

Postmenopausal Bleeding

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- Other gynecology
 - cervix or vaginal cancer
 - trauma
 - infectious
- Urologic
 - bladder cancer
 - trauma or infectious
 - post radiation
- G.I.
 - malignancy
 - hemorrhoids
- Metabolic/coag
 - anticoagulation therapy
 - thrombocytopenia

Definition

- Postmenopausal bleeding (PMB) refers to any uterine bleeding in a menopausal woman (other than the expected cyclic bleeding that occurs in women taking sequential postmenopausal hormone therapy).
- 5% of gynecologic office visits
- PMB = Endometrial Cancer until proven otherwise.

History: HPI

When did the bleeding start?

Is the first episode?

How much bleeding?

Are there any additional symptoms?

syncope, pain, cramps

Work-up

Causes of PMB

- Uterine pathology
- Other gynecology
- Urologic
- Gastrointestinal
- Metabolic/coag

Cause of bleeding	%
Endometrial atrophy	60-80
Exogenous estrogens	15-25
Endometrial or cervical polyps	2-12
Endometrial hyperplasia	5-10
Endometrial cancer	10
Miscellaneous (e.g., cervical cancer, uterine sarcoma, trauma)	10

Hsu Int J Geront: 2008

Work-up

- Past Medical History
 - Pregnancies
 - Gynecologic history: menstrual disorders, age at menarche and menopause
 - Ovarian tumors
 - Coagulation disorders
 - Atrial fibrillation
 - Any cancer: breast, colon, leukemia, myeloma
 - Prior therapy: radiation
 - Diabetes

Work-up

- Family history
Colon cancer, breast cancer, uterine cancer
Coagulation disorders
- Medications
Anticoagulents
Hormones
Chemotherapy
Aspirin
Tamoxifen

Incidence: Every Gyn Sees This

- In the United States:
~49,000 new cases this year
8,000 deaths
most common gynecologic malignancy - #4 cancer
- Avg age 58, 2-5% < 40
- 75% are confined to the uterus at time of diagnosis
- Overall survival 75%

ACS 1/13

Work-up

Physical examination

- Visible lesions on vulva, vagina, cervix
- Biopsy if lesion seen, otherwise Pap
- Examine urethra and rectum
- Endometrial biopsy
- Bimanual/rectovaginal to assess size, mobility, masses, tenderness

Endometrial Cancer: 3 Diseases

Type I	Type II	Familial
Low grade	High grade Lynch II	
Less invasion	More invasion	
Arising from AEH	Serous, clear cell	
Perimenopausal	Older	
Estrogen related	Poorer survival	
Obesity		

Sorosky AJOG 2008

Endometrial Thickness

- Meta-analysis from 13 studies: 2896 women; 259 cancers
- Went through the original data sets on each study
- Utilizing the following cut-offs of thickness:

endometrial thickness	sensitivity
5 mm	90%
4 mm	95%
3 mm	98%

- Authors recommend 3 mm cut-off (2 false negatives out of 100)
- ****Beware of Type II cancers****

Timmermans Ob Gyn 2010

Risk Factors

Factor	Relative Risk
• Overweight (lb)	
20-50	3
> 50	9
• Late menopause	1.7-2.4
• Exogenous estrogen use	1.6-12.0
• Diabetes	1.3-2.7
• Hypertension	1.2-2.1
• Parous	0.1-0.9
• Combined OCP's	0.1-1.0

Is Fat the Problem?

- In the menopause, adrenal gland continues to make androstenedione which gets converted by aromatase enzyme in peripheral fat to estrone predominantly. No progesterone to counteract.
- However, in pre-menopausal women often endometrial cancer occurs in concert with the metabolic syndrome
- Does insulin-resistance play a role?

Targeting Endometrial Cancer with Metformin in Obese Patients

- TRI funded study
- Burnett, Simmons PI
- Examine 40 obese women with Grade 1-2 endometrioid adenocarcinoma; randomize to 4 weeks of metformin vs nothing prior to staging
- Outcomes: proliferation markers in the uterus, circulating insulin, adiponectin, lipids
- Positive results suggest future direction as a treatment/preventive strategy

Insulin and Endometrial Cancer

- Women with PCOS have 4-fold increased risk of endometrial cancer; when adjusted for BMI, still had >2-fold increased risk.
- Increased serum insulin levels associated with increased risk of endometrial cancer
- High circulating insulin results in activation of the mTOR pathway that directly stimulates endometrial proliferation

Schmandt AJOG 2011

Signs and Symptoms

- PMB = endometrial cancer until proven otherwise
 - 15% with PMB have endometrial cancer
 - <5% found on asymptomatic Pap smear
- Signs of advanced disease

Metformin and Cancer

- Diabetics on metformin have lower incidence of hepatocellular, pancreas, breast and endometrial cancer
- Patients with the above cancers on metformin have longer survival
- Other oral hypoglycemic agents have no effect on cancer

Work-up

1. Pathology of Endometrium and Endocervix
2. Labs: include CA-125
3. Chest X-ray
4. CT if suspicious for metastatic disease
5. Physical examination (adenopathy, tumor spread, uterine size and mobility)

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Timmermans Ob Gyn 2010

Atypical Hyperplasia GOG Data

- 289 women over 5 years with AEH on biopsy underwent hysterectomy
- 42.6% had Endometrial Cancer in uterus
30.9% had myoinvasion
10.6% had invasion > 50%

Who should manage these women?

Trimble Cancer 106, 2006

Atypical Hyperplasia

- Pre-cancerous lesion
- Identical risk factors
- Difficult to differentiate from invasive cancer

Treatment surgical or medical

Medical therapy can be difficult

FIGO Surgical Staging (2009)

Stage I	Confined to the uterus
Ia	Less than ½ invasion
Ib	Greater than ½ invasion
Stage II	Involves the cervix but not beyond uterus
Stage III	Pelvis and nodes
IIIa	Serosa or adnexa
IIIb	Vagina and/or parametrium
IIIc1	Pelvic nodes
IIIc2	Para-aortic nodes
Stage IV	Outside the pelvis
IVa	bladder or rectal mucosa
IVb	distant mets, inguinal nodes

Atypical Hyperplasia Community Study

486 women identified in community with AEH 218 underwent hysterectomy

48% had Endometrial Cancer in final specimen

46% had >50% invasion and Grade 2

6% had Stage III or IV disease

Huh SGO 2009

Incidence of pelvic and para-aortic lymph node metastases in clinical stage I endometrial carcinoma

Histologic grade	n	Depth of myometrial invasion			
		None	Inner third	Middle third	Outer third
Percent pelvic lymph nodes involved					
1	180	0	3	0	11
2	288	3	5	9	19
3	153	0	9	4	34
Percent para-aortic lymph nodes involved					
1	180	0	1	5	6
2	288	3	4	0	14
3	153	0	4	0	24

Adapted from Creasman WT, Morrow CP, Bundy BN, et al, Cancer 1987; 60(8 Suppl):2035.

UpToDate

Recurrence Risk at 5 Years

Risk Factor	Recurrence Rate
Para-aortic nodes (+)	60%
LVSI	35%
Pelvic nodes (+)	25%
Adnexae (+)	25%
Washings (+)	22%
2 or more extrauterine sites	45%

Morrow Gyn Onc 1991

Robotic staging

- Single institution retrospective review:

	Open	Scope	Robot
	n=138	n=81	n=103
Pelvic nodes	11.5	17.4	20.5
PA nodes	3.0	6.3	12.0
Operative time(min)	146	213	191
EBL(cc)	266	146	75
Hospital stay(days)	4.4	1.2	1.0
Complications(%)	30.4	18.5	6.8

Bogges AJOG 2008

Risks of Advanced Surgical Stage Disease in Patients with Clinical Stage I Uterine Cancer

Author	Surgical stage			
	I	Ia	Ib	Ic
Creasman <i>et al.</i> [3]	477 (21 (76.8%))			
Orr [43]	121 (68 (72.0%))			
Wollson <i>et al.</i> [37]	106 (122 (86.8%))	32 (122 (26.2%))	65 (122 (63.5%))	25 (122 (26.5%))
Kadar [44]	287 (345 (81.8%))			
Faught <i>et al.</i> [10]	110 (269 (81.8%))	35 (220 (13.0%))	114 (220 (42.4%))	69 (220 (26.7%))
Chung <i>et al.</i> [14]	112 (185 (60.5%))	12 (112 (11.9%))	77 (112 (68.6%))	20 (112 (17.6%))
Totals	1339 (1744 (76.8%))	82 (454 (18.1%))	256 (454 (56.4%))	114 (454 (25.1%))

23 % Clinical Stage I had Advanced Disease
Clinical Impression Correlates Poorly With Disease Status

Orr Gyn Onc 1998

Benefit of Lymphadenectomy

- 12,333 women over 13 years SEER data
- No benefit seen in lymphadenectomy in low risk patients:
 Stage IA; Stage IB G1/2
- Benefit seen in intermediate/high risk and those with nodal metastases

Chan Cancer 2006

Method of Staging

- Meta-analysis of four randomized trials: Scope vs Open staging:

Survival

Overall and Disease-specific No Difference

Operative factors

Time Longer scope

EBL Less scope

Intra-operative complications No Difference

Lymph node yield

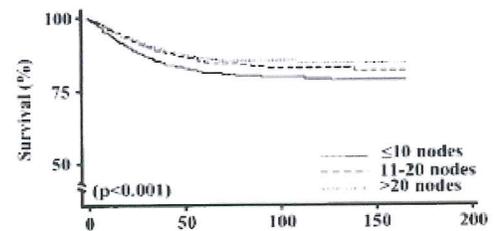
No Difference

Post-operative complications

Less scope

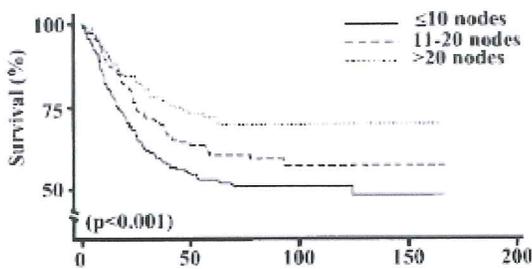
Palomba Gyn Onc 2009

Survival in Intermediate/High Risk



Chan Cancer 2006

Survival in IIIC-IV (nodal mets)



Chan Cancer 2006

The Mayo Criteria

- Removal of uterus with intraoperative pathologic assessment + BSO and cytology
- Omit lymphadenectomy if:
 - 1) No disease beyond corpus
 - 2) Endometrioid Grade 1 or 2, MI ≤ 50%, and tumor diameter ≤ 2 cm; or
 - 3) Endometrioid with no MI

? No Benefit to Lymphadenectomy

- Randomized trial 1408 women clinically low stage: ½ had TAH, BSO, wash, palpate nodes ½ had above plus lymphadenectomy of pelvic nodes
- No difference in overall or recurrence free survival
- No difference in use of post-operative radiation

ASTEC Lancet 2009

Prospective Trial at Mayo

- 422 women over 3 years
- 112 met criteria for no lymphadenectomy
20% had nodes removed: all negative
- 310 met criteria for lymphadenectomy
91% had nodes removed:
22% had positive nodes
16% of endometrioid
40% of nonendometrioid

Mariani Gyn Onc 2008

What is The Answer?

- Knowledge is good
- Knowledge is more expensive: cost of surgery, cost of pathology, increased patient risk
- Knowledge does not always make a difference
- One solution: target lymphadenectomy for those most at risk

Safety of Mayo Approach

- 1393 endometrial cancers (1999-2009)
- 385 met the low risk criteria
- 80 had lymphadenectomy (1 node positive)

	LND	non-LND	p
Post-op comps	37%	19%	<0.001
Cost (\$)	15,678	11,028	<0.001
CSS	97%	99%	0.32

11 patients recurred: 6 vaginal, none in pelvic or aortic node areas
Pts 6x more likely to die from other causes

Dowdy ASCO 5004 JCO 2012

Radiation Therapy in Stage I Disease

- PORTEC 1: Europe 1990-1997
- Deep invasion (G1, G2) or middle 1/3 (G2, G3)
- Randomized to Pelvic RT vs NFT

	Pelvic RT	NFT	p
Local recurrence	5.8%	15.5%	<.001
15 yr survival	52%	60%	.14
Chronic symptoms	43%	15%	<.001

Recommend no Pelvic RT in low- and intermediate-risk patients

Nout JCO 2011

Chemotherapy vs Radiation as Adjuvant Therapy

- Randomized trial 385 pts, Japan, >50% MI
- Low risk patients (IC, G1-2): no difference
- High risk patients (IC, G3; > IC):

	Radiation	Chemotherapy(CAP)	p
PFS	66.2%	83.8%	p=0.024
OS	73.6%	89.7%	p=0.006

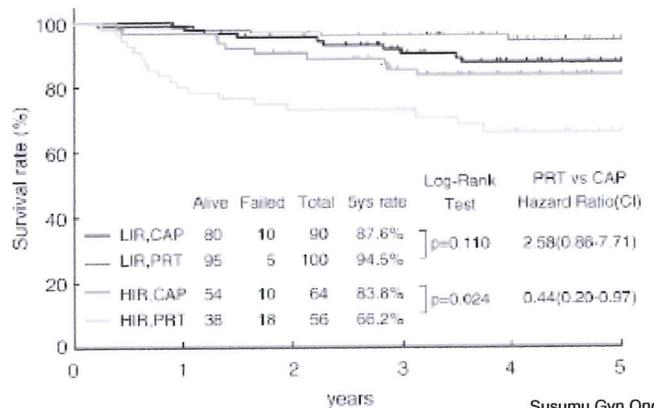
Susumu Gyn Onc 2008

? No Benefit in Adjuvant Radiation

- 905 women Europe intermediate or high risk
IA/IB G3; IC; IIA; pap serous/clear cell
- Lymphadenectomy optional, but nodes had to be negative
- Randomized to Whole Pelvic RT vs observation
- No survival or recurrence benefit seen

ASTEC Lancet 2009

Progression-Free Survival of Intermediate Risk



Susumu Gyn Onc 2008

Value of Brachytherapy PORTEC 2

- 427 patients: Europe 2002-2006
- Eligibility:
 1. Age >60 and Stage IC (G1,G2) or Stage IB (G3)
 2. Stage IIA
- Randomized to Pelvic RT vs Vaginal RT:
 - No difference in local or total recurrence
 - No difference in survival
 - Significantly higher GI toxicity with Pelvic RT

Nout Lancet 2010

Higher Stage Disease

- Chemotherapy remains mainstay: Carbo/Taxol
- Radiation used in selected cases

- GOG 258
Stage I or II Clear cell, Pap serous, or Undiff and (+) cytology
Stage III or IVA

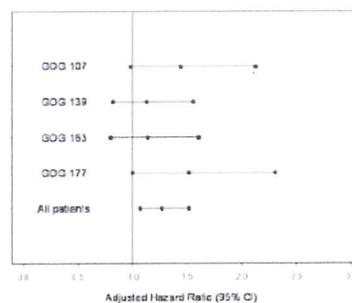
Randomize to:

Carbo/Taxol x 6 vs Cisplatin-RT then Carbo/Taxol x 4

Type II Endometrial Cancer

- Non-estrogen disease
- Older patients, thinner
- Often higher stage at diagnosis
- May have atrophic endometrium/thin endometrium
- Histologies: poorly differentiated, papillary serous, clear cell
- Prognosis much worse

GOG Randomized Trials: Hazard of Death Black vs White



Maxwell Cancer 2006

Racial Disparities in Endometrial Cancer

- 5YSR 1989-1994 for endometrial cancer were 86% in whites versus 54% in African-Americans
- Largest racial disparity for any type of cancer in SEER registry

Why the Disparity?

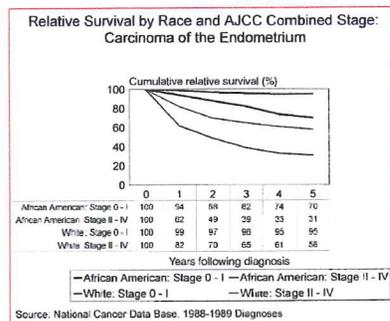
- Access to care issues: may play some role, although, stage for stage, still do worse
- Histology:

	White	AA
Adenocarcinoma	73%	62%
Clear cell	1%	3%
Papillary Serous	2%	6%
Poorly diff	18%	32%

- Biology of tumor

Hicks Cancer 1998

Racial Disparity



Hicks Cancer 1998

PTEN Mutations

- PTEN is a tumor suppressor gene
- Frequently mutated in early endometrial cancers
- Presence of mutation associated with better prognosis

140 stage III/IV endometrial cancers: 78 White; 62 AA

	White	AA	p=0.006
PTEN mutations	22%	5%	

Maxwell Clin Ca Research 2000

Her2-Neu

- Epidermal growth factor receptor
- Overexpression associated with poor prognosis
- More commonly expressed in Uterine Papillary Serous Carcinomas

Her2/Neu overexpression	White	AA
UPSC	24%	70% $p < 0.05$

Santin unpublished 2004

Cancers in HNPCC Women

Lifetime Risk:

Colorectal cancer	40-60%
Endometrial cancer	40-60%
Stomach	13%
Ovarian cancer	12%
Small bowel	5%

Schmeler Clin Trans Onc 2008

Type II Therapy

- Complete surgical staging
- Possible benefit to debulking
- Aggressive adjuvant therapy
- Most commonly chemotherapy: ovarian cancer regimens
- Close surveillance

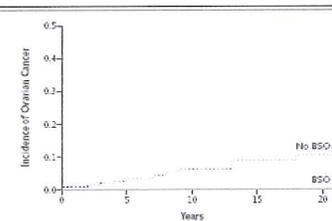
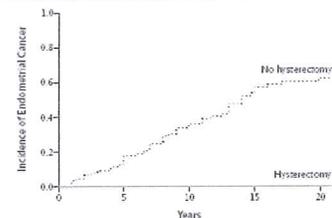
Prophylactic TAH, BSO

- 315 women with documented germ line mutations
 - 47 underwent TAH, BSO
 - 14 underwent TAH only
- Prophylactic surgery: No uterine, ovarian, peritoneal
Intact: 33% developed endometrial cancer
5% developed ovarian cancer

Schmeler NEJM 2006

Genetic Endometrial Cancer

- Lynch II syndrome: hereditary non-polyposis colon cancer families
- Genetic defect in mis-match repair enzymes
- Endometrial cancer most common cancer among women with this genetic disease
- BRCA with possible association with Papillary Serous uterine cancer

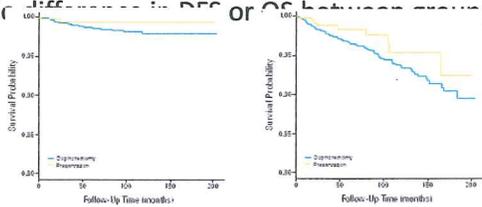


Ovarian Risk

Schmeler NEJM 2006

Preservation of Ovaries in Young Women

- SEER data of 3269 women ≤ 45 years old with endometrial cancer
- 402 had ovarian preservation
- No Difference in DFS or OS between groups



Wright JCO 2009

Conclusions

- Endometrial cancer is a spectrum of diseases
- Staging remains surgical, continue to define who benefits
- Adjuvant therapy trending toward chemotherapy and cuff radiation
- Wide racial disparity in outcome from this disease