemo dose IV, then oral dose calculated at 40% of ifosfamide dose given 2 and 6 hours after. Continuous infusions sometimes used

VII. Treatment of Febrile Neutropenia

A. Definition: Fever ($\geq 100.4^{\circ}\text{F}$) + Neutropenia ($\text{ANC} < 1000/\mu\text{l}$)

B. Workup: Comprehensive history and physical exam; CBC with differential and platelets; comprehensive panel; cultures of blood and urine; culture port, if present. If indicated by symptoms or findings, obtain Chest X-ray, wound cultures and stool culture for *Clostridium difficile*

C. Assess risk with MASCC Risk Index (www.NCCN.org Fever and Neutropenia Guideline)

Burden of illness	Points
No or mild symptoms	5
Moderate symptoms	3
No hypotension	4
No COPD	4
Solid tumor or no previous fungal infection	4
No dehydration	3
Outpatient status	3
Age ≤ 60 years	2

D. Risk score of ≥ 21 is LOW RISK

E. For Low Risk Patients: MASCC Score ≥ 21 , GOG performance status of 0-1, and no other high risks, treat as follows:

1. Outpatient therapy after 6-24 hour observation
2. Oral antibiotics with ciprofloxacin 500 mg PO q 12 hours and amoxicillin/clavulanate 500 mg PO q 8 hours. If PCN allergic, substitute clindamycin 300 mg po q 6 hours for amoxicillin

- F. For High Risk Patients: MASCC Score < 21, pneumonia, creatinine > 2 mg/dL, hepatic functions > 3x normal, or clinically unstable, treat as follows:
1. Admit to hospital
 2. IV monotherapy with either meropenem (Merrem) 1g IV q8 hours or cefepime (Maxipime) 2g IV q8 hours (if community acquired). Adjust doses for renal impairment
 3. If port or line infection suspected, start vancomycin 1 g IV q 12 hours, adjusted for renal function. Make sure drug is administered through the port.
 4. If *C. difficile* infection suspected, start metronidazole 500 mg PO q 8 hours.

G. Alter therapy if:

1. ANC ≤ 100/microliter with short latency < 10 days from chemotherapy, sepsis or clinically documented infection, severe comorbidity, and/or performance status of 3-4, add G-CSF (Neupogen or Neulasta) Continue until ANC ≥ 3000
2. If clinical condition unstable or if fever does not respond, add gentamicin or vancomycin depending on suspected source. Consider antifungal therapy
3. If culture reveals site-specific infection such as *Clostridium difficile*, add metronidazole

H. Duration of therapy

1. No identified infection: antibiotics for at least 4 days, continuing until > 24 hours afebrile and ANC ≥ 500/microliter
2. Positive blood culture: antibiotics for 14 days depending on organism
3. Pneumonia: 14-21 days of antibiotics

VIII. Treatment of Extravasated Vesicant (See UM Policy #63-01-077)

A. "An ounce of prevention is worth a pound of cure!"

- Always use a fresh IV site, flush the line (should note low resistance to flow), and check for back flash of blood (place IV bag on floor).
- Never use hand IV, infiltrated, or painful IV.
- Consider permanent central line placement for low risk access.

B. If infiltration occurs, aspirate as much drug back through IV as possible, then:

Drug	Treatment (List is not all inclusive. Includes drugs used in Gyn Onc)
Severe Vesicants: capable of tissue necrosis	
Dactinomycin Doxorubicin	Cold compresses. Elevate extremity. Consider sodium thiosulfate Ice packs, 30 min qid for 72 hours. Elevate extremity. Topical DMSO (99%), 2 ml 6 times per day x 7 days. Apply topical steroids bid x 3 days. Inject dexrazoxane IV 1000 mg/m ² per day x 2 days (Saghir)
Vincristine	Warm compresses. Avoid steroids or cooling.
Vinblastine	Warm compresses. Avoid steroids or cooling.
Vinorelbine	Warm compresses. Avoid steroids or cooling.
Venous Irritant: capable of local pain and irritation	
Cisplatin	Cool compresses. 10% sodium thiosulfate 2 mL SC per 100 mg cisplatin. If total extravasated platinum > 20 mL of > 0.5 mg/mL, may act as severe vesicant
Docetaxel	Cool compresses.
Doxil	Same as for doxorubicin
Etoposide	Warm compresses, 30 min qid for 24 hours. Hyaluronidase, (Wydase) 150 U/mL; 1-6 mL SC
5-Fluoruracil	Treat symptoms as they arise
Gemzar	Treat symptoms as they arise
Ifosfamide	Treat symptoms as they arise
Paclitaxel	Cold compresses. Hyaluronidase, (Wydase) 150 U/mL; 1-6 mL SC

- C. Consult Plastic Surgery for wound management
 - D. If ulceration occurs, prompt surgical debridement and possible skin grafting needed
- IX. Late Complications of Chemotherapy
- A. Ovarian Failure: risk a function of drug type, cumulative dose, and patient age.
Alkylators (e.g. cyclophosphamide) most strongly implicated.
 - B. Leukemia: relative risk increased 12 fold (range of RR 4.4-32). Greatest risk 4-5 years after chemotherapy. Long term chemotherapy implicated, particularly with alkylators (chlorambucil, melphalan), and less so with doxorubicin-cisplatin combination therapy.
- X. Calculations and Equations
- A. Body Surface Area (Dubois): $0.007184 \times (\text{cm}^{0.725}) \times (\text{kg}^{0.425})$
 - B. Creatinine Clearance (Cockcroft and Gault, females): $\frac{(140 - \text{age}) \times \text{kg} \times 0.85}{\text{Creatinine} \times 72}$
 - C. Creatinine Clearance (Jelliffe) $\frac{(98 - 0.8[\text{age} - 20])}{\text{Creatinine}^*} \times 0.9$
- *: The creatinine value must be ≥ 0.6 mg/dL. If measured creatinine is < 0.6 mg/dL, then set the value at 0.6 mg/dL
- D. Calvert Formula for Carboplatin Dosing: Use the Creatinine Clearance estimated from either the Cockcroft-Gault or Jelliffe methods:
Carboplatin dose = [Creatinine clearance + 25] x AUC
AUC = area under the curve, a chosen value between 4.5 and 7, that determines the dose intensity based on the chosen regimen
- XI. Multidrug Regimens used for Gynecologic Tumors Preprinted orders on file at <https://ummcpharmweb.med.umich.edu/chemotherapy/>
- BEP: Bleomycin / Etoposide / Cisplatin: (GOG 5-day regimen)** for ovarian germ cell and stromal tumors).
Bleomycin 20 U/m² IV (maximum 30 U) weekly
Etoposide 100 mg/m² IV daily x 5 days, repeat every 3 weeks
Cisplatin 20 mg/m² IV daily x 5 days, repeat every 3 weeks
Total of 3-4 cycles depending on adequacy of resection and tumor markers (if any)
- BEP: Bleomycin / Etoposide / Cisplatin: (3-day regimen)** for ovarian germ cell and stromal tumors). Ref: J Clin Oncol 1990; 8: 715-20
Bleomycin 10 Units / day over 18 hours each day x 3 days
Etoposide 100 mg/m² IV daily x 3 days, repeat every 3 weeks
Cisplatin 75 mg/m² IV, repeat every 3 weeks
Total of 3-4 cycles depending on adequacy of resection and tumor markers (if any)
- Cb-T: Carboplatin / Paclitaxel:** standard regimen for ovarian epithelial carcinoma
Taxol 175 mg/m² IV as 3 hour infusion, followed by
Carboplatin Calvert AUC 4.5 - 7 (usually 5 – 6) IV
Repeated every 21 days for 6 cycles
- Cisplatin-Gemzar** (two day regimen)
Cisplatin 75 mg/m² with 12.5 g mannitol in 1L 0.9 NS over 2 hours on day 1
Gemcitabine 1000 mg/m² in 500 mL 0.9 NS over 90 minutes on day 1 and 8

Neulasta 6 mg SC on day 9
Repeat cycle every 21 days

EMA-CO: Etoposide / Methotrexate / Atinomyacin D / Cyclophosphamide / Vincristine:
for high risk gestational trophoblastic neoplasms

Etoposide 100 mg / m² IV on days 1, 2.

Methotrexate 100 mg/ m² IV push followed by 200 mg/ m² IV over 12 hours on day 1. If brain mets present, Methotrexate dose is changed to 1000 mg/m² as 24 hour infusion. Urine must be alkalinized. If brain mets present, intrathecal methotrexate may be needed, although radiation therapy is an alternative. See GTN Chapter for details

Actinomycin-D 0.5 mg IV push on days 1, 2

Leucovorin 15 mg IV, IM or PO q 12 hours x 4 doses beginning 24 hours after methotrexate infusion complete. If high dose methotrexate used, then 9 doses

Cyclophosphamide 600 mg/ m² IV on day 8

Vincristine 1 mg / m² IV push on day 8

Cycle repeats every 2 weeks. Filgrastim support required.

EMA-EP: Etoposide / Methotrexate / Atinomyacin D / Etoposide / Cisplatin: for refractory, high risk gestational trophoblastic neoplasms

Etoposide 100 mg / m² IV on days 1, 2.

Methotrexate 1000 mg/ m² IV over 24 hours on day 1

Actinomycin-D 0.5 mg IV push on days 1, 2

Leucovorin 15 mg IV, IM or PO q 12 hours x 9 doses beginning 24 hours after methotrexate infusion complete

Etoposide 100 mg / m² IV on day 8

Cisplatin 80 mg / m² IV on day 8

Cycle repeats every 2 weeks. Filgrastim support required.

Gemcitabine / Docetaxel: for leiomyosarcoma (Hensley)

Gemcitabine 900 mg/m² IV on days 1 and 8

Docetaxel 100 mg/m² IV on day 8

Filgrastim 300 mcg SC on days 9 – 15

Cycle repeats every 21 days

Patients with prior pelvic radiation are dose reduced 25% for both chemo drugs

Ifosfamide-Taxol: for uterine carcinosarcoma

Paclitaxel 135 mg/m² over 3 hours on day 1 only.

Ifosfamide (1600 mg/m² standard dose, or 1200 mg/m² with prior pelvic RT) in 0.5 L 0.9 NaCl over 1 hour on days 1, 2, and 3.

Mesna 20% of ifosfamide dose administered IV prior to each dose of ifosfamide in addition to PO or IV at 4 and 8 hours after each ifosfamide dose

Intraperitoneal chemotherapy for ovarian cancer

See ovarian cancer chapter, section IX.A.4.e.

MAI: Mesna, Adriamycin and Ifosfamide: for uterine sarcomas. (Adapted from Antman)

Ifosfamide 1500 mg / m² / day as 1 hour infusion on days 1 - 3

Mesna 20% of IFX dose IV 15 minutes prior to each IFX dose in addition to 4 and 8 hours after each IFX dose

Doxorubicin 20 mg / m² / day as 24 hour infusion for days 1 - 3

RT sensitization

Platinum Regimen (Cervix)

Cisplatin 40 mg/m² IV as 2 hour infusion with 25 g mannitol and 1 g magnesium sulfate. Cap dose at 70 mg / m² / week

Administer weekly throughout radiation treatment

5 Fluorouracil Regimen (Vulva)

5 Fluorouracil 1000 mg / m² / day as 24 hour infusion on days 1-4.

Repeat every 4 weeks during radiation treatment

TAC: Paclitaxel / Doxorubicin / Carboplatin: GOG regimen for endometrial carcinoma (Duska)

Doxorubicin 45 mg/m² IV slow push on day 1

Paclitaxel 160 mg/m² IV as 3 hour infusion on day 1

Carboplatin AUC 5 IV as 1 hour infusion on day 1

Neulasta 6 mg SC on day 2

Cycle repeats every 3 weeks for 6 cycles

TAP: Paclitaxel / Doxorubicin / Cisplatin: GOG regimen for endometrial carcinoma (Fleming)

Doxorubicin 45 mg/m² IV on day 1

Cisplatin 50 mg/m² IV as 2 hour infusion with 25 g mannitol and 1 g magnesium sulfate on day 1

Paclitaxel 160 mg/m² IV as 3 hour infusion on day 2, > 24 hours after doxorubicin

Neulasta 6 mg SC on day 3

Cycle repeats every 3 weeks for 6 cycles

VAC: Vincristine / Actinomycin-D / Cyclophosphamide: GOG regimen for ovarian germ cell tumors)

Vincristine 1.5 mg/m² IV (maximum 2 mg), repeat every 2 weeks

Actinomycin-D 350 mcg/m² IV daily x 5 days, repeats every 4 weeks

Cyclophosphamide 150 mg/m² IV daily x 5 days, repeat every 4 weeks

Total of 4-6 cycles depending on adequacy of resection and tumor markers (if any)

Other Regimens

AC: Adriamycin + cisplatin: for endometrial cancer

CI: Cisplatin + ifosfamide: for cervical carcinoma

CP: Cisplatin + paclitaxel for cervical cancer

CT: Cisplatin + topotecan for cervical cancer

VCPBAE: Vincristine, cyclophosphamide, cisplatin, bleomycin, doxorubicin, etoposide for small cell neuroendocrine ovarian cancer

VAC-EI: Vincristine, doxorubicin, cyclophosphamide, etoposide, ifosfamide for pPNET tumors

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Revised 2/2010

Perioperative Management

I. Preoperative risk stratification

Usual risk of death within 30 days of surgery estimated to be 0.7% to 1.7%

A. American Society of Anesthesiologists (ASA) Classification

Class	Description	Mortality (%)
I	No chronic medical problems	0.1
II	Optimal control of mild chronic disease	0.7
III	Severe disease that limits activity without incapacitation	3.5
IV	Severe, incapacitating disease with constant threat to life	18.3
V	Moribund, death likely within 24 hours with or without surgery	93.3
E	Emergency operation	

B. Functional capacity

1. Duke Activity Status

Peri-operative cardiac and long-term risks increased in patients unable to meet a 4-MET demand during normal daily activities

MET = metabolic equivalent. 1 MET = Oxygen consumption (VO₂) of a 70-kg, 40-year old man in a resting state is 3.5 mL / kg-minute

Estimated Energy Requirements for Various Activities

1 MET	Can take care of self, eat, dress, use toilet, walk around the house, walk a block or two at 2-3mph
4 METs	Climb flight of stairs, walk up a hill, walk on level ground at 4 mph, run a short distance, scrub floors, move furniture, golf
10 METs	Strenuous activity, swimming, skiing

2. New York Heart Association Functional Classification of Heart Disease

Class	Tolerated Specific Activities
I	Carry 24 lb object up 8 steps, walk 5 mph, carry 80 lb object, shovel snow
II	Walk 4 mph, rake or weed garden, sexual intercourse, walk up 8 steps
III	Make bed, push lawn mower, shower, walk 2.5 mph, dress
IV	None of above

II. Cardiovascular System

A. Cardiac Risk Stratification for Noncardiac Surgical Procedures (Eagle)

Clinical Predictors of Increased Perioperative Cardiovascular Risks (Myocardial infarction, Heart Failure, Death)

1. Major (Reported cardiac risk often greater than 5%)

Unstable coronary syndromes; acute or recent MI with evidence of important ischemic risk; unstable or severe angina (Canadian class III or IV); decompensated heart failure; significant arrhythmias including high-grade A-V block, symptomatic ventricular arrhythmias in presence of underlying heart disease, supraventricular arrhythmias with uncontrolled ventricular rate; severe valvular disease

2. Intermediate (Reported cardiac risk generally less than 5%)

Mild angina (Canadian class I or II), previous MI by history or pathological Q waves, compensated or prior heart failure, diabetes (insulin dependent), renal insufficiency

3. Minor (Reported cardiac risk generally less than 1%)

Advanced age, abnormal ECG (LVH, LBBB, ST-T abnormalities), rhythm other than sinus (e.g. atrial fibrillation), low functional capacity (cannot climb one flight of stairs with a bag of groceries), history of stroke, uncontrolled hypertension

B. Cardiac Risk Index (Goldman)

1. Risk Factors	Points
Age > 70 y	5
MI < 6 mo ago	10
S3 Gallop or JVD	11
Aortic Stenosis	3
EKG ≠ Sinus or PAC's	7
EKG > 5 PVC's/Min	7
PO ₂ <60, PCO ₂ >50, K ⁺ <3.0, HCO ₃ <20, BUN >50, Creat >3.0, Abnormal SGOT, or bedridden	3
Intraperitoneal / thoracic/aortic surgery	3
Emergency surgery	4

2. Risk of Non-cardiac Surgery

Points	Class	Morbidity	Mortality
0-5	I	0.7%	0.2%
6-12	II	3%	1%
13-25	III	11%	3%
≥26	IV	12%	39%

C. Revised Cardiac Risk Index (Lee)

1. Risk Factors (add total score)

High risk surgical procedure (Intraperitoneal, intrathoracic, vascular), ischemic heart disease (excluding previous revascularization), CHF, Hx of stroke or TIA, pre-op insulin therapy, preop creatinine >2.0 mg/dl

2. Surgical Event Rate

Class	Events	Event Rate
I (0 risk factors)	2/488	0.4 %
II (1 risk factor)	5/567	0.9%
III (2 risk factors)	17/258	6.6%
IV (≥3 risk factors)	12/109	11.0%

Major events included MI, cardiac arrest, pulmonary edema, complete heart block

D. Dobutamine Stress Echocardiography for Risk Stratification

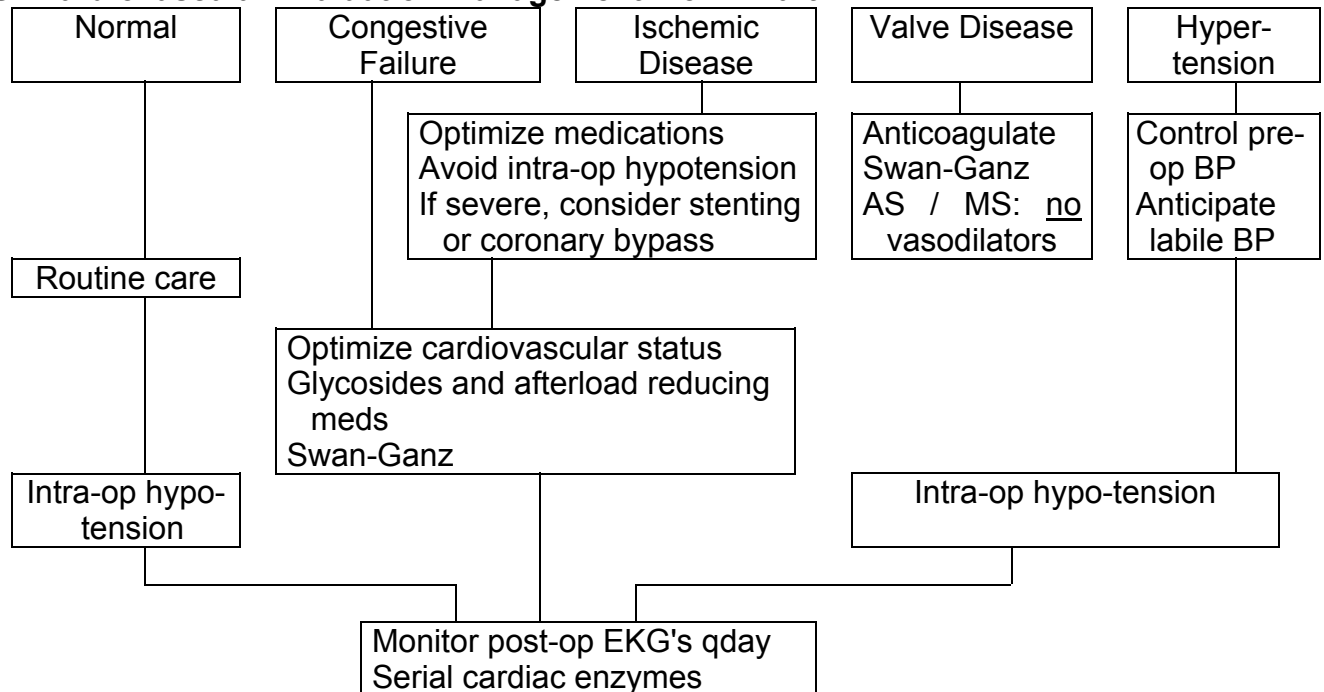
High negative predictive value (98-100%), but low positive predictive value (14-25%)

E. Anesthetic risks for specific heart problems

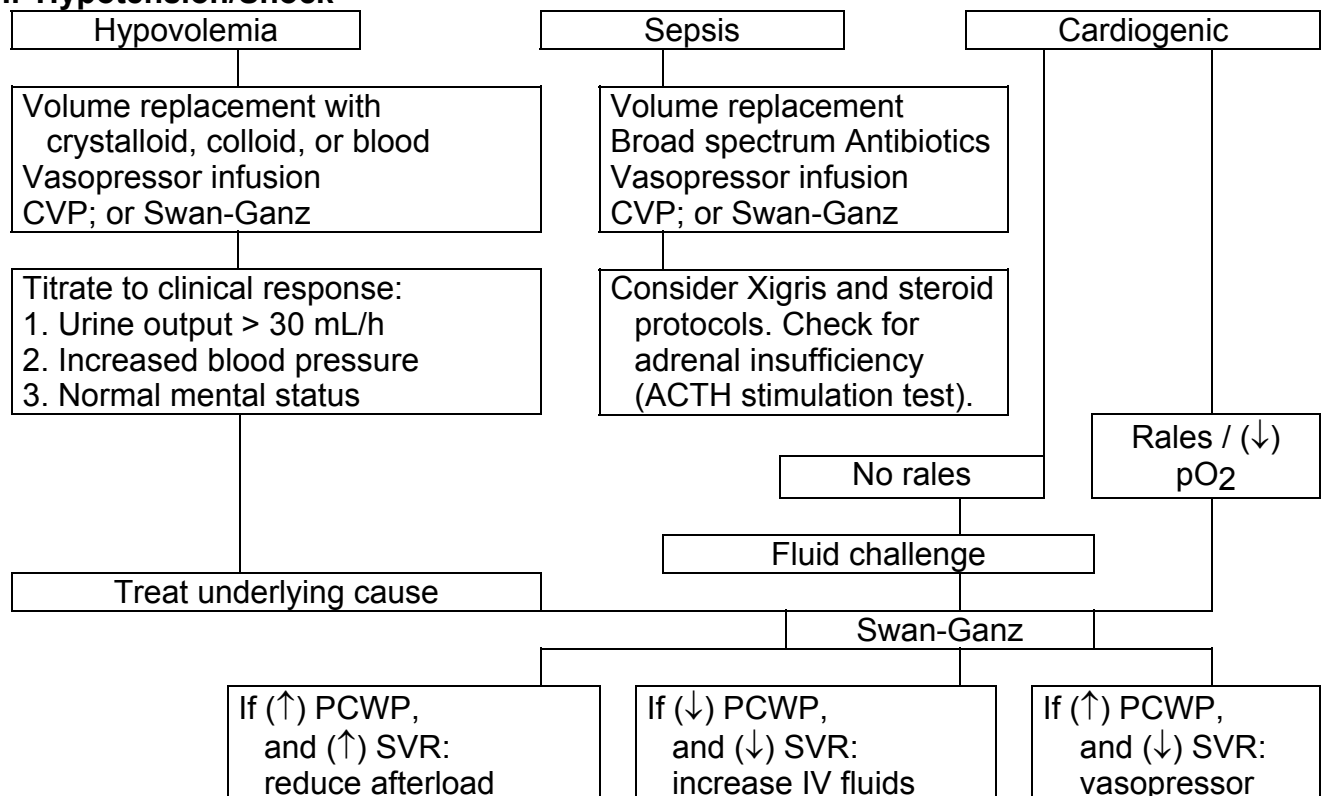
- Angina: if stable, risk low. If unstable, mortality risk 2.4%. Use Swan-Ganz catheter and anti-anginal medications. Consider CABG (cumulative mortality risk 2.3%)
- Recent MI: recurrent MI with / without Swan-Ganz 5.7% / 37% for MI ≤ 3 months old, 2.3% / 16% for 4-6 months old. Delay elective surgery ≥ 6 months post-MI
- Valvular disease
 - AS: fixed output. 13% mortality risk for significant AS. Avoid regional anesthesia and hypovolemia
 - AR: bradycardia and high peripheral resistance increase regurgitation
 - MS: overload causes pulmonary edema, hypovolemia causes severe drop in output. Small shifts in volume cause large changes in cardiac output
 - MR: afterload reduction reduces regurgitation
- CHF: high risk post-op pulmonary edema. Risk 3% for NYHA Class I, 25% for Class IV. Pulmonary edema established in < 1 hour post-op in 70% of affected patients

5. Arrhythmia / Conduction Disturbance: treat according to type. Beware of electrosurgery with pacemaker patients. Swan-Ganz insertion in patients with LBBB may cause complete block
6. HTN: diastolic should be ≤ 110 pre-op. Watch for rebound HTN off medications
- F. Post-op MI risk high if intra-op hypotension occurs (40% drop for ≥ 15 min). Risk peaks 3-5d. Silent MI accounts for 60% of all post-op MI's.

G. Cardiovascular Evaluation/Management Flow Chart

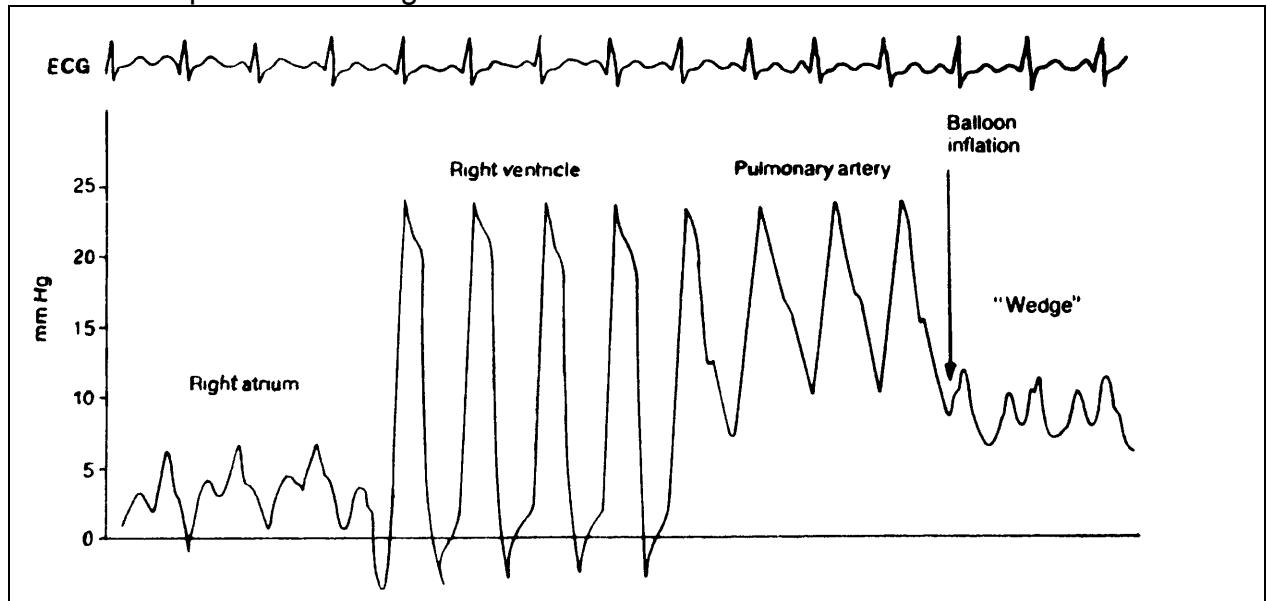


H. Hypotension/Shock



I. Monitoring Values and Equations

1. Systemic Vascular Resistance (SVR) = $[(\text{MAP} - \text{PAWP}) / \text{CO}] \times 80$, where MAP = mean arterial pressure = $1/3(\text{SBP} - \text{DBP}) + \text{DBP}$, CO = cardiac output, PAWP = pulmonary artery wedge pressure. Normal SVR = 1170 dynes / sec / cm^{-5} (range 700-1600).
2. Swan-Ganz Catheter pressures, normal: RA 0-8 mmHg, RV 15-30 / 2-8 mmHg, PA 15-30 / 4-12 mmHg, PAWP 8-12 mmHg (measured at end-expiration)
3. Cardiac Index (CI) = CO / BSA , where CO = cardiac output, BSA = body surface area. Normal CI = 2.5 - 3.5 L/min/ m^2
4. Swan-Ganz pressure tracing



J. Pressors

1. Dopamine. Increases renal, cerebral, and mesenteric flow at low doses (<5 mcg/kg/min). CO increases without changing BP. At doses >10 mcg/kg/min, α receptor stimulation causes vasoconstriction, increased BP and pulmonary edema. Adverse effects: arrhythmia, ischemia, tissue necrosis (antidote: phentolamine 10 mg in 15 mL saline), nausea, MAO inhibitor (vasospasm) and phenytoin (hypotension) interactions. Premix: 400 or 800 mg in 250 mL D5W. Dose: 2-20 mcg/kg/min
2. Dobutamine. Stimulates cardiac α and β -1 receptors and peripheral β -2 receptors, resulting in increased CO and decreased SVR. CO increases and PAWP decreases without changing BP. Adverse effects: arrhythmia, ischemia, nausea. Premix: 1000 mg in 250 mL D5W. Dose: 2.5-20 mcg/kg/min
- * Dopamine and Dobutamine are complementary when used concurrently
3. Norepinephrine. Stimulates cardiac β -1 receptors and peripheral α receptors, resulting in inotropic and vasopressor effects. Adverse effects: arrhythmia, ischemia, tissue necrosis (antidote: phentolamine 10 mg in 15 mL saline). Prepare: 4 mg in 250 mL D5W. Dose: 2-12 $\mu\text{g}/\text{min}$
4. Amrinone. Phosphodiesterase inhibitor that has both positive inotropic and vasodilator actions. Combined effects produce an increase in cardiac stroke output without an increase in cardiac stroke work. Indicated as single agent therapy for low output states caused by systolic heart failure. Initial loading dose 0.75 mg/kg, followed by continuous infusion ranging from 5 to 10 mcg/kg/min.

K. Vasodilators

1. Nitroprusside. Arterial and venous vasodilation. Adverse effects: ischemia, thiocyanate toxicity. Premix: 50 mg in 250 mL D5W with 500 mg sodium thiosulfate. Dose: 0.5-8 $\mu\text{g/kg/min}$
2. Nitroglycerine. Increases venous capacitance and dilates coronary arteries. Adverse effects: headache, hypotension. Premix: 100 mg in 250 mL D5W. Dose: 50-200 $\mu\text{g/min}$. Sublingual dose: 0.3-0.4 mg SL q5 min up to 3 doses

L. Anti hypertensive Medications

1. Esmolol. Ultra-short-acting, cardioselective, β -adrenergic blocking agent. Onset of action within 1 minute, with duration of 10–20 min. Metabolized via rapid hydrolysis of ester linkages by red blood cell esterases independent of renal or hepatic function. Available for IV use both as a bolus and as an infusion. Particularly useful in severe postop hypertension. It is a suitable agent in situations in which the cardiac output, heart rate, and blood pressure are increased. Typically given as a 0.5–1 mg / kg loading dose over 1 min, followed by an infusion starting at 50 mcg/kg-min and increasing up to 300 mcg/kg-min.
2. Fenoldopam. Dopamine DA1 agonist, short acting and has advantage of increasing renal blood flow and sodium excretion. Structure is similar to that of dopamine, but is highly specific for DA1 receptors and is 10 times more potent than dopamine as a renal vasodilator. Rapidly metabolized by conjugation in the liver, without cytochrome P450 enzymes. Onset of action is within 5 min, and maximal achieved by 15 min. Duration of action is 30 - 60 min, with the pressure gradually returning to pretreatment values without rebound once infusion stopped. No adverse effects reported. Starting dose is 0.1 mcg / kg-min. Causes a consistent dose-related decrease in blood pressure in the dose range 0.03–0.3 mcg / kg-min. Improves creatinine clearance, urine flow rates, and sodium excretion in severely hypertensive patients with both normal and impaired renal function. Is drug of choice in severely hypertensive patients with impaired renal function
3. Labetalol. A selective α_1 - and nonselective β -adrenergic receptor blocker with an α / β blocking ratio of 1 / 7. Metabolized by liver to form inactive glucuronide conjugate. Hypotensive effect begins within 2 – 5 min after IV dosing, reaching a peak at 5 – 15 min and lasting for about 2 – 4 hours. Because of β -blocking effects, heart rate is maintained or slightly reduced. Unlike pure β -adrenergic blocking agents that decrease cardiac output, maintains cardiac output. Reduces systemic vascular resistance without reducing total peripheral blood flow. Cerebral, renal, and coronary blood flow is maintained. Used in pregnancy - induced hypertensive crises because little placental transfer occurs, mainly due to the drug's negligible lipid solubility. Labetalol may be given as a loading dose of 20 mg, followed by repeated incremental doses of 20 – 80 mg given at 10 - min intervals until the desired blood pressure is achieved. Alternatively, after the loading dose, an infusion starting at 1–2 mg / min is titrated until the desired effect is achieved. Bolus injections of 1–2 mg/kg produce precipitous fall in blood pressure and should be avoided.
4. Nicardipine. A second generation dihydropyridine derivative calcium channel blocker with high vascular selectivity and strong cerebral and coronary vasodilator. 100 times more water soluble than is nifedipine, and therefore can be administered IV. Onset of action of is 5 - 15 min with duration of 4 – 6 hours. Crosses the blood – brain barrier and reaches CNS, where it binds to L-type calcium channels primarily in the hippocampus. IV nicardipine reduces cardiac and cerebral ischemia.

Appropriate dosage is independent of weight, with an initial infusion rate of 5 mg / hour, increasing by 2.5 mg / hour every 5 min to a maximum of 30 mg / hour.

5. Hydralazine. A direct acting vasodilator. Following IM or IV administration, initial latency period of 5 – 15 min is followed by a progressive and often precipitous fall in blood pressure that can last up to 12 hours. Although circulating half - life is about 3 hours, the half - life of effect on blood pressure is 100 hours. Because of prolonged and unpredictable antihypertensive effects and the inability to titrate the drug's hypotensive effect effectively, hydralazine is best avoided in the management of hypertensive crises.
6. Clonidine. α_2 -adrenergic receptor agonist. Dose: 0.1 mg sublingual for postop HTN.
7. **CAUTION:** Hold ACE inhibitors in the immediate post-op period due to risk of pronounced hypotension that is not correctable with IV fluid bolus.

III. Pulmonary System

- A. Pulmonary disease categories with significance for surgery and anesthesia
 1. Obstructive: asthma, chronic bronchitis, emphysema, COPD
 2. Restrictive
 - a. Musculoskeletal: scoliosis, multiple sclerosis, myasthenia gravis
 - b. Pleural: malignant effusion, mesothelioma
 - c. Interstitial-alveolar: pulmonary edema, interstitial fibrosis, lymphocytic CA
 3. Vascular: pulmonary hypertension, pulmonary embolus
 4. Smoking: increases mucus, carboxy - Hb inhibits myocardial O₂ extraction

B. Pre-operative Assessment

1. Patient-Related Risk-Factors: (Smetana)

Risk Factor	Type of Surgery	Incidence of Pulmonary Complications (percent)		Unadjusted Relative Risk Associated with factor
		Present	Absent	
Smoking	CABG Abdominal	39 15-46	11 6-21	3.4 1.4-3.4
ASA>II	Unselected Thoracic/abdominal	26 26-44	16 13-18	1.7 1.5-3.2
Age>70	Unselected Thoracic/Abdominal	9-17 17-22	4-9 12-21	1.9-2.4 0.9-1.9
Obesity	Unselected Thoracic/abdominal	11 19-36	9 17-27	1.3 0.8-1.7
COPD	Unselected Thoracic/Abdominal	6-26 18	2-8 4	2.7-3.6 4.7

2. Other risk factors: (Smetana)

Risk Factor	Type of Surgery	Incidence of Pulmonary Complications (percent)		Unadjusted Relative Risk Associated with factor
		Present	Absent	
Surgery lasting > 3 hours	Unselected Thoracic/abdominal	10-53 40	3-15 11	1.6-5.2 3.6
General Anesthesia	Unselected Thoracic/abdominal	8-19 28-32	0-17 11-12	1.2-infinity 2.2-3.0
Intra-op pancuronium	Unselected	17	5	3.2

3. Significant postoperative pulmonary complications: Pneumonia, respiratory failure, prolonged need for mechanical ventilation, bronchospasm, atelectasis, exacerbation of COPD or other chronic lung
4. Procedure related risk factors: Upper abdominal and thoracic surgery carry the greatest risk of postoperative pulmonary complications, ranging from 10 to 40 %
5. Preoperative clinical evaluation: Most important part of the pulmonary risk assessment. Clinical findings are generally more predictive of pulmonary complications than spirometry results.
 - a. Elicit history of exercise intolerance, chronic cough, or unexplained dyspnea
 - b. Physical exam:
 - i. Auscultation for wheezes and crackles
 - ii. Observation of I : E ratio. Normal: 1 : 2 - 3. Observation of FVC. Normal < 3 - 4 sec.
 - iii. Percussion of level of diaphragm.

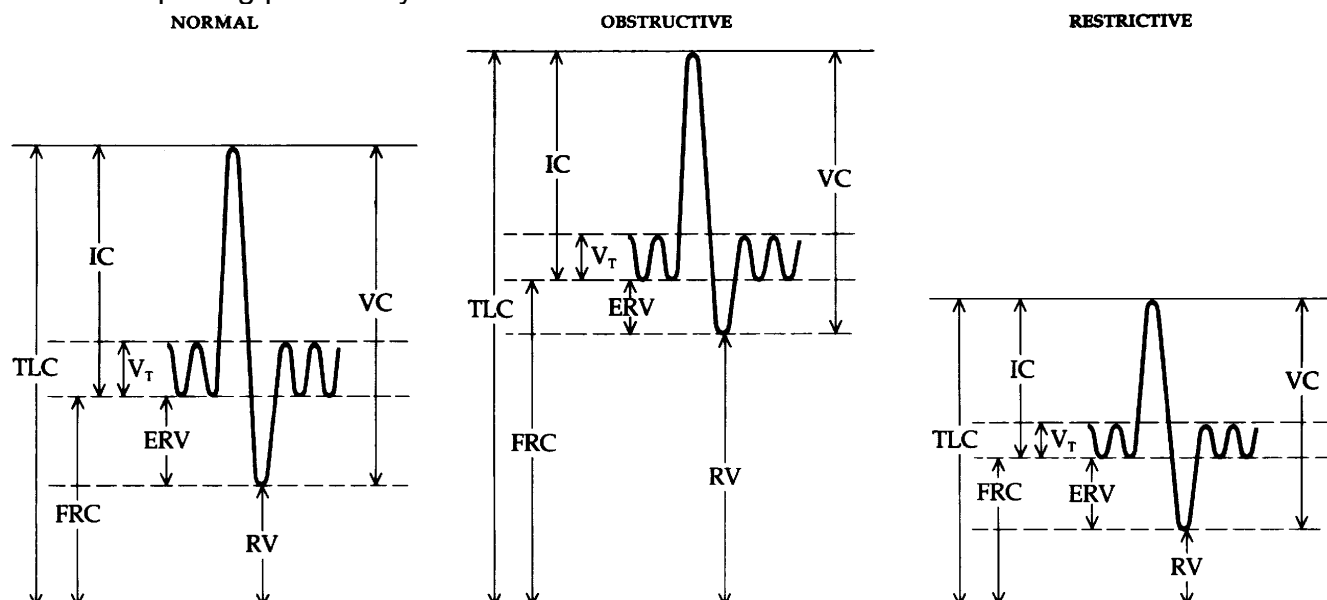
	End Expiration	End Inspiration
Normal	Scapula (S)	S(↓)10-15 cm
Obstructive Disease	Below Scapula	Little Change
Restrictive Disease	Above Scapula	Little Change

- c. Indications for detailed testing: Consider testing for thoracic or upper abdominal surgery patients and for those with symptoms of cough, dyspnea, or exercise intolerance that remain unexplained after careful history and physical. In addition spirometry may be helpful in a patient with COPD or asthma in assessing if the amount of airflow obstruction has been optimally reduced

6. Pulmonary Function Tests
 - a. Spirometry. $FEV_1 < 1L$, $FEV_1/FVC < 75\%$, or $MMV < 50\%$ predicted indicate high risk
 - b. $PaO_2 < 50$, wide A-a gradient, or $PaCO_2 > 45$ may indicate high risk

The results of preoperative pulmonary function testing should not be used to deny surgery to a patient

7. Interpreting pulmonary function tests



8. Pulmonary Complication Risk Reduction Strategies (Smetana and Qaseem)

a. Preoperative

- i. Encourage cessation of smoking for at least 8 weeks
- ii. Treat airflow obstruction in patients with COPD or asthma
- iii. Administer antibiotics and delay surgery if respiratory infection is present
- iv. Begin patient education regarding lung expansion maneuvers

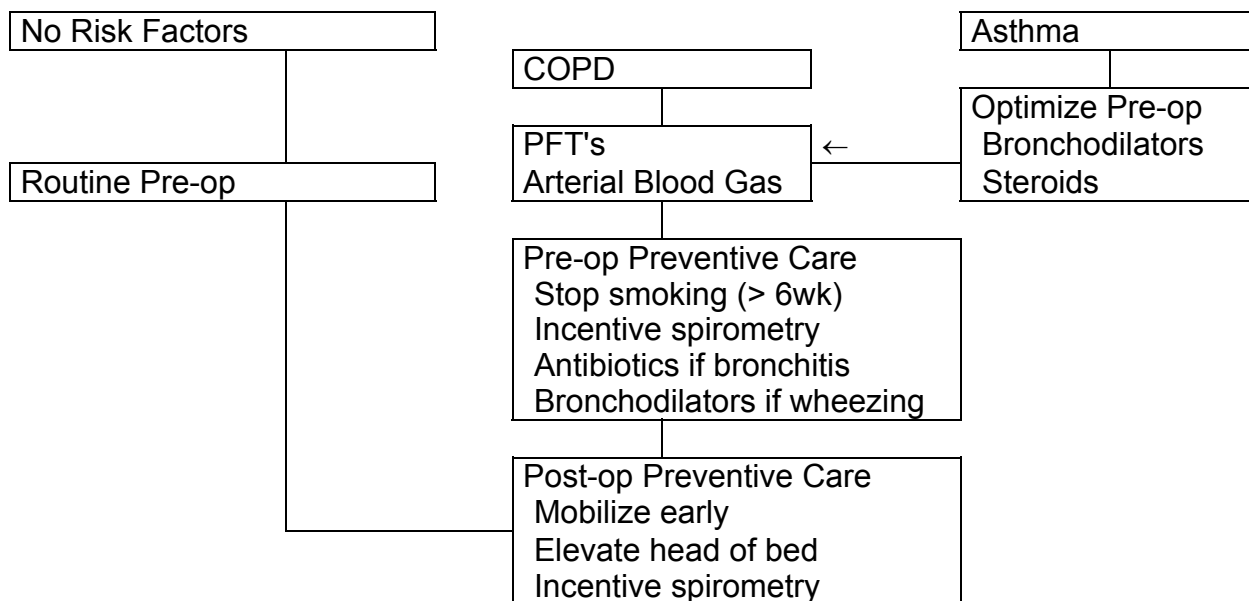
b. Intraoperative

- i. Limit the duration of surgery to < 3 hours
- ii. Use spinal or epidural anesthesia
- iii. Avoid the use of pancuronium
- iv. Use laparoscopic procedures when possible

c. Postoperative

- i. Employ deep breathing exercises or incentive spirometry
- ii. Use continuous positive airway pressure
- iii. Use epidural anesthesia for postoperative pain control
- iv. Consider intercostals nerve blocks

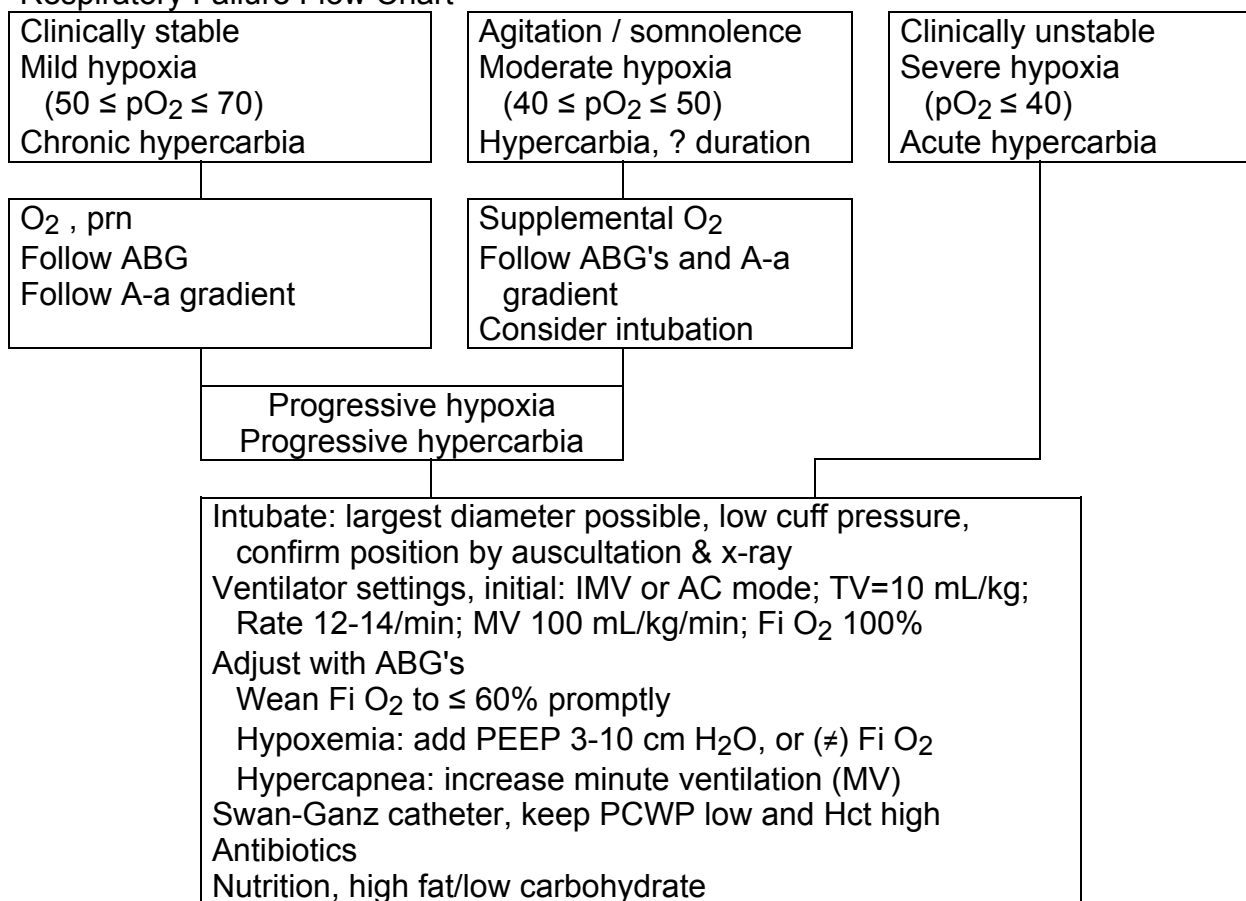
C. Pulmonary Evaluation/Management Flow Chart



D. Post-Operative Morbidity (atelectasis, pneumonia)

1. With normal Pre-op PFT's: 3%; with abnormal PFT's: 70%
2. Vital capacity decreases 45% 1-2 days post-op

E. Respiratory Failure Flow Chart



F. Weaning

1. Wean to IMV ≤ 10 , $\text{FiO}_2 \leq 40\%$.
 - a. Reduce or eliminate sedating medications
 - b. For difficult to wean patient consider pressure support
 - c. For difficult to wean patient on TPN, reduce carbohydrates and increase lipids to reduce CO_2 production
2. Order weaning parameters: TV ≥ 5 mL/kg, VC ≥ 10 mL/kg, NIF ≤ -20 cm H₂O, $\text{FiO}_2 \leq 40\%$, RR < 25 /min, Compliance $[\text{TV} / (\text{PIP} - \text{PEEP})] \geq 40$ mL / cm H₂O
3. Procedure: 20-30 min on T-tube. If RR < 25 / min and P < 120 , then extubate. If borderline, then get ABG. If $\text{PaO}_2 \geq 60$, $\text{PaCO}_2 \leq 40$, then extubate

G. Calculation of A-a gradient

$$\text{P(A - a)O}_2 = [(\text{P}_\text{B} - \text{PH}_2\text{O})\text{FiO}_2 - (\text{PaCO}_2 \times 1.2)] - \text{PaO}_2,$$

where P_B = barometric pressure, and $\text{PH}_2\text{O}=47$ (vapor pressure of water)

Normal ≤ 15 mm Hg on room air. Age adjusted normal = $2.5 \text{ mm Hg} + 0.25(\text{age})$

H. Bronchodilators

1. Metaproteranol (Alupent) inhaler. A β -2 agonist. Dose: 2 puffs q 4-6 hours.
2. Albuterol (Ventolin) inhaler. A β -2 agonist. Dose: 2 puffs q 4-6 hours.

IV. Renal System

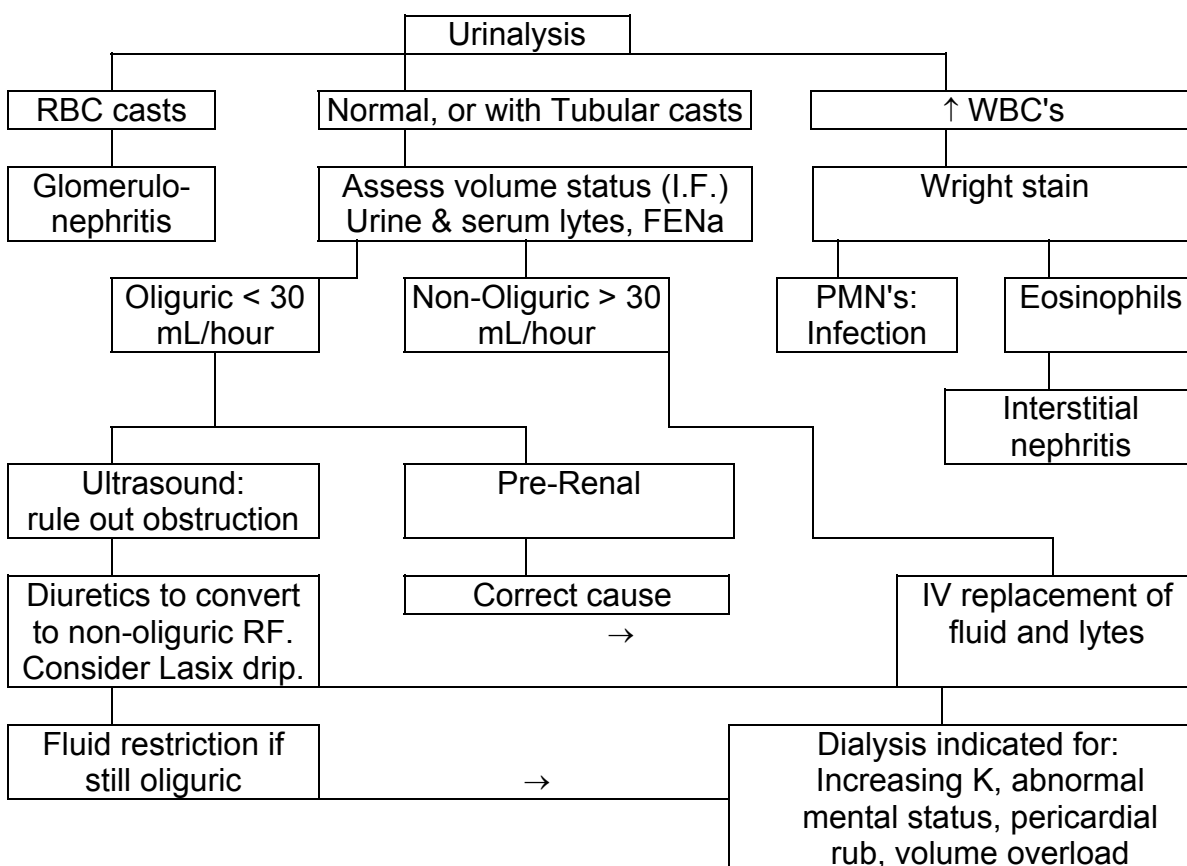
A. Types and Causes of Perioperative Renal Failure

1. Pre-renal
 - a. Etiology: hypovolemia, CHF, sepsis
 - b. Diagnosis: assess volume and cardiac status (see flow chart I.F. above)

2. Renal
 - a. Etiology
 - a. ATN from ischemia, intra-op hypotension, antibiotics, radiocontrast, sepsis
 - b. SIADH (usually transient and not associated with rise in creatinine):
anesthetics, narcotics, chemotherapy drugs, tumors
 - b. Diagnosis: urinalysis, urine and serum electrolytes and osmolality
3. Post-renal: catheter obstruction, urethral or ureteral obstruction, stones
4. Differentiating pre-renal from renal etiology

	Pre-renal	Renal
BUN/Creat ratio	> 20:1	≤ 20:1
Urine osmolality	350 - 500 mOsm/kg	< 350 mOsm/kg
Urine NA ⁺	< 20 mEq/L	> 40 mEq/L
FENa	< 1%	> 1%

B. Flow Chart for Management of Rising Creatinine



C. Calculations

1. **FENa:** $[(U_{Na} \times P_{Cr}) / (P_{Na} \times U_{Cr})] \times 100$. Normal ≤ 1%
2. **Anion Gap (AG)** = $Na^+ - (Cl^- + HCO_3^-)$. Normal 12 ± 4 mEq / L
3. **Osmolality (serum)** = $2 [Na^+ + K^+ \text{ (in mEq/L)}] + \text{urea (mg / dL)} / 2.8 + \text{glucose (mg/dL)} / 18$
4. **Deficit of HCO₃⁻** = $(\text{body weight, kg})(0.4)(\text{desired} - \text{measured HCO}_3^-)$

D. Acid-Base problems

1. Metabolic acidosis
 - a. Increased anion gap: renal failure, lactic acidosis (e.g. shock or sepsis), keto-acidosis, drug intoxication
 - b. Normal anion gap: loss of HCO_3^- and accompanying K^+ from diarrhea, ureteral diversion, renal tubular acidosis; obstructive nephropathy
2. Metabolic alkalosis: emesis, nasogastric suction, diuretic use, Cushing's syndrome
3. Respiratory acidosis: ventilatory failure
4. Respiratory alkalosis: anxiety, sepsis, salicylates, hypoxemia, hyperthyroidism

V. Hematologic System

A. Thromboembolic Complications

1. Virchow's Triad (stasis, intimal injury, hypercoagulability)
2. Risk factors: (Schunenann)

Surgery, previous VTE, myeloproliferative disorder, trauma, pregnancy, obesity, immobility / paresis, exogenous hormones, smoking, malignancy, increasing age, varicose veins, cancer therapy, heart / respiratory failure, central venous catheters, inflammatory bowel disease , nephrotic syndrome, thrombophilias

3. Absolute Risk of DVT in Hospitalized Patients (Schunemann)

Patient Group	DVT Prevalence (%)
Medical patients	10-20
General surgery, gynecologic surgery, urologic surgery, neurosurgery	15-40
Stroke	20-50
Hip or knee arthroplasty	40-60
Major trauma	40-80
Spinal cord trauma	60-80
Critical care patients	10-80

4. Levels of Thromboembolism Risk in Surgical Patients Without Prophylaxis (Geerts)

Level of Risk	DVT	PE	Prevention
Low Risk: Minor surgery in pts < 40 y with no other risk factors	2 % calf 0.4 % proximal	0.2 % clinical <0.01 % fatal	Aggressive mobilization
Moderate Risk: Minor surgery in pts with risk factors, OR Surgery in pts aged 40 - 60 yr with no other risk factors	10 – 20 % calf 2 – 4 % proximal	1 – 2% clinical 0.1 - 0.4% fatal	LDUH (q12h), LMWH, GCS, or IPC
High Risk: Surgery in pts > 60y, or 40-60y with additional risk factors (prior VTE, cancer, hypercoagulability)	20 – 40% calf 4 – 8% proximal	2 – 4% clinical 0.4 - 1.0 fatal	LDUH (q8 hr), LMWH, or IPC
Highest Risk: Surgery in patients with multiple risk factors (age >40y, cancer, prior VTE, hip or knee arthroplasty, major trauma)	40 – 80% calf 10 – 20% prox.	4–10% clinical 0.2 - 5.0% fatal	LMWH, oral VKAs (INR, 2-3), or IPC/GCS+LD UH or LMWH

Prevention Key: LDUH = Low dose unfractionated heparin; LMWH = Low molecular weight heparin; GCS = graduated compression stockings; IPC = intermittent pneumatic compression; VKA = Vitamin K antagonist.

5. Prophylaxis
 - a. Mini-dose heparin: 5000 Units SC bid or tid. Thrombocytopenia rare. May be ineffective for patients with gyn malignancy
 - b. Pneumatic compression stockings
 - c. Low molecular weight heparin
 - i. Enoxaparin (Lovenox): 40 mg SC daily or if weight > 150 kg, then 30 mg SC BID. Reduce dose for renal impairment. Do not administer with ketorolac (Toradol) due to risk of hemorrhage
 - d. Greenfield filter: for patients at high risk who cannot be anticoagulated
6. Summary of Recommendations for gynecologic surgery (Schunemann 2004)
 - a. Patients undergoing brief procedures \leq 30minutes for benign disease require only early, aggressive mobilization
 - b. Patients undergoing laparoscopic gyn procedures, in whom additional VTE risk factors are present should receive thromboprophylaxis with one or more of the following: LDUH, LMWH, IPC, or GCS (See key in section V.A.4 above)
 - c. Thromboprophylaxis should be used in all patients undergoing major gynecologic procedures.
 - i. Major gynecologic surgery for benign disease, without additional risk factors should receive LDUH 5000 U bid. Alternatives include daily LMWH, or IPC started just before surgery and used continuously while the patient is not ambulating
 - ii. Patients undergoing extensive surgery for malignancy, and for patients with additional risk factors for VTE should receive LDUH 5000 U tid, or a higher dose LMWH. Alternative considerations include IPC alone continued until hospital discharge, or a combination of LDUH or LMWH plus mechanical prophylaxis with GCS or IPC
 - iii. For patients undergoing major gynecologic surgery it is suggested that prophylaxis continue until discharge from hospital. **In patients who are at particularly high risk, including those who have undergone cancer surgery and who are > 60 years of age, or have a previous history of VTE, it is suggested that prophylaxis continue for 2 to 4 weeks after hospital discharge.**
7. Pulmonary embolus
 - a. Diagnosis suggested by history, symptoms, and high clinical suspicion
 - b. Spiral CT scan or V / Q scan may be used for diagnosis
 - c. Gold standard is angiography, but morbidity is higher
 - d. Treatment: full therapeutic anticoagulation with LDUH or LMWH
- B. Transfusions: selective use indicated due to risk of infection, and transfusion reactions

VI. Endocrine System

A. Diabetes (Jacobson 1999)

1. Surgical stress and some general anesthetic agents increase counter regulatory hormones (epinephrine, norepinephrine, glucagons, growth hormone, and cortisol) and increase insulin resistance, thereby increasing hepatic glucose production and decreased peripheral insulin utilization. This leads to hyperglycemia and ketogenesis in pts with type 1 diabetes.

2. Operative morbidity and mortality in critically ill patients is decreased with tight glucose control. Post-operative goals and approaches to critically ill patients should target glucose 150 to 200 mg / dL. (Van den Berghe), although morbidity is better if glucose levels are maintained < 150 mg/dL.
3. On morning of surgery, give 1/2 usual dose of antihyperglycemics. Patients taking metformin should discontinue the drug on the day of surgery because complications or alterations in renal function arising intraoperatively may potentiate the risk of developing lactic acidosis. Maintain post-op glucose control with individualized sliding scale regimen using subcutaneous insulin on a sliding scale. In pts who are critically ill or who fail to respond to subcutaneous protocols, change to insulin drip
4. Watch for signs of lactic acidosis (sepsis), ketoacidosis (hyperglycemia), electrolytes disturbances, and end-organ diseases (heart, kidneys, eyes) in diabetics

B. Thyroid Disease

1. Hypothyroidism: Does not appreciably increase operative risk, but initiation of medication should not be delayed. Watch for pericardial effusion; decreased inspiratory reserve volume, stroke volume, EKG voltage and SVR
2. Hyperthyroidism: Thyroid storm occurs in 10% of hyperthyroid patients undergoing surgery. Elective surgery should be delayed 3 months while disease controlled with PTU. For emergency surgery, treatment with β -blocker indicated

C. Steroid Dependence

1. Patients on chronic steroid treatment (≥ 7.5 mg prednisone daily) have suppressed hypothalamic – pituitary - adrenal axis and require steroid pulse perioperatively. HPA axis can remain suppressed for a year after completing steroid therapy
2. Usual steroid pulse: Hydrocortisone, 100 mg IVPB q6 - 8h. Pulse duration and rate of taper customized to fit patient needs
3. Signs of HPA axis insufficiency: malaise, low fever, nausea, arthralgia, electrolyte disturbances
4. Use of steroids in HPA suppressed patients can be of benefit, especially in patients who are critically ill and experiencing evidence of sepsis. (Annane)

VII. Gastrointestinal System

- A. Pre-op bowel prep
Fleets AcuPrep or 4 liters Golytely, or 2 bottles magnesium citrate given about 18 hours preop
- B. Post-op gastric erosions common in critically ill patients. 5% will have hemodynamically significant bleeding (80% mortality)
- C. Gastric Erosion Prophylaxis:
 1. IV H2 blockers (e.g. Zantac 50 mg IVPB q8h)
 2. Nasogastric tube administered antacids, titrate gastric fluid to pH \geq 3.5

VIII. Prophylactic Antibiotics: warranted for all gynecologic oncology surgery. 1-2 doses of cefoxitin (dose: 2 gm prior to incision then Q6 hours x 3 doses) or cefazolin adequate. First dose should be given 1-2 hours before incision.

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12/25/2006 RK Reynolds and William M. Burke, MD

Tools and Equipment for the Art of Surgery

I. Clamps and Forceps

A. Atraumatic tissue clamps

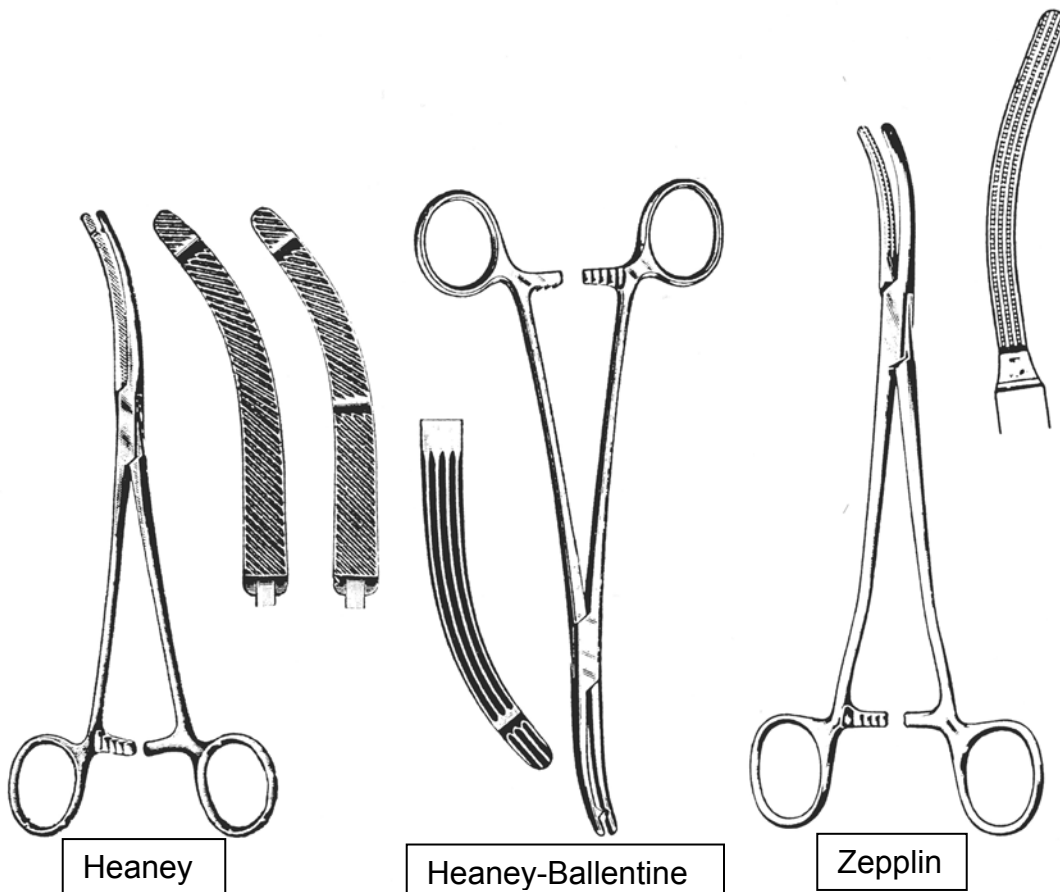
1. Allis. Good for traction on vaginal mucosa or peritoneum.
2. Allis-Adair. Wider jaw than regular Allis.
3. Babcock. Good for grasping bowel, round ligament and IP ligament.
4. Intestinal clamps. Non-crushing clamps to occlude bowel for anastomosis without spill. May be used shod (rubber or foam pad) or unshod.

Allen	Bainbridge
Dennis	Doyen
Glassman	Mayo
Scudder	

B. Crushing (traumatic) Clamps

1. Clark clamp. Long clamp with vascular jaw. For tunneling ureters.
2. Hysterectomy clamps
 - Heaney. Crosshatched jaw. Tissue can slip. Intermediate length.
 - Heaney Ballentine. Longitudinal ridge in jaw causes less slippage.
 - Zeppelin. Longitudinal ridge in jaw. Various lengths and degrees of curvature.

Hysterectomy Clamps



3. Hemostat. Crushing clamps for vascular pedicles.
 - Coller. Delicate tip with long jaws. Good dissector.

Crile / Rochester. Standard hemostat.

Mosquito. Delicate and short.

Pean / Kelly. Heavy duty.

Tonsil. Not for clamping soft tissue such as omentum due to cross hatch jaw pattern at tip only.

4. Kocher. Traumatic but able to hold tension on fascia due to tooth at tip of jaw.

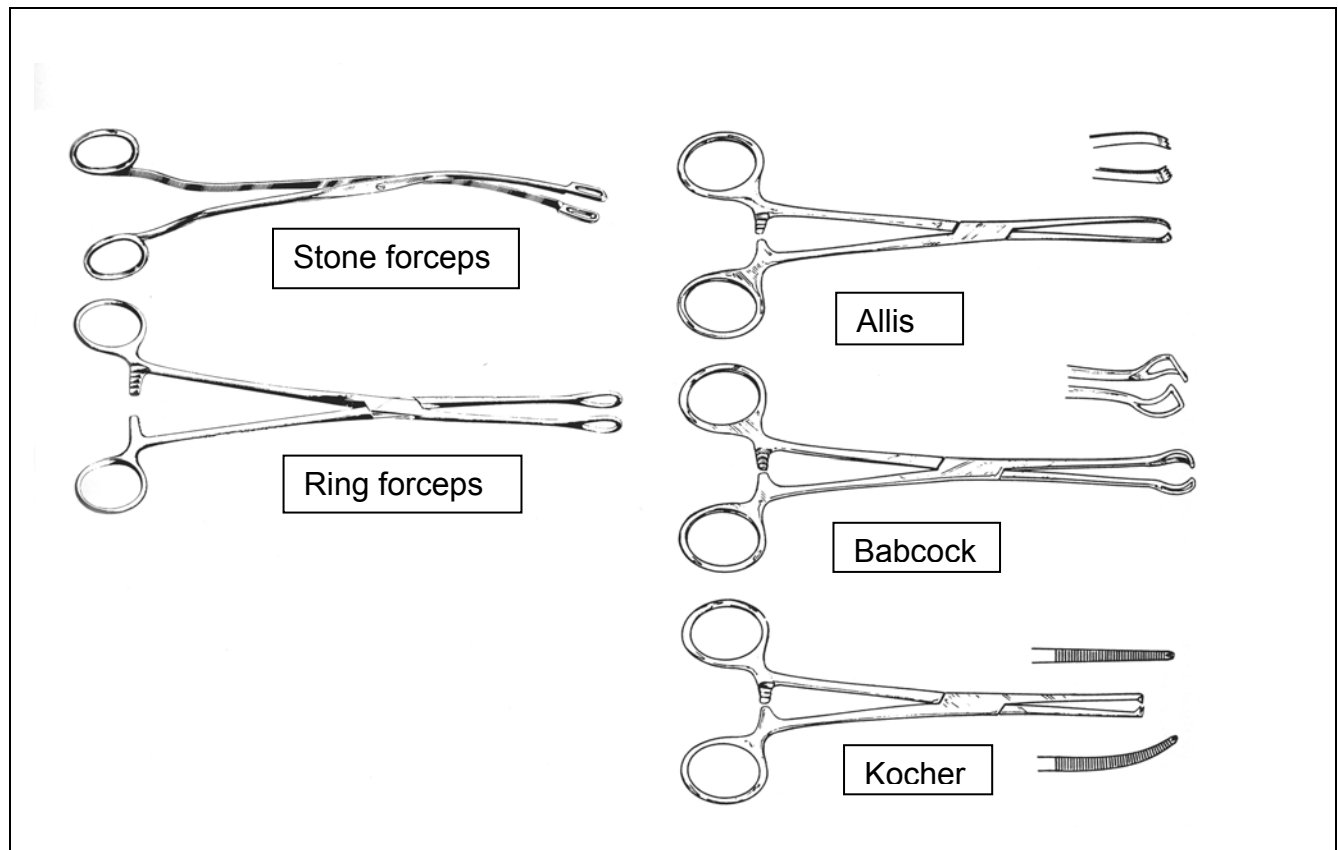
5. Right angle / Mixter. Good for dissecting. May let tissue slip when cut due to jaw design.

6. Tenaculum. Teeth penetrate tissue to apply traction.

Barrett: single tooth

Schroeder vulsellum: double tooth

Leahy vulsellum: triple tooth



C. Forceps. For grasping tissue.

1. Adson. Delicate and short, with or without teeth and needle holding serrations. For skin

2. Bonney. Heavy and has needle holding serrations. For fascia.

3. DeBakey. Atraumatic with longitudinal groove in non-crushing jaw. For vessels

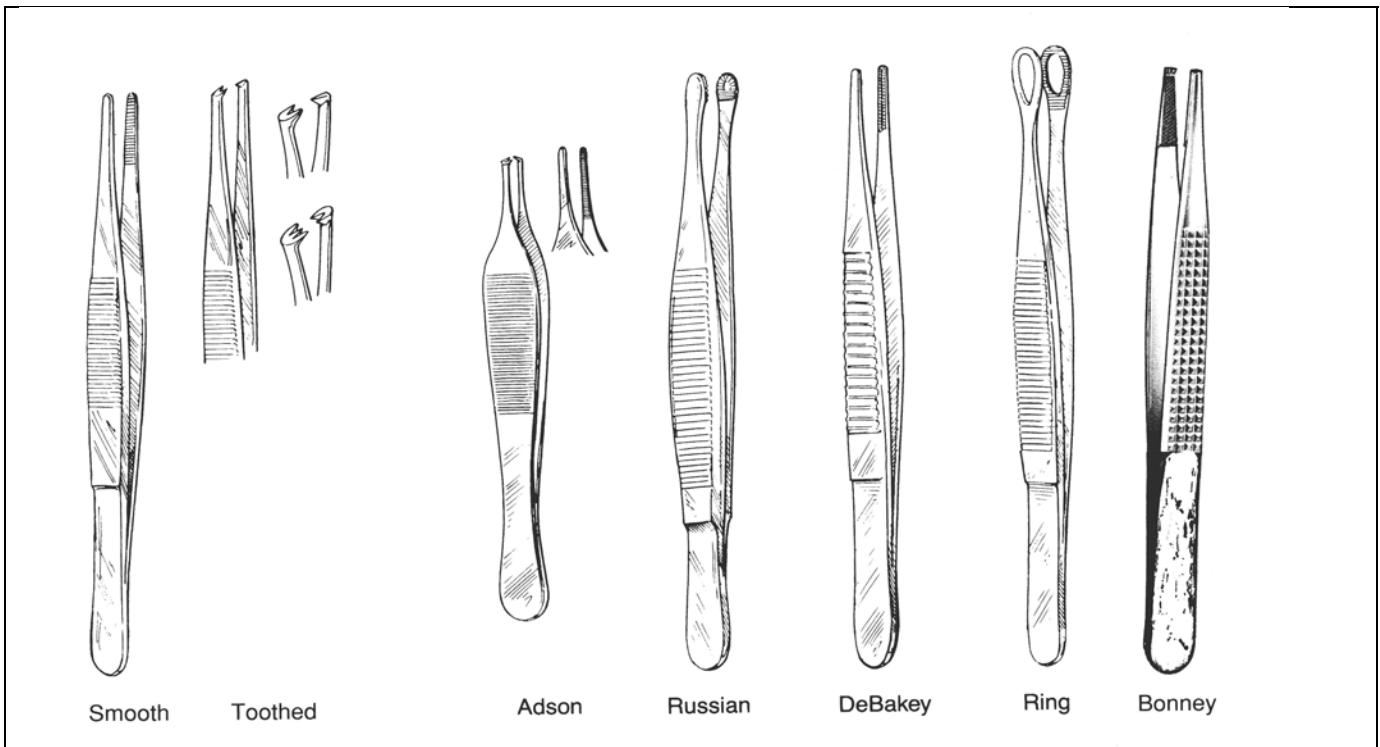
4. Potts. Very fine tip, with or without teeth. For ureters

5. Ring / Sponge

6. Russian. Firm grip on tissue although traumatic as well.

7. Singley. Atraumatic with fenestrated oval tip. For lymphadenectomy.

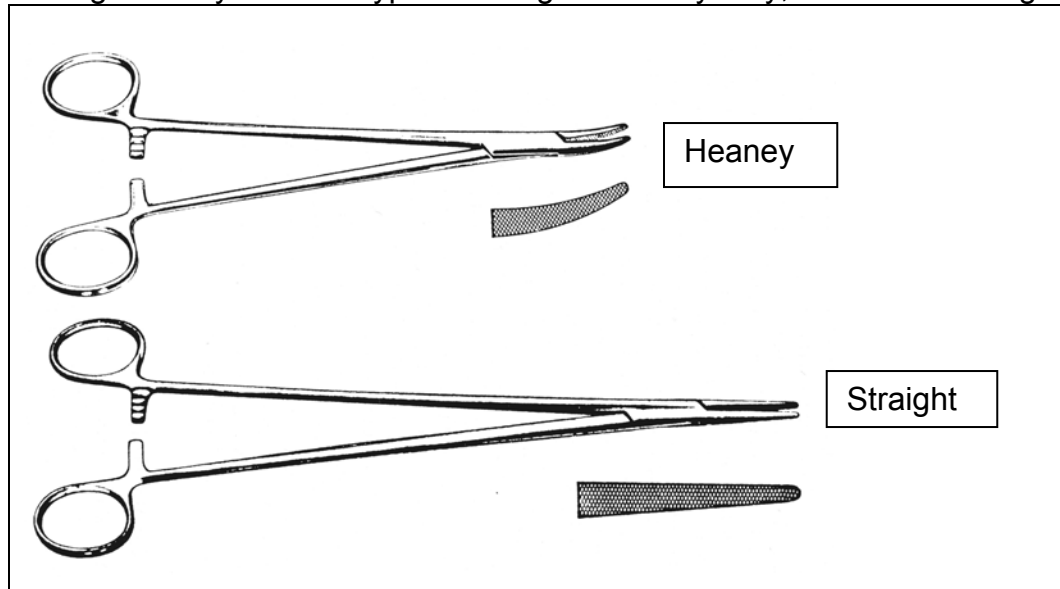
8. Tissue. With or without teeth. For skin or non-delicate tissue



II. Needle Holders

Heaney. Curved jaw. Best for vaginal surgery.

Straight. Many different types from light to heavy duty, and short to long length.



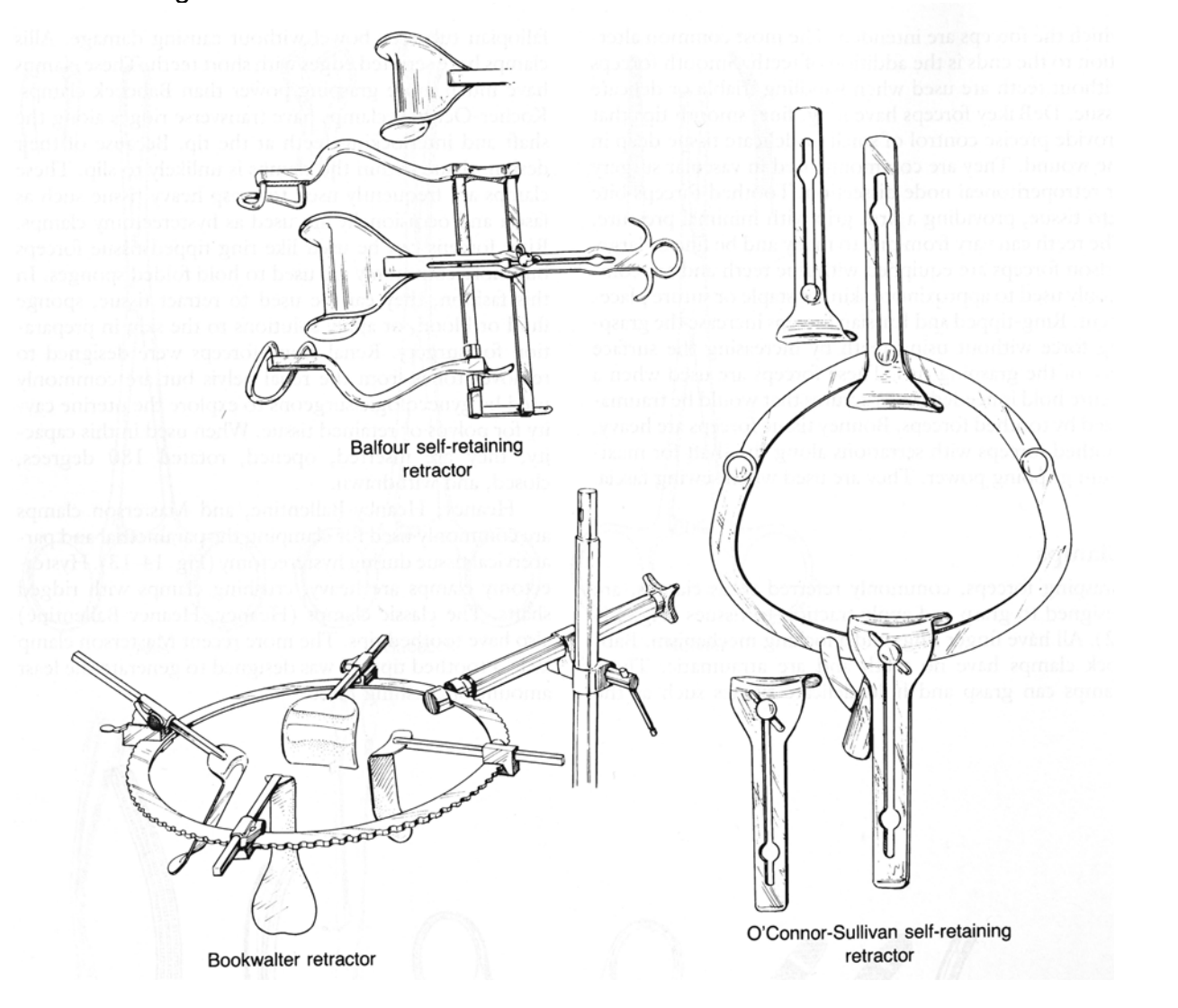
III. Retractors

A. Self retaining

1. Balfour. Self-retaining design with or without c-arm. Does not retract deep structures.
2. Bookwalter. Complex but very flexible self-retaining design. Able to retract deep structures. Post clamps to OR table
3. Denis Browne. Lightweight self-retaining ring for small incisions. Does not retract deep structures.

4. Gelpi. Single tooth with locking handle. Good for perineal exposure.
5. Lone Star. Self-retaining ring for perineal exposure.
6. O'Connor O'Sullivan. Self-retaining design for small incisions. Does not retract deep structures.
7. Weitlaner. For inguinal node dissection. Sharp or blunt tooth designs.

Self-Retaining Retractors



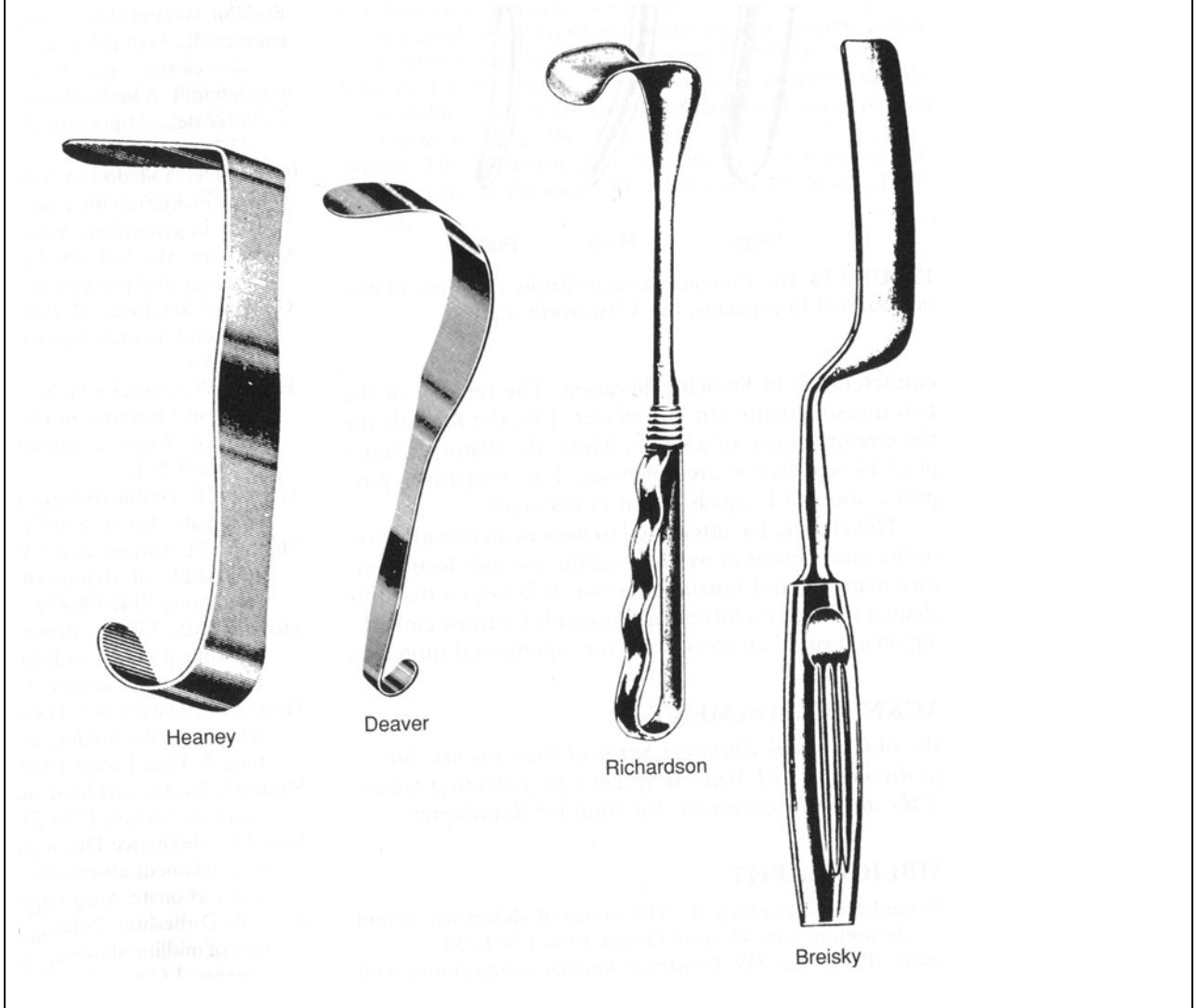
B. Hand held retractors

1. Abdominal

- Army-Navy: Small. For superficial tissues.
- Brewster: Curved, shallow blade, straight handle. For intermediate tissue depth.
- Deaver. Curved, deep blade
- Harrington / Sweetheart. Deep.
- Israel. Rake design good for skin flap elevation.
- Kelly. Larger version of the Richardson.
- Malleable / Ribbon. Can be bent to shape.
- Richardson
- St. Marks. Very deep for the "Midwest" patient
- Vein / Cushing. For retracting vessels

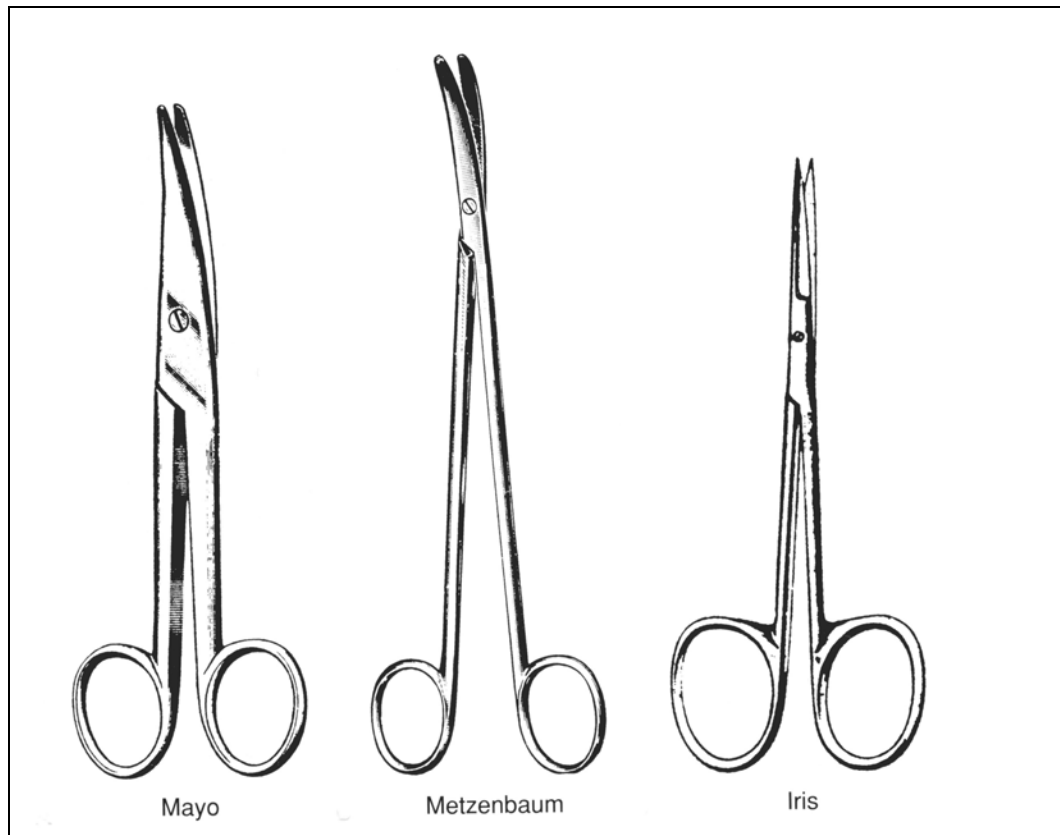
2. Vaginal
Breisky. Long, offset straight design for vaginal surgery.
Heaney
Weighted
Auvard. Long weighted speculum
Sims

Hand Held Retractors



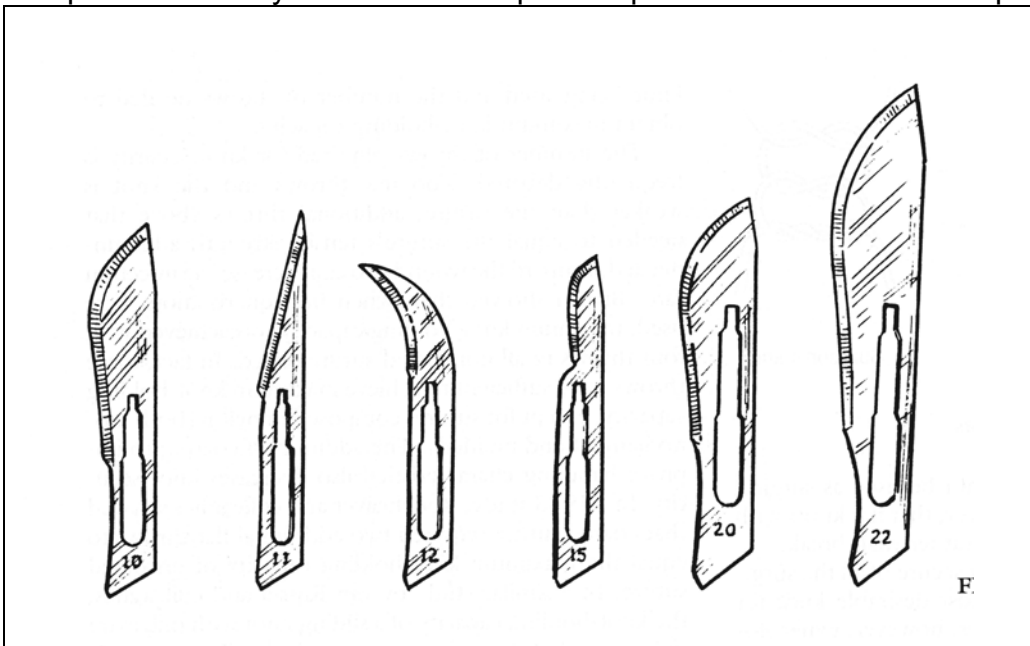
IV. Scissors

- Bandage. For cutting dressings. Not for tissue.
- Iris. Fine scissors with pointed blades.
- Jorgenson. Heavy right angle design for vaginal cuff.
- Mayo. Heavy short scissors. Straight or curved. Straight used for suture cutting, curved for fascia or dense tissue
- Metzenbaum. Delicate, long or short, curved. For dissecting soft tissue.
- Nelson. Long heavy scissors, curved or straight. For firm or rubbery tissues, e.g. uterosacral ligament.
- Potts-Smith. Delicate angled scissors with pointed tips. For urinary conduits or other fine cutting.



V. Scalpels

Blades are numbered. #10 used for most skin incisions. #15 used for small incisions or peritoneal entry. #11 used for laparoscopic incisions and cone biopsies.



VI. Curettes. For scraping tissue. In gyn this is usually for endometrium.

Heaney. Small, serrated tip. Good for polyp removal. Good tactile feedback.

Novak. Hollow with serrated tip for office or OR biopsy. Some tactile feedback.

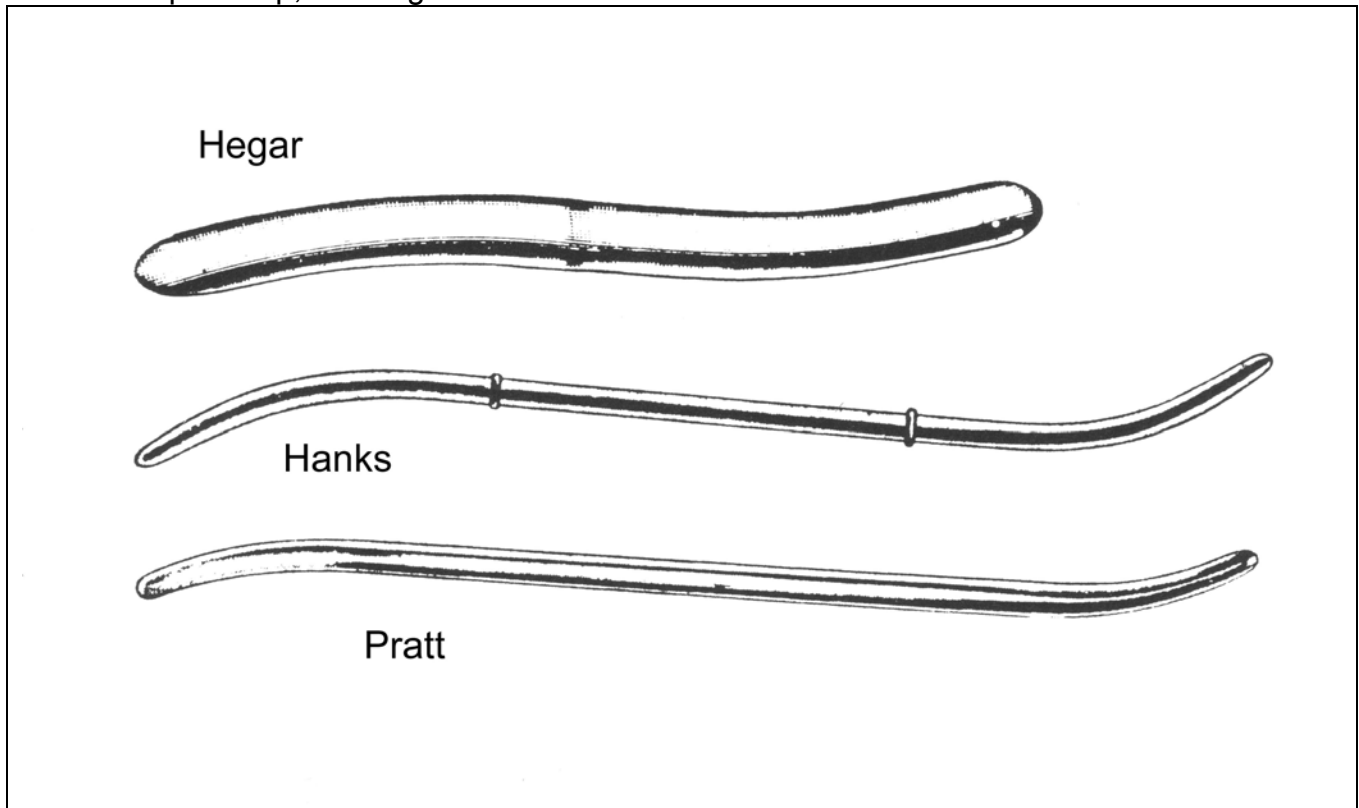
Sharp. Many sizes and lengths.

VII. Dilators. For dilating the endocervix

Hegar. Blunt tip, somewhat traumatic to firm cervix.

Hank. Tapered tip with flange to indicate depth.

Pratt. Tapered tip, no flange.



VIII. Suction Tips

Pool tip. Used to aspirate large volumes of fluid such as ascites.

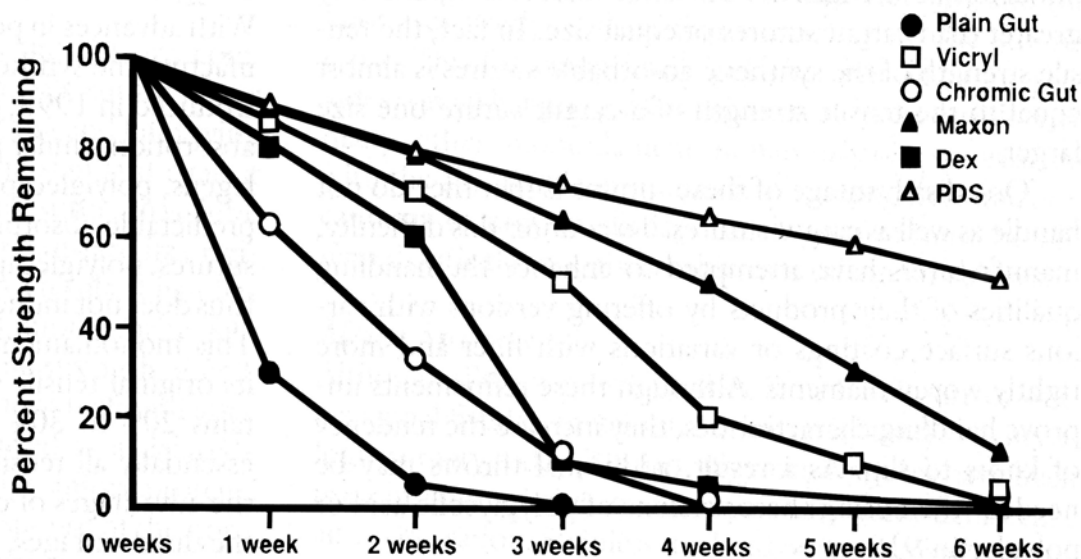
Yankauer

IX. Sutures

Absorbable	Tissue Reaction	Absorption Rate	Strength
Plain Gut	Moderate	7-10 days	1
Chromic Gut	Moderate	21-28 days	2
Monocryl	Slight	Fast	
Vicryl (polyglactin 910)	Mild	40% at 2 weeks	3
Dexon (Polyglycolic acid)	Mild	40% at 2 weeks	3
PDS (Polydioxanone)	Slight	Delayed	4

Permanent	Tissue Reaction	Strength
Silk	Moderate	2
Prolene / Novofil (Polypropylene)	Minimal	4
Ethibond (Braided synthetics)	Minimal	4
Nylon	Low	4

Strength of Suture Over Time



X. Needles

Cutting. For skin only.

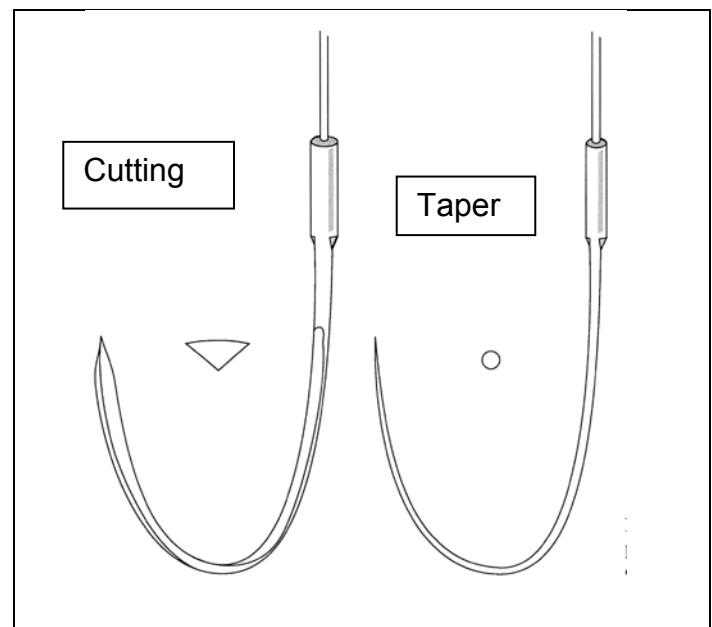
Keith. Straight needle with cutting tip.

Taper. Many sizes and degrees of curvature. RB (very small for delicate tissue), SH (fine needle for soft tissue), CT (general closure), UR (urology needle with more circular arc)

Swaged. Needle must be cut from suture.

Do not try to pull off. Needle can fly.

Controlled Release ("Pop-Off"). Important to pull off at correct angle.



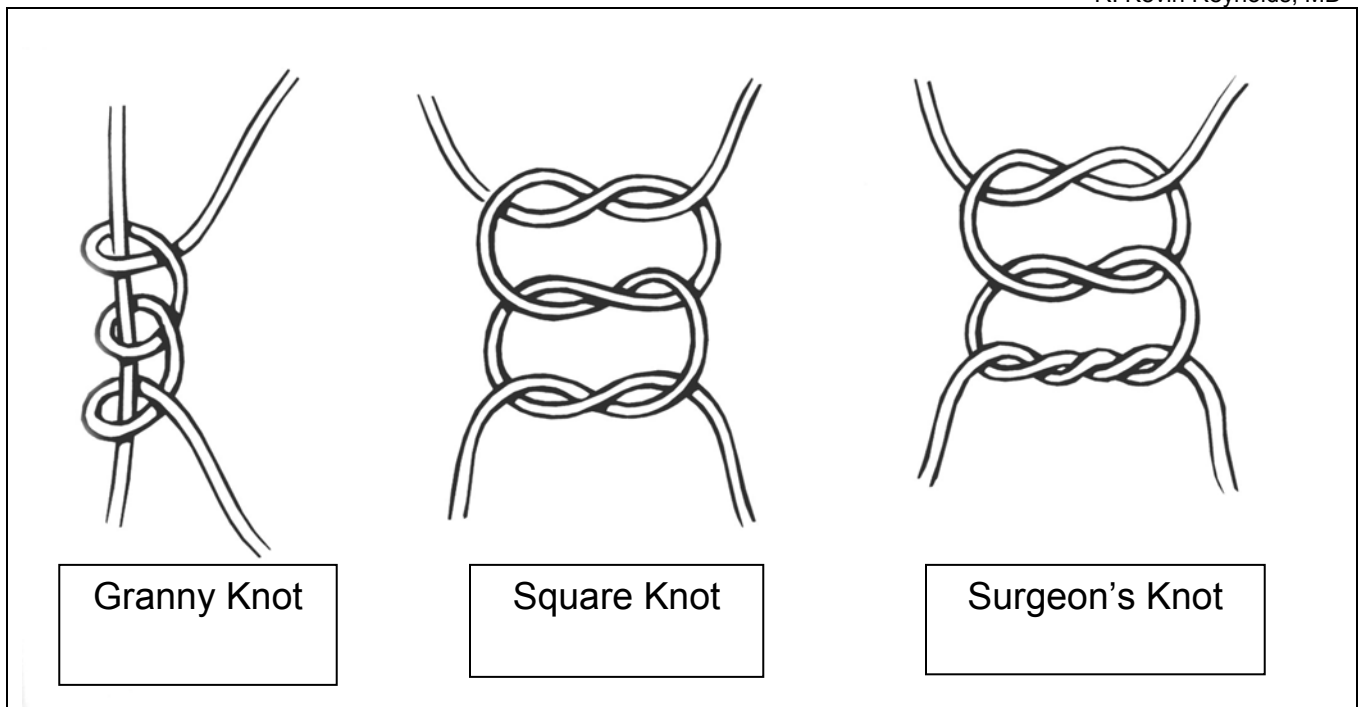
XI. Knots

Granny. Bad because it slips

Square. Good because it does not slip

Surgeons. Good for fascia because first throw holds tight even when tissue on tension but not easily tensioned on vascular pedicles or soft tissue.

Best knot for monofilament mass closure on fascia is surgeons + surgeons + square knot.



XII. Energy Tools

A. Electrosurgery. Use of radiofrequency current to divide or coagulate tissue for hemostasis.

1. Water Tower Analogy

Volts equals water column (pressure)

Current equals volume of water through pipe over time

Resistance equals diameter of pipe

Ohm's Law: $V=IR$

2. Types of electrosurgery in clinical use

Monopolar

Bipolar

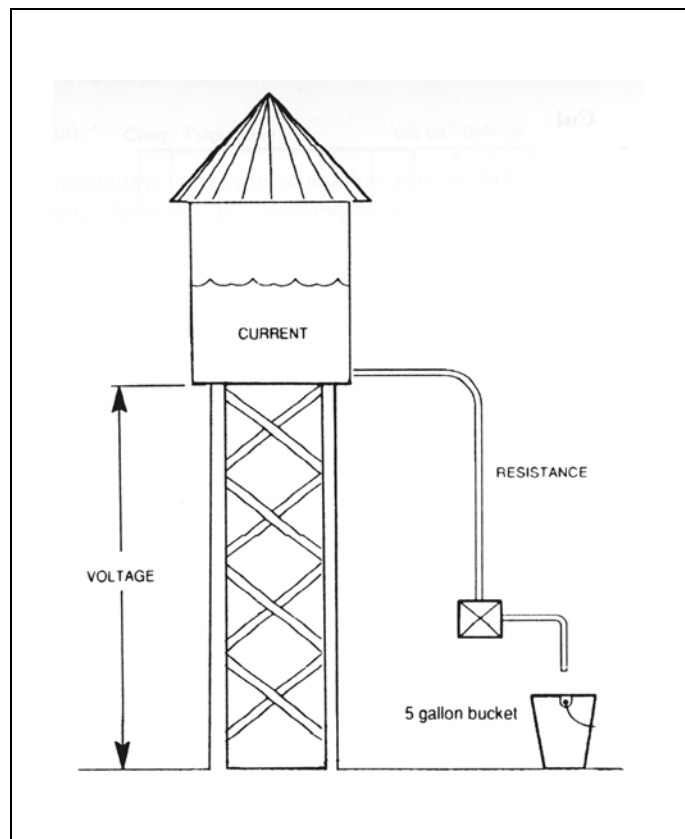
Cutting. High voltage sine wave.

Divides tissue with less thermal damage than coagulation.

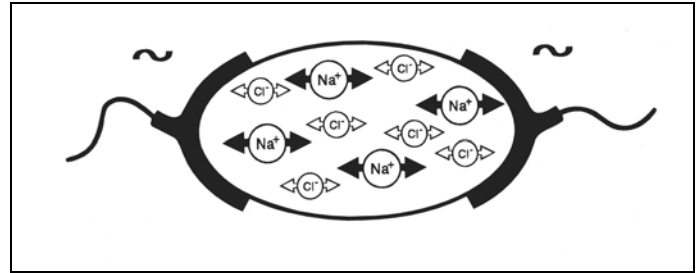
Coagulation. Spark gap current heats tissue to coagulate vessels. Devitalizes tissue.

Blend. Mixture of cutting and coagulation.

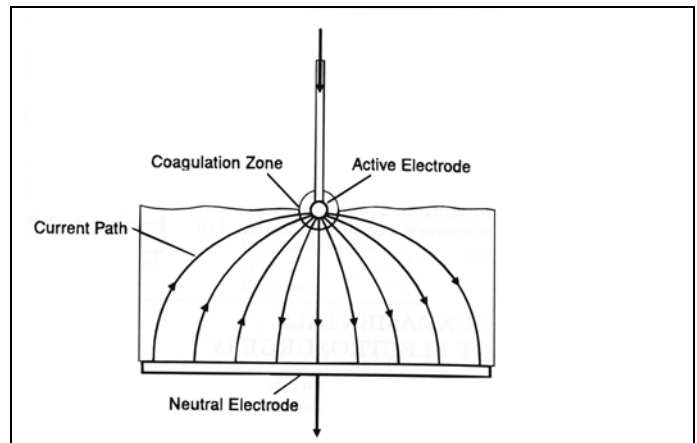
Argon beam



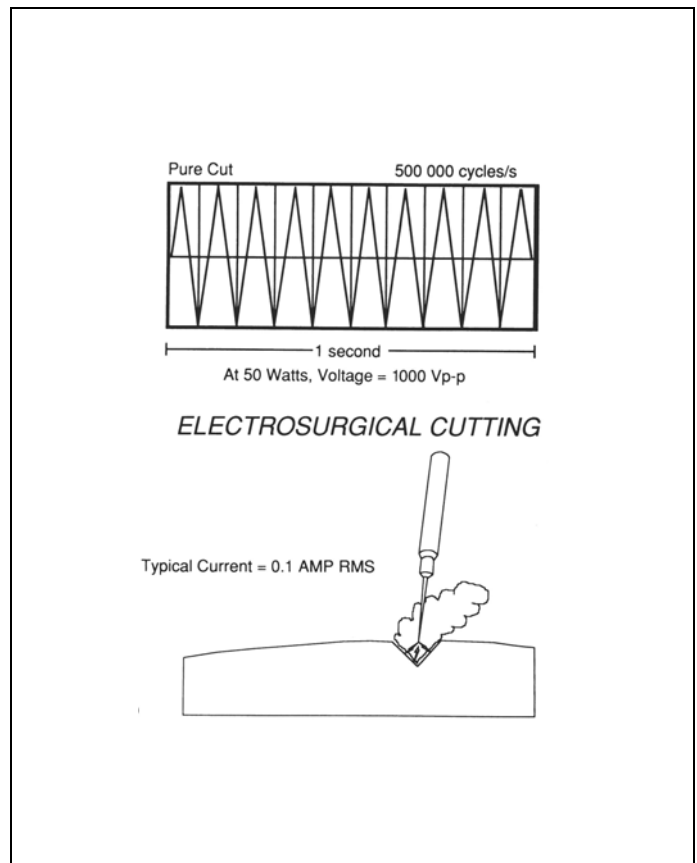
3. **Electrosurgical Effect on Cells**
Radiofrequency current transfers energy to intracellular ions. Sine wave results in oscillation of ions, imparting heat to intracellular water causing cell to burst

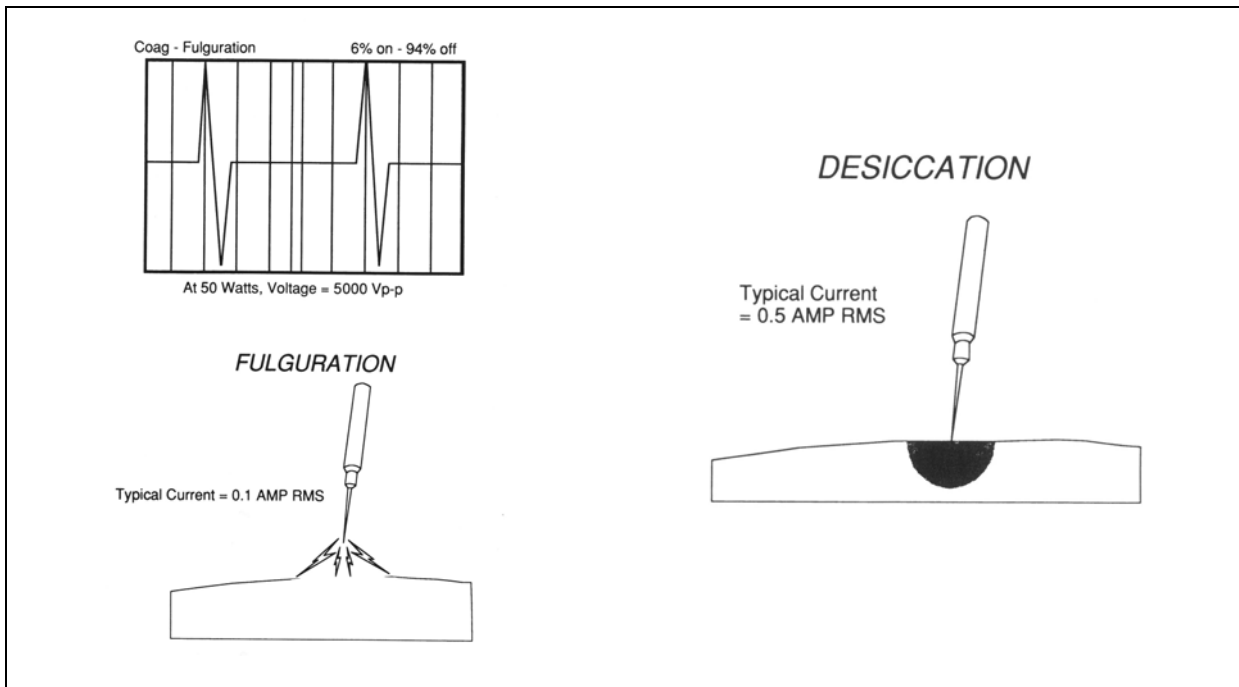


4. **Current Path Through Tissue**
Current passes from the electrode through tissue and returns through the ground electrode



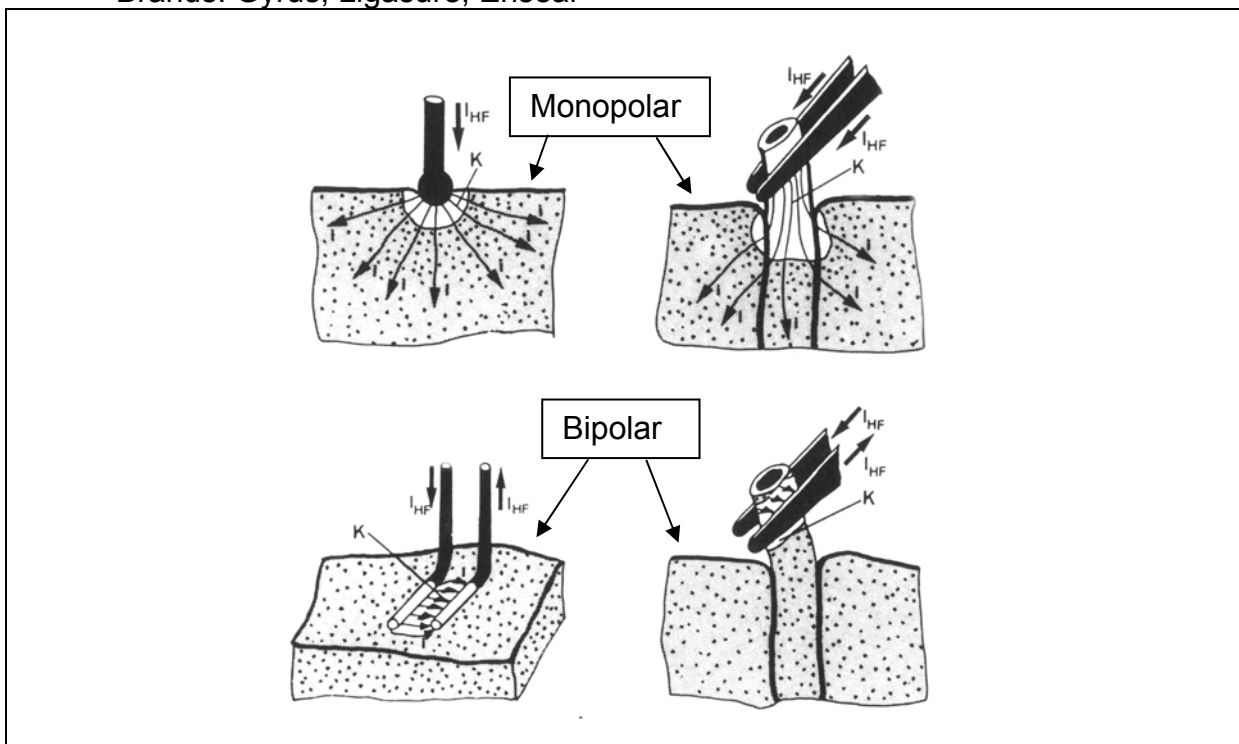
5. **Effect of Waveform on Tissue**
 - a. **Cutting**
Sine wave
Low voltage (1000 volts at 50 Watts power)
Current arcs to tissue across steam envelope
Less heating of tissue than coagulation waveform
 - b. **Coagulation (Fulguration)**
Uses spark gap current
High voltage (5000 volts at 50 watts)
Current arcs to tissue
Causes heating and necrosis of tissue
 - c. **Desiccation**
Uses spark gap current
High voltage (5000 volts at 50 watts)
Direct contact to tissue
Causes heating and necrosis of tissue





6. Monopolar vs. Bipolar

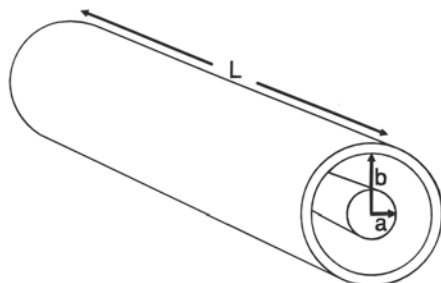
- Monopolar: Current passes from electrode to grounding pad through body of patient. More risk!
- Bipolar: Current passes from active electrode to return electrode only. Less surrounding tissue damaged
- Bipolar Vessel Sealers
 - Microprocessor controls current to tissue to cause controlled tissue melting
 - Capable of sealing vessels up to 7 mm
 - Brands: Gyrus, Ligasure, Enseal



7. Complications of Electrosurgery

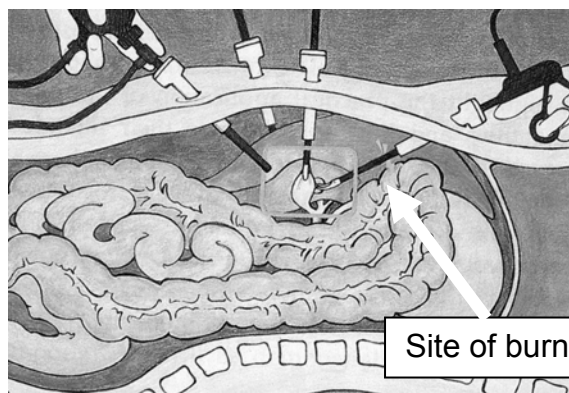
- Injury to adjacent structures by arcing or heating tissue
Poor technique
Instrument failure
- Consequence of injury may be delayed (e.g. bowel perforation or ureteral stricture)
- Capacitance: Occurs when energy is transferred to adjacent metal structure through an insulator. Can cause injury remote from instrument tip

Capacitance is produced by the conductor within the insulated shaft of laparoscopic instruments



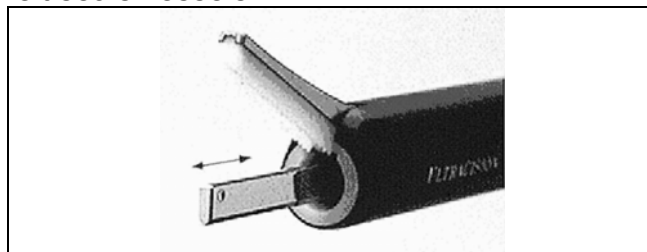
$$\text{Capacitance: } C = \frac{2\pi \epsilon_0 K l}{L_N \left(\frac{b}{a}\right)}$$

Capacitance injury can occur out of the visual field (rectangle) if an organ is near to the instrument shaft

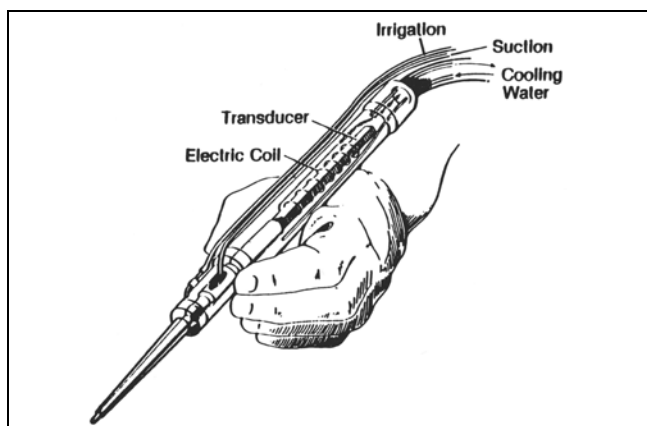


B. Mechanical. Uses ultrasonic energy transmitted to tissue as mechanical vibration to heat tissue. Results in cell lysis. Protein melt seals vessels.

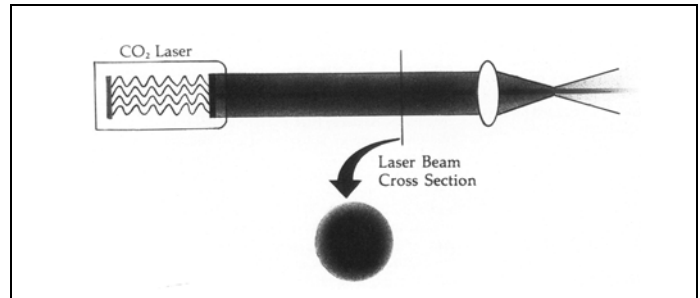
- Shears and scalpels. Instrument shaft oscillates at 25-55 KHz. Used for dividing small vessels, ovarian cystectomy, colpotomy incision. Several brands: Harmonic, Autosonics



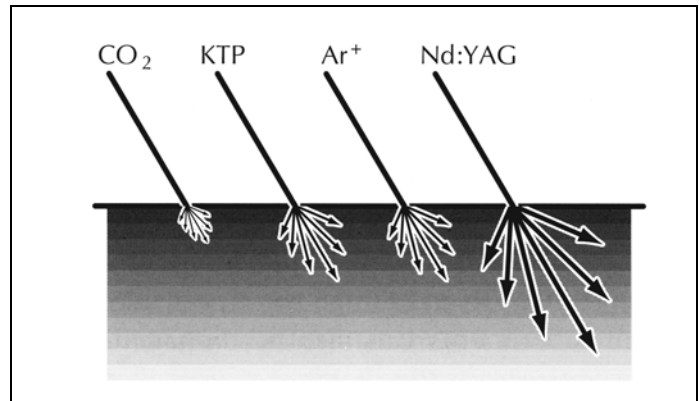
- Cavitron Ultrasonic Surgical Aspirator (CUSA). Oscillates at 55Khz. Used for tumor debulking. Shakes tumor apart



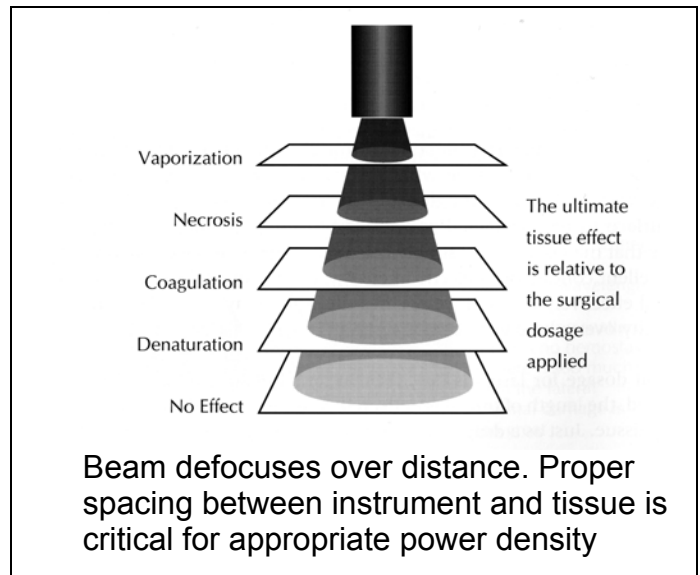
C. Laser. Light Amplification through Stimulated Emission of Radiation. Generates a coherent beam of light: in-phase, single frequency. Wavelength and energy determines interaction with tissue.



1. Wavelength and laser type. The primary laser used for gynecology is the CO2 laser. It is an infrared laser (10,600 nanometer wavelength). Absorption occurs superficially by intracellular water resulting in controlled surface ablation. In contrast, YAG lasers penetrate deeply and coagulate vessels, which is useful for bleeding tumor.



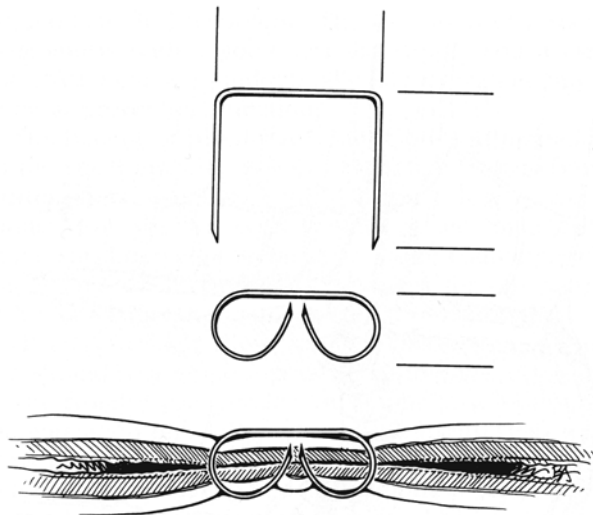
2. Power density determines whether tissue will be coagulated or vaporized. Power Density = power/spot size = watts/ πr^2 . To ablate without char, power density should be 750-1000 watts per cm^2 .
3. Laser modes. Determines energy delivery as a function of time.
Continuous
Intermittent
 Superpulse
 Chopped pulse
 Silk Touch: motorized beam pattern improves cosmetic results
4. Eye protection is required for safety.



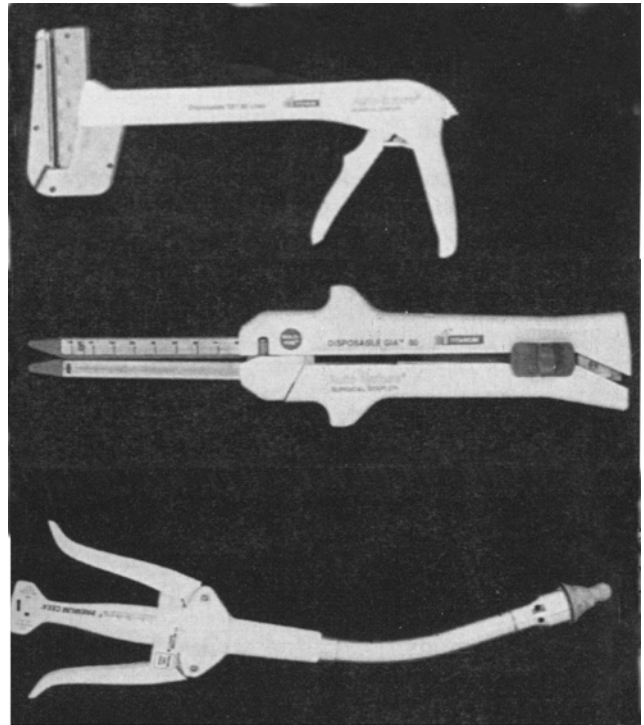
XIII. Staplers

A. Bowel

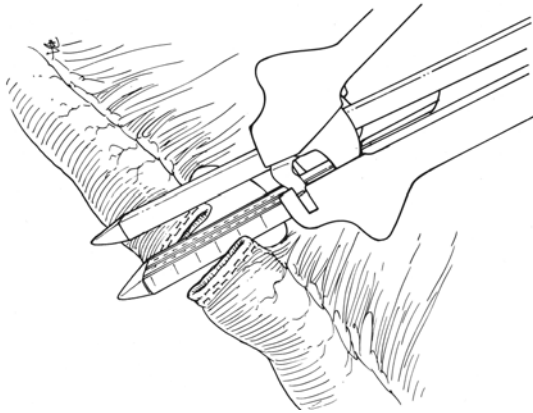
1. Gastrointestinal anastomosis (GIA). Staples and divides. Use 3.8mm staples on small bowel. Use 4.8mm staples on colon or inflamed bowel. Available in different lengths and for both laparotomy and laparoscopy procedures. Used for dividing and anastomosis of bowel. Can be used for broad ligament and IP ligament (expensive)
2. Thoracoabdominal (TA). Staples without dividing. Available in different lengths and with roticulating tip for placement deep in pelvis. Used for bowel division and anastomosis.
3. End-to-end anastomosis (EEA). Staples and divides with concentric ring design. Available in different diameters. Use largest diameter that bowel will accept.



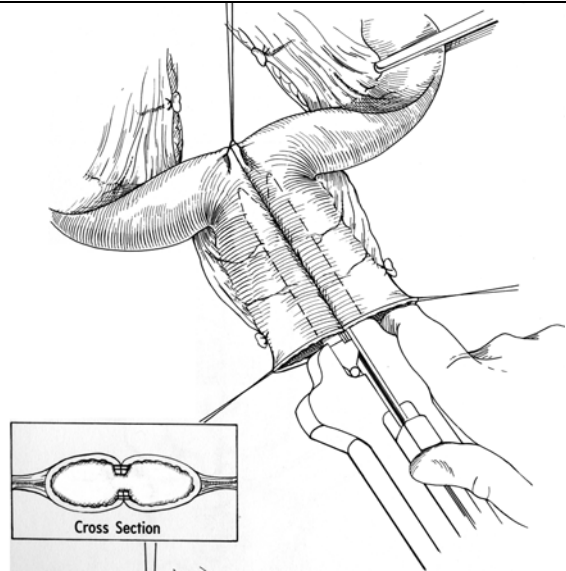
Profile of bowel staples. "B" shape allows approximation without compromise of blood supply.

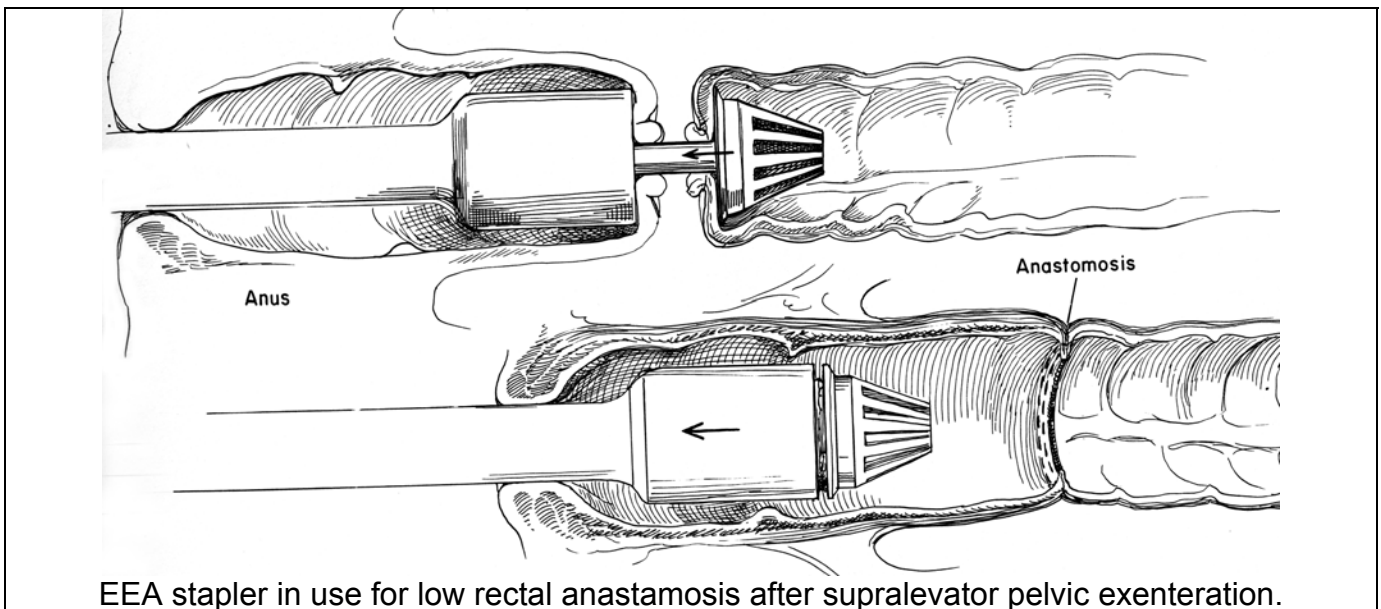
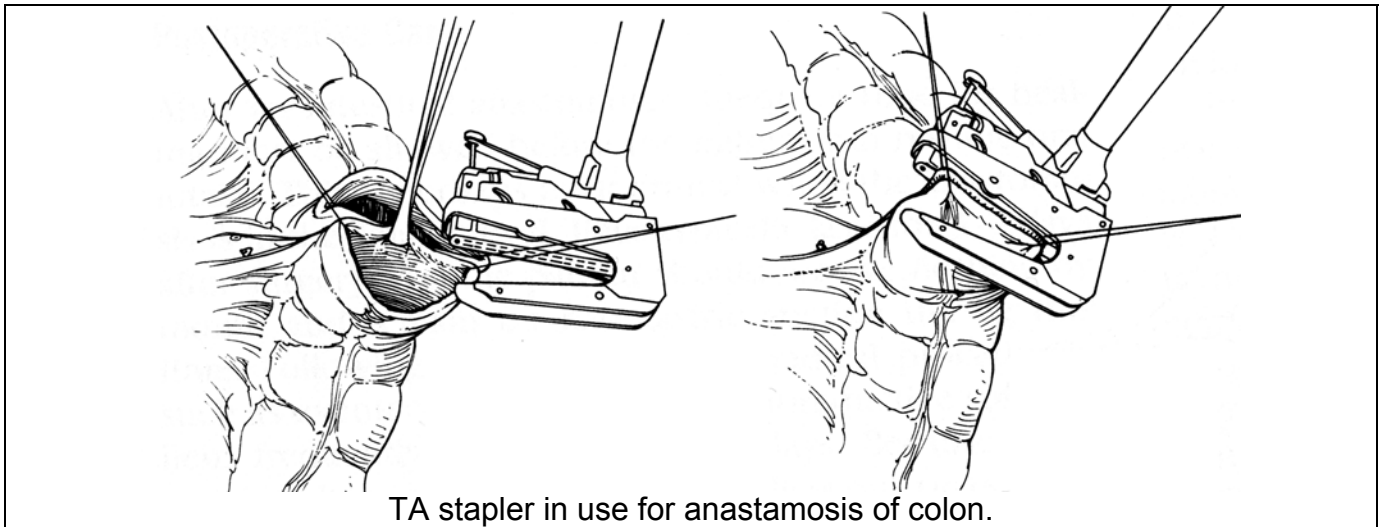


From top to bottom: TA stapler, GIA stapler, and EEA stapler



GIA stapler in use to divide bowel (above) and to anastomose bowel (right).





- B. Skin
- C. Others
 - 1. Ligate-divide-staple (LDS). Gas powered stapler for dividing soft tissues such as omentum.
 - 2. Fascial staples. For hernia repairs.

Appendix: Out-of-Date Staging Rules (for interpretation of literature)

Cervix

FIGO Staging for Cervix, Revised 1995	
0	Carcinoma in situ
I	Carcinoma confined to the cervix (Disregard extension to corpus)
I a 1	Measurable invasion ≤ 3 mm in depth and ≤ 7 mm in diameter
I a 2	Measurable invasion > 3 and ≤ 5 mm in depth and ≤ 7 mm in diameter
I b 1	Lesion of > 5 mm depth and/or > 7 mm diameter, but ≤ 4 cm in diameter
I b 2	Lesion of > 4 cm diameter
II	Tumor extends beyond the cervix but not to the pelvic wall. Tumor may involve vagina, but not the lower 1/3
II a	No parametrial involvement
II b	Parametrial involvement
III	Tumor extends to the pelvic wall, or may involve the lower 1/3 of vagina.
III a	No extension to pelvic wall
III b	Extension to pelvic wall. Includes hydronephrosis or non-functioning kidney
IV	Spread beyond the true pelvis or involvement of bladder or rectal mucosa
IV a	Spread to adjacent organs
IV b	Spread to distant organs

Endometrium

FIGO Staging for Endometrium (Revised 1989)	
I	Tumor confined to uterine corpus
I a	No myometrial invasion
I b	$< 1/2$ myometrial invasion
I c	$> 1/2$ myometrial invasion
II a	Tumor involves endocervical mucosa, no stromal invasion
II b	Endocervical stromal invasion
III a	Invasion involving uterine serosa, adnexae, and/or positive peritoneal cytology
III b	Vaginal metastases
III c	Pelvic/Para-aortic node metastases
IV a	Invasion of bladder or bowel mucosa
IV b	Distant metastases, including inguinal nodes, or intra-abdominal disease
Grade 1	$\leq 5\%$ of non-squamous solid growth pattern
Grade 2	6-50% of non-squamous solid growth pattern
Grade 3	$> 50\%$ of non-squamous solid growth pattern

Sarcoma

FIGO Staging for Uterine Sarcoma, Prior to 2009	
I	Tumor confined to uterine corpus
II	Tumor involves cervix
III	Tumor confined to true pelvis
IV	Distant metastases

Vulva

TNM system (FIGO, Revised 1995)	
T1:	Tumor confined to vulva, ≤ 2 cm in largest diameter.
T1a	Tumor invades ≤ 1 mm
T1b	Tumor invades > 1 mm
T2:	Tumor confined to vulva, > 2 cm in largest diameter.
T3:	Tumor of any size with spread to urethra, vagina, or anus.
T4:	Tumor of any size infiltrating bladder or rectal mucosa, and/or fixed to bone.
N0:	No lymph node metastases.
N1:	Unilateral regional node metastases.
N2:	Bilateral regional node metastases.
M0:	No clinical metastases.
M1:	Spread to pelvic nodes or distant metastases.

Stage Grouping	
Stage I:	T1a-b N0 M0
Stage II:	T2 N0 M0
Stage III:	T3-2-1 N0-1 M0
Stage IVa:	T3-2-1 N2 M0; T4 N(any) M0
Stage IVb:	T(any) N(any) M1

GOG Toxicity Criteria

Grade	1	2	3	4
Blood / Bone Marrow				
WBC / Gran.	3.0 - 3.9 / 1.5 - 1.9	2.0 - 2.9 / 1.0 - 1.4	1.0 - 1.9 / 0.5 - 0.9	< 1 / < 0.5
Platelets	75 - 99.9	50 - 74.9	25 - 49.9	< 25
Hb / Hct	> 10.0g / > 30%	8.0 - 10.0g / 24 - 30%	6.5 - 7.9g / 19.5 - 23.9%	< 6.5g / < 19.5%
Lymphocytes	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
Hemorrhage	Mild, No transfusion	Gross, 1 - 2 units transfused	Gross, 3 - 4 units transfused	Massive, > 4 units transfused
Coagulation				
Fibrinogen	0.75-0.99 x N	0.5-0.74 x N	0.25-0.49 x N	<0.25 x N
PT	1.01-1.25 x N	1.26-1.5 x N	1.51-2 x N	>2 x N
PTT	1.01-1.66 x N	1.67-2.33 x N	2.34-3 x N	>3 x N
Gastrointestinal				
Nausea	Intake reasonable	Intake decreased	No significant intake	-
Emesis	1 per 24 h	2 - 5 per 24 h	6 - 10 per 24 h	> 10 per 24 h, or TPN
Diarrhea	Increase of 2 - 3 per day over normal	Increase of 4 - 6 per day, or moderate cramping	Increase of 7 - 9 per day, or severe cramping	Increase of ≥ 10 per day, or bloody stool, or need for TPN
Constipation	Mild	Moderate	Severe	Ileus > 96 hours
Stomatitis	Painless edema or ulcer, or mild soreness	Painful edema or ulcer, but can eat	Painful edema or ulcer, and can't eat	Requires TPN
Mechanical	< 3 days ileus	Ileus, requires NG; narrow segment on X-ray or edema on proctoscopy	Surgically correctable defect, no stoma	Fistula, perforation, or chronic bleeding requiring diversion
Operative	Repair mucosal defect	Resect enterotomy	Temporary diversion	Permanent diversion
Bilirubin	-	< 1.5 x N	1.6 - 3.0 x N	> 3.0 x N
Transaminase	< 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Alk. Phos.	< 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Liver - Clinical			Pre - coma	Hepatic coma
Urinary Tract				
Creatinine	< 1.5 x N	1.5 - 3.0 x N	3.1 - 6.0 x N	> 6.0 x N
Proteinuria	1+ or < 3 g/L	2 - 3+ or 3 - 10 g/L	4+ or > 10 g/L	Nephrotic syndrome
Hematuria	Microscopic only	Gross, no clots	Gross, with clots	Transfusion required

Bladder / Ureter, Acute	Dysuria, frequency, repair 1° bladder injury	Bacterial UTI; Injury w/ reanastomosis or reimplantation,	Fistula or obstruction w/ 2° repair, loss of 1 kidney	Obstruction of 2 kidneys, V-V fistula w/ diversion
Operative	Bladder atony post-op	Transient atony >6 w	Atony, requiring intermittent self catheterization	-
Bladder, Chronic	Dysuria, frequency; minimal telangiectasia with edema on cystoscopy	Bladder volume <150 mL; moderate telangiectasia or superficial ulceration on cystoscopy. Gross hematuria	Severe pain; deep mucosal ulceration on cystoscopy. Hematuria requiring transfusion. Permanent unilateral loss of kidney	Decreased volume requiring diversion or catheter; fistula; bilateral loss of renal function requiring dialysis

Heart / Blood Pressure

Dysrhythmia	Asymptomatic, transient, no treatment needed	Recurrent or persistent, no treatment needed	Requires treatment	Hypotension, V-tach, V-fib; requires monitor
Cardiac function	Asymptomatic, E.F. ≥80% of baseline	Asymptomatic, E.F. <80% of baseline	Mild C.H.F., responds to treatment	Severe or refractory C.H.F.
Ischemia	Non-specific T-wave flattening	Ischemic ST-T wave change suggesting ischemia; asymptomatic	Angina, no evidence M.I.	Acute M.I.
Pericardium	Asymptomatic effusion, no intervention required	Pericarditis (pain, rub E.C.G. changes)	Symptomatic effusion, requires drainage	Tamponade, drainage urgently required
HTN	Asymptomatic, transient ↑ > 20mmHg or BP >150/100 if previously normal. No treatment required	Recurrent or persistent ↑ >20 mm Hg or BP >150/100, no treatment required	Treatment required	Hypertensive crisis
Hypotension	No treatment required, includes orthostatic hypotension	Requires fluid replacement, no hospitalization	Requires Rx and hospitalization, resolves < 48 h	Requires Rx and hospitalization, resolves > 48 h
Venous problems	Superficial phlebitis, or 1° suture repair of injury with grade 0-1 blood loss	Ischemia not requiring surgery; or 1° suture repair of injury with ≥ Grade 2 hemorrhage	P.E.; or bypass of injured vessel	P.E. requiring embolectomy or caval ligation

Arterial problems	Spasm, or 1° suture repair of injury with grade 0-1 blood loss	Ischemia not requiring surgery; or 1° suture repair of injury with ≥ Grade 2 hemorrhage	Occlusion, thrombosis, or injury requiring bypass or resection	M.I. or resection of limb or organ
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Pulmonary

Pulmonary	Asymptomatic, Abnormal P.F.T	Dyspnea on significant exertion	Dyspnea at normal activity	Dyspnea at rest
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Neurologic

Sensory	Mild paresthesia, loss of D.T.R.	Mild-moderate objective sensory loss, moderate paresthesia	Severe objective sensory loss; paresthesia that interferes with function	-
Motor	Subjective weakness; no objective findings	Mild objective weakness; no significant impairment	Objective weakness, with impairment	Paralysis
Cortical	Mild somnolence or agitation	Moderate somnolence or agitation	Severe somnolence or agitation, confusion, hallucination	Coma, seizure, toxic psychosis
Cerebellar	Slight incoordination, dysdiadokinesis	Intention tremor, dysmetria, nystagmus, slurred speech	Locomotor ataxia	Cerebellar necrosis
Mood	Mild anxiety or depression	Moderate anxiety or depression	Severe anxiety or depression	Suicidal ideation
Headache	Mild	Moderate or severe but transient	Unrelenting and severe	-
Hearing	Asymptomatic loss, noted on audiometry only	Tinnitus	Functional hearing loss, correctable	Deafness, not correctable
Vision	-	-	Symptomatic subtotal loss of vision	Blindness

Skin / Allergy

Skin	Scattered, asymptomatic maculo-papular eruption or erythema	Scattered maculo-papular eruption, with pruritus or other symptoms	General, symptomatic maculo-papular or vesicular eruption	Exfoliative or ulcerative dermatitis
Wound	Cellulitis; incisional separation	Superficial infection; incisional hernia	Abscess; fascial defect without evisceration	Necrotizing fasciitis; fascial defect with evisceration
Local Injury	Pain	Pain, and swelling, with inflammation; or phlebitis	Ulceration	Plastic surgery indicated

Alopecia	Mild hair loss	Pronounced or total hair loss	-	-
Allergy	Transient rash, drug fever <100.4°F	Urticaria, mild bronchospasm, drug fever ≥100.4°F	Serum sickness or bronchospasm requiring treatment	Anaphylaxis
Lymphedema	Mild	Moderate, requiring compression; or lymphocyst	Severe, limiting function; or lymphocyst requiring surgery	Severe, limiting function, with ulceration
Infection				
Infection	Mild	Moderate	Severe	Life threatening
Fever	37.1-38°C 98.7-100.4°F	38.1-40°C 100.5-104°F	>40°C or 104°F for <24 hours	>40°C or 104°F for >24 hours, or hypotension

Metabolic

Weight gain or loss	5 - 9.9%	10 - 19.9%	> 20%	-
Hyperglycemia	116 - 160	161 - 250	251 - 500	> 500, or ketoacidosis
Hypoglycemia	55 - 64	40 - 54	30 - 39	< 30
Amylase	< 1.5 x N	1.5 - 2 x N	2.1 - 5 x N	> 5 x N
Hypercalcemia	10.6 - 11.5	11.6 - 12.5	12.6 - 13.5	> 13.5
Hypocalcemia	7.8 - 8.4	7 - 7.7	6.1 - 6.9	< 6.1
Hypomagnesemia	1.2 - 1.4	0.9 - 1.1	0.6 - 0.8	< 0.6

Coagulation

Fibrinogen	0.75 - 0.99 x N	0.5 - 0.74 x N	0.25 - 0.49 x N	< 0.25 x N
PT	1.01 - 1.25 x N	1.26 - 1.5 x N	1.51 - 2 x N	> 2 x N
PTT	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 x 3 x N	> 3 x N

Performance Status

GOG Score	Karnofsky Score	Activity Level
0	90-100	Fully active, unrestricted activities of daily living
1	70-80	Ambulatory, but restricted in strenuous activity
2	50-60	Ambulatory, and capable of self care. Unable to work. Out of bed for greater than 50% of waking hours
3	30-40	Limited self care, or confined to bed or chair 50% of waking hours. Needs special assistance
4	10-20	Completely disabled, and no self care
5	0	Dead

Important Web Addresses	Address
UM Documentation, Coding, HIPAA Compliance	www.med.umich.edu/i/compliance/
UM Paging and Clinical Resources, including CareWeb if in house	www.med.umich.edu/clinical
CareWeb, from outside of hospital Reference tab: dictation instructions, medical and pharmacy references, literature search, UM policies, clinical calculators	www.med.umich.edu/clinical
UM Gyn Oncology Home Page	www.med.umich.edu/obgyn/
UM GYO Clinical Trials Home Page	www.med.umich.edu/obgyn/gynonc/clinicalresearch.htm
American Cancer Society (ACS)	www.cancer.org
American College of Ob/Gyn (ACOG)	www.acog.org
American College of Surgeons (ACOS)	www.facs.org
American Society for Colposcopy and Cervical Pathology (ASCCP) (guidelines for diagnosis and treatment of dysplasia)	www.asccp.org
National Comprehensive Cancer Network (NCCN) (guidelines for diagnosis and treatment)	www.nccn.org
National Library of Medicine (literature searches)	www.nlm.nih.gov
PDQ (listing of clinical trials)	www.nci.nih.gov
Society of Gynecologic Oncologists (SGO)	www.sgo.org
Women's Cancer Network (WCN) (addresses of gyn oncologists nationwide)	www.wcn.org

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