Current Management of Gynecologic Malignancies 2010

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Who is a gynecologic oncologist?

- Fully trained board certified OB/GYN with 2-4 years of added fellowship training.
- Trained in comprehensive management of women with gynecologic malignancies.
- Training consists of: Specialized surgical training, chemotherapy, radiation therapy and supportive care.
- Basic science research project is required to sit for oral board exams

My specific training

- Medical school: University of Colorado
- Residency: University of Colorado
- 3 years of general ob/gyn practice and general boards
- Fellowship: Massachusetts General Hospital
- Gynecologic Oncology practice Denver (’88-99)
- Research at the National Cancer Institute in Cancer vaccines (00-01)
- Practice in Rapid City (01-present)

Ovarian Clear Cell Carcinoma

- Case history: MB is a 48 year old woman with sudden onset of abdominal pain while on vacation in Montana. CT showed a large abdominal-pelvic mass.
- Patient gives history of noticing a “bulge” in her abdomen for over one year.
- No history of major illnesses
- Referred for Gynecologic Oncology care for surgery with full staging.

Surgery

- TAH/BSO
- Peritoneal washings
- Pelvic and para-aortic lymphadenectomy
- Multiple peritoneal biopsies
- Appendectomy

GOG # 41: Surgical Staging of Ovarian Cancer

- Objective: To determine the natural history of ovarian cancer
- Conclusions: Poor correlation between visual inspection and histologic evaluation
- Up staged: 9 of 97 Clinical stage I (to II or III)
  15 of 43 Stage II (to III)

Clinical stage I: Nodal disease 0/93 pelvic nodes, but 4/95 para-aortic nodes positive

Principles of management of epithelial ovarian cancer

- Accurate, comprehensive surgical staging and cytoreduction
- Early stage
  - Assign risk
  - Adjuvant therapy for high risk

  Advanced Stage

  Cytoreduction

  Post-op chemotherapy

  Recurrent Disease

  Judicious use of surgery

  Chemotherapy and rarely radiation therapy

Management of Early Stage Disease

- Low Risk
  - IA or IB with grade 1 or 2

  High Risk

  I Grade 3

  II

  IC Ruptured capsule,ascites, positive cytology, clear cell histology

Early Stage Outcomes

- Low Risk patients
  - Greater than 95% long term survival

  High Risk patients (GOG 95)

  For patients treated with chemotherapy

  31% decreased risk of recurrence

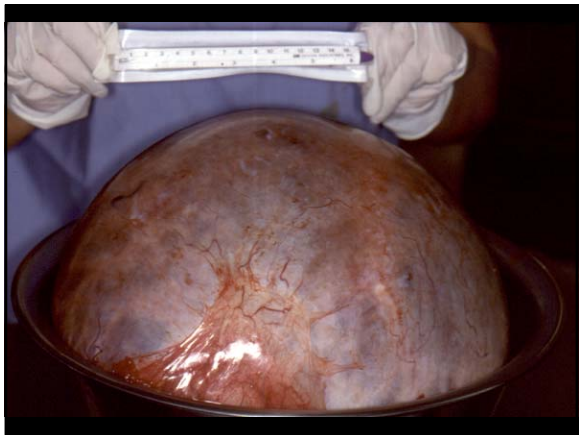
  77% recurrence free at 5 years

  84% survival at 5 years

  Survival and Progression Free Interval by stage

  5 year PFI Stage I 77%, Stage II 65%

  8 year Survival Stage I 73%, Stage II 64%



Is Stage One Disease the Same Disease as Stage III

Stage I disease is usually "picked up" due to the size of the mass, not from "screening"

Stage III disease is usually diagnosed when ascites accumulates and causes symptoms

Example of microscopic stage III disease vs. huge stage I disease

Screening for Ovarian Cancer

There is currently NO screening test for ovarian cancer

Screening for Ovarian Cancer

- Ca125 and ultrasound do not improve survival in ovarian cancer and should not be used for screening as it gives the patient a false sense of security.
- There is no screening test for ovarian cancer currently because we do not know the natural history of ovarian cancer.
- Ovarian cancer confined to the ovary (Stage I disease, with 90% 5 year survival is a different disease than Stage III disease.

Proteomic Protein Patterning as Biomarker Tool for Ovarian Cancer Detection

- Low molecular weight serum protein profiling may reflect the pathologic state of organs
- A bioinformatics tool was developed and used to identify proteomic patterns in serum that distinguish benign vs. malignant.
- Sensitivity was 100% and specificity 95% and PPV of 94% compared with a PPV of 34% for Ca 125
- On going prospective, population-based evaluation of proteomic pattern technology as a screening tool for ovarian cancer

Screening

- Now with a test that potentially has a 100% specificity, we need to determine if the test becomes positive before microscopic disease develops throughout the peritoneum.
- On the horizon is the "Ovarian Pap". Use a 9mm laparoscope to sample the epithelium of the ovary and test it with genomics and proteomics rather than histology.
- Molecular biology is the great hope for prevention of ovarian cancer.

BRCA Mutations in relation to Ovarian cancer

- A patient with a BRCA mutation has a lifetime risk of ovarian cancer of 27% to 44%.
- Risk reducing surgery (BSO) can decrease the risk by 95%. Recommended after age 35 if done with child bearing.
- Use of oral contraceptives in women with BRCA mutations can decrease their risk of ovarian cancer by 50%
- Prophylactic oophorectomy also reduces their risk of breast cancer by nearly 50%

Good news for Ovarian Cancer Patients

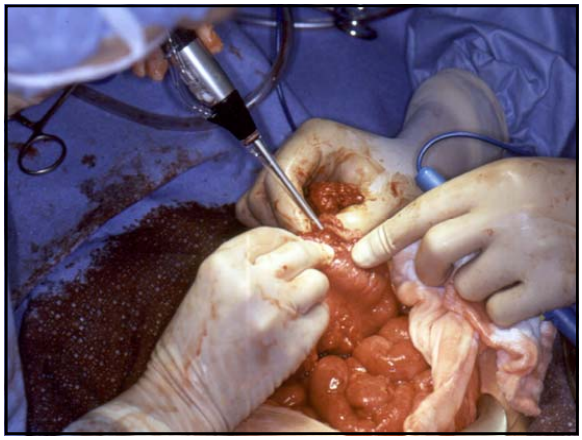
- Disease specific survival has shown continuous improvement over the past 30 years.
- 5 year survival has increased from 37% in 1973-1979 to 43% for 1990-1997.

Primary Tumor Debulking

- Retrospective studies only
- Difficult to do prospective study
- Studies suggest that primary cytoreductive surgery is beneficial and can be performed with acceptable morbidity

Who Should Operate on Ovarian Cancer Patients?

- Multiple studies have shown that patients operated on by gynecologic oncologists for ovarian cancer are fully staged significantly more often than when treated by benign gynecologists or general surgeons.
- Ovarian debulking should only be done by gynecologic oncologists as they are specifically trained in this procedure.
- Gynecologic oncologists are more familiar with the natural history of the disease and thus know when and when not to operate.
- It does make a difference



Primary Tumor Debulking

- Optimal tumor debulking not only prolongs survival, but is associated with more complete responses to chemotherapy.
- Could be related to fact that chemotherapy agents have a smaller absolute number of tumor cells and higher proportion of dividing cells.
- May also be related less immunosuppressive effect of bulky tumors. Cell-mediated immunity has been shown to have a direct relationship to tumor burden.

Chemotherapy in ovarian cancer

- Even for women with advanced ovarian cancer, therapeutic interventions, primarily because of the use of debulking surgery and improved chemotherapy regimens, have been shown to improve survival.
- Major advances in the chemotherapeutic treatment of ovarian cancer have been in platinum based regimens
- In 1992 GOG study demonstrated a gain in survival of 1 year (from 2 to 3 years) for those treated with palitaxel/cisplatin compound

Chemotherapy in ovarian cancer

- Introduction of carboplatin replacing cisplatin in combination with Taxol has further decreased the morbidity of chemotherapy.
- With newer drugs, better antiemetic regimens and growth factors, chemotherapy no longer carries the same morbidity.

NCI Clinical Announcement,1/05/06

- Results of three GOG intraperitoneal chemotherapy protocols showed significant overall survival and progression free survival.
- GOG 114: PFS (28 months vs 21 months) and overall survival 63 months vs 52 months).
- GOG 172: PFS 18.3 vs 23.8, OS 49.7 vs 65.6
- Intraperitoneal chemotherapy has greater toxicity in abdominal discomfort, neurotoxicity and fewer patients were able to complete full six cycles.

IP Therapy: Alternative Perspective

- New GOG trial comparing weekly Taxol and q3week Carboplatin plus Avastin vs.
- IP Carboplatin, IV Taxol q3weeks plus Avastin vs.
- IP Cisplatin, IV Taxol q3weeks plus Avastin all with maintenance Avastin

Conclusions

- Surgery can be critical in increasing survival as well as quality of life in women with ovarian cancer.
- Chemotherapy is better tolerated and newer regimens have increased survival as well as quality of life
- New molecular based therapies “designer” chemotherapy
- Screening still has not been shown to increase survival, as the true “natural history” of the disease is unknown

BRCA Genes, How Common Are They?

- Mutations occur in only 0.1% of general pop.
- Mutations occur in only 2% of high risk populations (Ashkenazi Jewish)
- BRCA mutation is present in only 1-3.3% of unselected breast cancer patients
- BRCA mutation is present in 12-30% of Ashkenazi Jewish breast cancer patients
- Screening test is very expensive > $3000.
- Must selectively screen patients

US Prevention Task Force Recommends Screening for Family Histories with:

- 2, First degree relatives breast Ca, one of whom was diagnosed < 50.
- Combination of 3 or more first or second degree relatives with breast Ca
- Combination of both breast and ovarian among first and second degree relatives
- First degree relative with bilateral breast cancer
- Combination of 2 or more first or second degree relatives with ovarian cancer
- First or second degree relative with both breast and ovarian
- Any male breast cancer

Why Screen for BRCA genes?

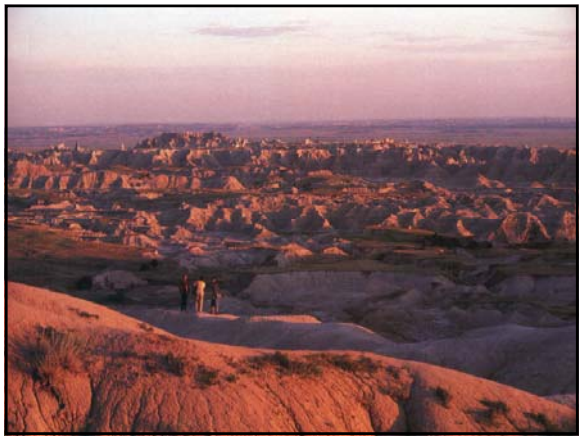
- Effects medical and surgical management of patients who are positive.
- Risk of ovarian cancer in positive patient is 40% , recommend a prophylactic oophorectomy
- Screen for breast cancer with mammograms and MRIs
- Treat breast cancer differently, ie. Avoid radiation therapy
- Consider prophylactic mastectomies

Risks of Screening

- Emotional problems for patients who test positive
- Worry will be unable to obtain insurance
- If negative, patient might not have routine screening

Who Should Order Gene Testing?

- Individuals need to be counseled regarding the results of the tests, both positive and negative.
- Test the individual who has the disease if possible
- Family members should be tested for positive patients mutation (one 10^{th} the price)
- Always take a detailed family history
- Other genes may cause breast and ovarian cancer (example: Lynch syndrome)



Case Presentation: Cervical cancer

- D.M. is a 55 y.o. with 14 month history of postmenopausal bleeding. She developed irregular bleeding and "just thought it was menopause". Pap smear revealed atypical cells cannot rule out high grade lesion. Told to return in 6 months for a pap, but did not return for 12 months. At that time she had a gross cervical lesion with biopsy consistent with an invasive squamous cell carcinoma.
- Pet/CT revealed no evidence of pelvic or para-aortic disease

Cervical cancer con't.

- Staged as a clinical Stage IB1 cervical cancer. Patient was offered radical hysterectomy vs. primary chemo/rads.
- Underwent radical hysterectomy with deep invasion and lymph-vascular space involvement.
- Two risk factors on final pathology
- Treated with chemo/rads as adjuvant therapy.

Cervical Cancer

- Cervical cancer has decreased in the last 50 years by over 70% due to the screening pap test.
- Half of the cervical cancers diagnosed in the United States are in women who have never been screened. An additional 10 % of cancers occur in women who have not been screened within the past five years.
- The largest gain in reducing cervical cancer incidence could be attained by increasing screening rates in unscreened populations.

Role of HPV in Cervical Cancer Screening

- 93-100% of cervical cancers contain DNA from high-risk HPV types.
- High risk types may lead to high or low grade intraepithelial lesions. High grade lesions may progress to cervical carcinoma if left untreated.
- The purpose of screening , in addition to detecting cervical cancers at an early stage, is to detect and treat high grade lesions to prevent progression to cancer.
- HPV testing currently is being used as a secondary screen in lesions of undetermined significance, but has recently been FDA approved as primary screening in women over 30 years of age.

New American Cancer Society Screening Guidelines

- When to start screening? Three years after the onset of sexual intercourse. Rational: Evidence suggests that there is little risk of missing an important cervical lesion until three to five years after initial exposure to HPV. If screening too early, may result in over diagnosis of cervical lesions that will regress spontaneously, leading to inappropriate intervention, which may result in more harm than good.
- The need for cervical cancer screening should not be the basis for the onset of gynecologic care.

New American Cancer Society Screening Guidelines

- When to discontinue screening? Women who are age 70 and older with an intact cervix and who have had three or more documented, consecutive, technically satisfactory normal cervical cytology tests, and no abnormal cytology tests within the 10 year period prior to age 70 may elect to cease screening.
- Screening is recommended for women who have not been previously screened, have a history of cervical cancer, or are immunocompromised.
- Women should discuss their individual situations with their health care providers to determine when to stop screening.

When to stop?

- Women 70(ACS) or 65(USPSTF) and older women with an intact cervix and 3 normal Paps and no abnormals within 10 years prior to 70.
- Rational: While ¼ of cervical cancers and 41% of deaths occur in women over 65, most had no Pap in the last 5 years
- Cervical cancer in older women is almost entirely confined to unscreened and underscreened women
- If sexually active and exposed to high risk HPV, very low risk of new lesion since little active metaplasia

New American Cancer Society Screening Guidelines

- Screening Interval:
- 21-29 y.o. every 2 years
- Low risk 30-64 years old with 3 consecutive normal paps, every 3 years
- Hysterectomy, most do not need further paps

New American Cancer Society Screening Guidelines: New Technologies

- Liquid based pap: Cervical screening may be performed every two years using liquid based cytology.
- HPV typing: Use as screening in women over 30 and as a secondary screen in women with an ASCUS pap

New American Cancer Society Screening Guidelines: New Technologies

- HPV DNA Testing with Cytology for the Screening of Cervical Cancer and Its Precursor Lesions: HPV DNA testing with cytology for primary cervical cancer screening has been approved by the FDA for women over 30 and if both tests are negative, screening may be performed every three years.
- More frequent screening would not significantly improve sensitivity, but would likely result in over-evaluation and potential over treatment of transient HPV infections.

New American Cancer Society Screening Guidelines: Conclusions

- Changes in screening recommendations are unlikely to have a significant impact on the low incidence of cervical cancer in the US
- The large impact for changes in screening with new technology will be for the 50 million women screened each year who have an abnormal result and undergo additional procedures.
- These technologies may reduce patient discomfort, anxiety and inconvenience as well as health care costs.

Future Directions for reducing the incidence of cervical cancer

- HPV Vaccines: Studies of HPV-16 virus like particle vaccine showed a 100% efficacy in one study.
- Phase I trials have demonstrated safety and immunogenicity.
- Multiple HPV high risk types make effective vaccine more difficult to accomplish
- Although gains in life expectancy may be modest at the individual level, population benefits are substantial.

Efficacy of HPV Quadrivalent vaccine

- Four protocols involving 8400 cases: 100% protection from HPV16 or 18 related CIN 2/3 or AIS
- Three protocols involving 7800 cases:95.2% protection from HPV 6,11,16 or 18 related CIN (CIN 1, CIN2/3, or AIS
- Three protocols involving 7900 cases: 98.9% protection from HPV 6, 11, 16,18 related genital warts

Most Important Role of Primary Care Providers

- Recommend all females ages 9-26 have the HPV vaccine
- Explain that women still need to be screened with Pap smears

Case Presentation: Endometrial Ca

- W.M. is a 77 y.o. G5P5 with a nine month history of post menopausal bleeding.
- Saw her primary care MD in May with complaint and was treated with premarin cream
- Continued to bleed and sought care again in December.
- Jan. endometrial biopsy showed Grade 1 endometrial Ca
- TAH/BSO with full staging revealed invasion to > 50% of myometrium with extensive pelvic and para-aortic nodal involvement with microscopic disease

Case presentation: Endometrial CA

- 37 year old morbidly obese female with a history of irregular menses since menarche. She often skipped menses for 3-6 months at a time.
- Developed heavy continuous bleeding for several months.
- Endometrial biopsy revealed Grade 1 endometrial cancer

Perimenopausal Bleeding and Postmenopausal Bleeding

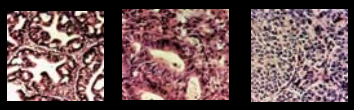
- Always endometrial cancer until proven otherwise.
- If endometrial biopsy is normal and bleeding persists, do a dilation and curettage.
- Diagnosis of endometrial cancer deserves referral to a Gynecologic Oncologist

Two types of Endometrial Cancer

- "Good Prognosis" type: Hormonally related, ie. Exogenous or endogenous relative estrogen excess
- Classic patient is obese
- "Aggressive" type: Abnormal bleeding in thin, elderly female.

Pre-operative predictors: Grade D&C vs Hysterectomy

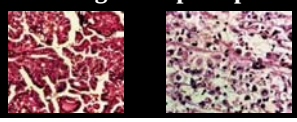
	Hysterectomy Grade		
D&C Grade	1	2	3
1	75%	20%	5%
2	23%	65%	11%
3	20%	35%	50%



(Sant Cassia et al, *Gynecol Oncol* 35,362, 1989)

No Invasion, no worries?

- **More patients diagnosis by endometrial Bx**
- **Clear cell and serous variants are at increased risk for nodal disease in the absence of myometrial invasion:**
  - Takeshima et al *J Obstet Gynecol* 88:280, 1996
  - Cirisano et al, *Gynecol Oncol* 77:55, 2000
  - Gehrig et al, *Obstet Gynecol* 97:153, 2001
- **UPSC diagnosed pre-operatively: 40-77%**



Treatment of Endometrial Cancer

- Surgical staging with total hysterectomy with removal of tubes and ovaries
- Most staging surgeries are now done laparoscopically
- Staging includes peritoneal washings and lymph node dissection
- Further therapy is based on risk factors on final pathology

Adjuvant Therapy based on surgical staging

- Whole pelvic radiation therapy vs. vaginal cuff radiation
- Chemotherapy in addition to radiation
- Newer chemotherapy agents (Taxol) have shown better responses in endometrial cancers that previous regimens.

Chemotherapy in endometrial cancer

- GOG 122: Doxorubicin-cisplatin significantly improves PFS and OS compared to WAR
- GOG 177: Doxorubicin-cisplatin vs Doxorubicin-cisplatin-paclitaxel produces an improvement in PFS and OS at the cost of increased peripheral neuropathy.
- Future GOG trials try to define optimal chemotherapy regimen

Conclusions

1) All EC patients are at risk for nodal disease

2) Pre-op and intraoperative assessment of prognostic features are unreliable

3) All patients should have access to pelvic and aortic lymphadenectomy if indicated at surgery

4) LND reduces need for adjuvant radiation

5) LND cost effective & safe

6) Cancer patients deserve subspecialty care; It is not just the surgery, it is knowing the natural history of the disease and the changes in care patterns