Objectives

• Radiation Physics
  - Production of Radiation
  - Properties of Radiation

• Radiation Biology
  - Cellular Mechanism of Radiation Effect
  - Factors That Affect Radiation Efficacy

• Gynecologic Radiation Oncology
  - Cervical
  - Endometrial
  - Vaginal/Vulvar
Cancer Facts and Figures

- Cancer Rates
  - Breast: 192,370
  - Endometrium: 42,160
  - Ovary: 21,550
  - Cervix: 11,270
  - Vulva: 3,580
  - Vagina and other: 2,160
  - Total: 273,090

- 30 to 50% of Cancer Patients Have Radiation Therapy

Radiation Physics

- Electromagnetic spectrum

Ionization
Radiation Safety and Terms

- Time and Distance
- Shielding
- Units:
  - Gray: The absorption of energy in Joules per kilogram
  - One Gray = 100 rads
  - Sievert: The dose equivalent (biologic effect) in Joules per kilogram.

The Four R’s of Radiobiology

- Repair of Sublethal Damage
- Reoxygenation
- Reassortment of Cells in the Cell Cycle to Sensitive Phase (M and G2)
- Repopulation

Radiation Biology

- Well oxygenated blood (Hg>10) increases cell kill per dose of irradiation
Hypoxia
Tumor outgrows blood supply

The Therapeutic Ratio

Linear Accelerator
Depth Dose Curves For Photons and Electrons

- Linear accelerator
  - Photon beam irradiation
  - Skin sparing
  - Increased depth dose
  - Less penumbra (sharper definition of beam edges)
  - Increased dose homogeneity at depth

- Electron beam radiation
  - Uniform dose dependent upon energy selected
  - Rapid dose fall off at depth

Brachytherapy

- Application of Radioactive Sources Directly to Tumor Site
- Permanent versus Temporary
- Isotope Selection
  - Energy and Half-life
- Delivery Accuracy
  - Fluoroscopy/MRI/Peripheral loading
- Conformality

Isotopes

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Energy (MeV)</th>
<th>T1/2</th>
<th>HVL cm. (lead)</th>
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<tbody>
<tr>
<td>Radium 226</td>
<td>0.83</td>
<td>1622 y</td>
<td>1.4</td>
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<tr>
<td>Cobalt 60</td>
<td>1.25</td>
<td>5.26 y</td>
<td>1.1</td>
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<tr>
<td>Cesium 137</td>
<td>0.662</td>
<td>30 y</td>
<td>0.65</td>
</tr>
<tr>
<td>Iridium 192</td>
<td>0.38</td>
<td>74.2 d</td>
<td>0.3</td>
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</table>
Brachytherapy

- **Low Dose Rate (LDR) 3.3cgy/Min**
  - Typical Fletcher-suit implant of the cervix; 48 hr. x 2
  - With a dose of 35-45 Gy to point A
  - In-patient
  - Hospital staff exposure
  - High maintenance; DVT, compression stockings, IV

- **High Dose Rate (HDR) 20cgy/Min**
  - Ring and tandem; 500cgy to point A in 15 min.
  - Outpatient procedure
  - No staff exposure
  - Low maintenance

High Dose-Rate Brachytherapy

- A method for the temporary implantation of radioactive sources
- May be used with multiple fractions as in external beam radiation therapy
- Afterloaded by remote control using computer dosimetry
- Intracavitary applicators available

Staging Cervix Cancer

- **Stage I confined to cervix**
  - Stage IA - invades stroma - microscopic
    - max 5 mm depth x 7 mm horizontal spread
  - Stage IB - visible tumor confined to cervix
    - IB1 less than or equal to 4 cm
    - IB2 greater than 4 cm
Staging Cervix Cancer

• Stage II Extends beyond uterus but not to pelvic sidewall or lower third of vagina
  - Stage IIA Without parametrial invasion
    - IIA1 less than or equal to 4 cm
    - IIA2 greater than 4 cm
  - Stage IIB With parametrial invasion

• Stage III Extends to pelvic sidewall, lower third of vagina, or hydronephrosis
  - Stage IIIA involves lower third of vagina without pelvic sidewall involvement
  - Stage IIIB extends to pelvic sidewall or hydronephrosis/nonfunctioning kidney

• Stage IVA
  - Involves mucosa of bladder or rectum or extends beyond the true pelvis

• Stage IVB
  - Distant metastases
Treatment Cervix Cancer

- Stage IA1 - Fertility, LVSI, Operable?
  - Cone + LND
    - Pos Margin? Repeat Cone vs Trachelectomy
    - LVS1? Radical Trachelectomy and LND +/- PALN sampling
  - Total Hx = Extrafascial Hx = Simple Hx
  - For LVSI (-) and No Desire for Fertility
  - Medically Operable
  - Cone + LND
    - Pos Margin? Repeat Cone vs Trachelectomy
    - LVSI? Radical Trachelectomy and LND +/- PALN sampling
  - Total Hx = Extrafascial Hx = Simple Hx
  - For LVSI (-) and No Desire for Fertility
  - Medically Operable
  - Pelvic Radiation with Brachytherapy

- Stage IA2 - Fertility
  - Cone + LND
    - Pos Margin? Repeat Cone vs Trachelectomy
    - LVSI? Radical Trachelectomy and LND +/- PALN sampling
  - Total Hx = Extrafascial Hx = Simple Hx
  - For LVSI (-) and No Desire for Fertility
  - Medically Operable
  - Pelvic Radiation with Brachytherapy

- Stage IB - Surgery, RT, Chemo-RT
  - Radical Hysterectomy LND +/- PALN Sampling
  - Chemo/RT - esp IB2
  - Radical Trachelectomy and LND
  - Selected Cases <2cm
  - Fertility Sparing
  - Stage IIA - Rad Hx + LND, PALN
    - Radical Hysterectomy LND +/- PALN Sampling
  - Chemo/RT - esp IIA2
  - Hx After Chemo/RT
    - Improved pelvic control not OS
    - Post-op RT (IA2, IB, or IIA1) cf GOG 92
    - Large Primary, Deep Stromal Invasion, LVSI
    - Pelvic RT +/- Chemo

- Stage IIB-IIIB
  - Chemo/RT
  - Consider PET/CT or MRI
  - Consider PALN Sampling

- Stage IVA
  - Chemo/RT
  - Extraperitoneal LND
  - Extended Field Chemo/RT

- Stage IVB (DM)
  - Chemotherapy
  - RT Palliation
Cervical Cancer ICRT

• Importance of Brachytherapy
• Applicators
  - Fletcher-Suit
  - Delcos
  - Nucletron
• Point A and Point B

Randomized Trials: Cervix

<table>
<thead>
<tr>
<th>Trial</th>
<th>Eligibility</th>
<th>Treatment</th>
<th>CDDP Dose</th>
<th>OR</th>
<th>Ref</th>
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<tr>
<td>GOG-85</td>
<td>IIB-IVA</td>
<td>PT + RT 50 mg/m²</td>
<td>0.79</td>
<td>JCO 17:1339 (1999)</td>
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<td>GOG-120</td>
<td>IIB-IVA</td>
<td>RT/HU vs RT/CDDP</td>
<td>0.57</td>
<td>NEJM 340:1144 (1999)</td>
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<tr>
<td>GOG-123</td>
<td>IB &gt; 4 cm</td>
<td>RT/CDDP/Hx 40 mg/m² x 6</td>
<td>0.51</td>
<td>NEJM 340:1154 (1999)</td>
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<tr>
<td>RTOG-9001</td>
<td>IB-IVA</td>
<td>RT/CDDP/FU 75 mg/m² x 3</td>
<td>0.48</td>
<td>NEJM 340:1137 (1999)</td>
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<tr>
<td>SWOG-8797</td>
<td>IB-IVA</td>
<td>RT vs RT/CDDP/FU 50 mg/m² x 2</td>
<td>0.50</td>
<td>Gyn Oncol 72:443 (1999)</td>
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</table>

Cervical Cancer ICRT

• Importance of Brachytherapy
• Survival Rate with ICRT
  * 43% vs 21% MDACC Stage IIIB 1096 pts
• Applicators
  - Fletcher-Suit
  - Delcos
  - Nucletron
• Point A and Point B
Fletcher–Suit Method

- Optimal Placement Technique
- Applicators
- Dose Optimization
- Prescription Rules

High Dose-Rate (HDR) Method

- “HDR” After-loading Machine Ir-192
  - ~50 cGy per Minute
- Compare to Cesium
  - 45-60 cGy per Hour for LDR
- Radiobiologic Disadvantage Overcome by Fractionation (5-8 Fractions)
- Outpatient Treatment
- Daily Set-up Reproducibility
- Interstitial Template Brachytherapy
Advantages of HDR Method

- Outpatient Treatment
- Patient Comfort
- Reduced Radiation Exposure to Staff
- Reduced Risk of DVT
- Daily Set-up Confirmation by Fluoro
- Equivalent Tumor Control and Complication Rates

HDR Cervix Stent and Brachytherapy
Brachytherapy, Points A & B

• Point A is defined as the point being 2 cm above the mucous membrane of the lateral vaginal fornix and 2 cm lateral to the center of the uterine canal.
  - This is meant to correspond to the paracervical triangle in the medial edge of the broad ligament, where the uterine vessels cross the ureter. (This definition has been modified)

• Point B is defined on the horizontal plane at point A but 5 cm lateral from midline.
  - This is meant to represent the obturator lymph nodes.
Intergroup Trial
INT0107/SWOG8797/GOG109/RTOG9112

<table>
<thead>
<tr>
<th>Stage</th>
<th>Surgery</th>
<th>Irradiation</th>
<th>S+XRT</th>
<th>S+XRT+C</th>
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<tr>
<td>IA</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>NA</td>
</tr>
<tr>
<td>IB</td>
<td>86</td>
<td>85</td>
<td>90</td>
<td>93</td>
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<tr>
<td>IIA</td>
<td>76</td>
<td>76</td>
<td>75</td>
<td>88</td>
</tr>
<tr>
<td>IIB</td>
<td>50</td>
<td>60</td>
<td>68</td>
<td>80</td>
</tr>
<tr>
<td>I1IA</td>
<td>30</td>
<td>59</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>I1IB</td>
<td></td>
<td></td>
<td>25</td>
<td>45</td>
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</table>

Results

- 4 year progression free
  (P<.01)
- 4 year actuarial survival
  P<.01
- Pelvic Recurrence
- Distant Metastasis
- Local and Distant Failure

Intergroup Trial
INT0107/SWOG8797/GOG109/RTOG9112

<table>
<thead>
<tr>
<th>RT</th>
<th>Chemo-RT</th>
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<tbody>
<tr>
<td>RT</td>
<td>Chemo-RT</td>
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- 4 year progression free
  63% 80%
- 4 year actuarial survival
  71% 81%
- Pelvic Recurrence
  17% 6%
- Distant Metastasis
  11% 7%
- Local and Distant Failure
  4% 3%
Endometrial Carcinoma

• The Most Common Gynecological Malignancy With Approximately 43,470 Cases In 2010 And 7,950 Deaths
• Accounts For 13% Of All Female Cancers
• Seventh Leading Cause Of Death From Malignancy In Females

Endometrial Cancer

• Stage I: Limited to the Corpus
  - Stage IB: Invades more than one-half of the myometrium
  - Stage IA: Invades less than one-half of the myometrium

• Stage II: Invades Cervical Stromata
Endometrial Cancer

Stage IIIA  Involves serosa and/or adnexa
Stage IIIB  Involves vagina or parametrium
Stage IIIC  Involves pelvic and/or para-aortic lymph nodes

Stage IVA  Involves bladder or bowel
Stage IVB: Distant metastases

Grade, Depth And Nodal Metastasis
Creasman et al.: Cancer 60: 2035–204, 1987

<table>
<thead>
<tr>
<th>Depth of Invasion</th>
<th>Pelvic Grade 1 (N=180)</th>
<th>Pelvic Grade 2 (N=288)</th>
<th>Pelvic Grade 3 (N=155)</th>
<th>Para-Aortic Grade 1 (N=180)</th>
<th>Para-Aortic Grade 2 (N=288)</th>
<th>Para-Aortic Grade 3 (N=153)</th>
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<tbody>
<tr>
<td>Endometrium 0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inner</td>
<td>3</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Middle</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Deep</td>
<td>2</td>
<td>11</td>
<td>22</td>
<td>1</td>
<td>8</td>
<td>15</td>
</tr>
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</table>
Patterns Of Recurrence

- In General, About 50% Of Pelvic Recurrences Are In The Vagina And >75% Are In The Upper 1/3
- This Is What Led Many To Advocate Vaginal Brachytherapy (Limiting Treatment Length!)
- Vaginal Recurrence In 15% Of Patients With >1/3 Myometrial Invasion And G3 Histology
- Two Prospective Randomized Studies
  - Roberts (GOG-99) 19 Pelvic Recurrences In 202 Patients Without XRT Compared To 1 Of 188 Receiving Pelvic XRT
  - Aalders Pelvic Recurrence Decreased From 15% To 0% With Pelvic XRT

Recent Data

- GOG study
  - 390 patients
  - Intermediate risk
    - Grade III
    - Myometrial Invasion >1/3
  - Vaginal XRT 0/58 vaginal recur
  - Pelvic XRT 2/17 vaginal recur
  - Surgery alone 4/13 vaginal recur

Reasons for XRT in Endometrial Cancer

- Incidental finding at TAH
- Any of the previous risk factors
- Stage IIB, IIIC, IVA and IVB
- Incompletely surgically staged
- Papillary serous or clear cell
Patients with grade 1 or 2 cancers with either no invasion or less than 50% myometrial invasion (MI), especially when no other high risk features are present, can be safely observed after hysterectomy.

Vaginal cuff brachytherapy is as effective as pelvic radiation therapy at preventing vaginal recurrence for patients with grade 1 or 2 cancers with ≥50% MI or grade 3 tumors with <50% MI.

Patients with grade 3 cancer with ≥50% MI or cervical stroma invasion may benefit from pelvic radiation to reduce the risk of pelvic recurrence.

There is limited evidence for a benefit to vaginal cuff brachytherapy following pelvic radiation.

Multimodality treatment is recommended for patients with positive nodes or involved uterine serosa, ovaries or fallopian tubes, vagina, bladder, or rectum.

**APOPHENA**

*Apophenia* (æpəˈfɪniə) is the experience of perceiving patterns or connections in random or meaningless data.
Endometrial Carcinoma
Survival by stage

- Stage 5 year survival %
  - I (S+XRT) 90
  - II (S+XRT) 85
  - II (XRT) 80
  - III (XRT) 36

Vulvar Carcinoma

- Stage I, II
  - Surgery of Primary Site
  - Radical Vulvectomy & IFND
  - XRT in place of IFND in patients with N0 disease who refuse or are medically unfit to withstand groin dissection. GOG Study Stehman, FB 1992 suggests that XRT is inferior but this is not borne out in other GOG Peterselt, MG 1993 due to poor design.
  - Radiation Therapy alone for medically unfit
  - Adjuvant XRT if >2 ipsilateral LN

- Stage III/IV
  - Modified Radical Vulvectomy & IFND
  - Radical Vulvectomy & IFND
  - Adjuvant XRT 45-50 Gy if capillary-lymphatic space invasion and tumor thickness >3mm. Pelvic and groin LN XRT if >2 LN+
  - Preop XRT and 5FU in selected patients. Thomas 1991
  - 5FU +/- Cisplatin + XRT in surgically unfit Pt. Cr 50-90%, 36 Mon Median PFS 47-64%
Conclusions

• Understanding Radiation Physics and Biology
• Integration of Modalities
  - Surgery
  - External Radiation
  - Intracavitary Brachytherapy
  - Chemotherapy
• Implant Geometry, Technique, and Dose Evaluation

Thank you