Radiation Treatment for Gynecologic malignancies

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Topics to discuss

■ Define electromagnetic radiation and its general mechanisms of actions.
■ Discuss methods of radiation protection
■ Review literature in regards to the role of radiation treatment (RT) in the management of gynecologic malignancies
  ► Cervical carcinoma
  ► Endometrial carcinoma
  ► Vulvar carcinoma
■ Questions

Physical and biological principles of radiation treatment
The spectrum of electromagnetic radiation

Non-ionizing radiation

- People use and are exposed to non-ionizing radiation sources every day. This form of radiation does not carry enough energy to ionize atoms or molecules.
- Microwave ovens, global positioning systems, cellular telephones, television stations, FM and AM radio, baby monitors, cordless phones and garage-door openers all use non-ionizing radiation.
- Other forms include the earth’s magnetic field and magnetic field exposure from proximity to transmission lines, household wiring and electrical appliances.

Examples of low frequency waves
Ionizing radiation

- Some types of radiation have enough energy that they can knock electrons out of their orbits around atoms, upsetting the electron/proton balance and giving the atom a positive charge. Electrically charged molecules and atoms are called ions.

- The radiation that can produce ions is called ionizing radiation.

How we generate radiation beam?

The atom

- Accelerating electrons, then use to treat superficial lesions (Electron beam)
- Accelerating electrons, make it to hit tungsten target, creates photon beams (X-rays) to treat deep tumors
- Accelerating nuclear contents (proton beams or neutron beams using cyclotrons)
- Using radioactive sources (such as cobalt-60, Iridium 174, Iodine-125, radiopharmaceuticals [Iodine-131] etc.)
General mechanisms of radiation damage

Principles of radiation biology (4Rs)
- **Reoxygenation**: occurs when radiation is delivered in multiple fractions to cells that may be relatively resistant due to hypoxia.
- **Redistribution**: is defined by cells that survive a dose of radiation due to synchronisation in resistant phases of the division cycle and redistributing into more sensitive phases.
- **Repopulation**: describes cells responding to lethal injury by repopulating or regenerating themselves.
- **Repair**: occurs following sub lethal cellular injury

Radiation Protection (dose reduction to staff)
- **ALARA (as low as reasonably achievable)**
- Minimize exposure by considering these factors
  - Time
  - Distance
  - Shielding.
- Absorbed dose: Gray (Gy)
  - Doses to microscopic disease is ~ 50 Gy
  - Doses to macroscopic disease such as cervical cancer is ~ 85 Gy
Technological advances in radiation treatment
Apple laptop 1989  IBM laptop 1986 (30 #)

Early 1950s  2016

Management of cervical cancer
Epidemiology of cervical carcinoma

- It is becoming rarer in US and Western Europe (mainly due to screening, vaccination and early diagnosis of precancerous lesions)
- In 2018, 570K women were diagnosed with cervical cancer globally.
- Worldwide, 311K women died of cervical cancer in 2018. It is the leading cause of cancer deaths in Eastern, Western, Central and Southern Africa.
- Related to human papillomavirus (mainly HPV 16, 18) infection.

Age-standardized incidence (per 100000 women-years) (Arbyn et al 2018 Lancet 2019)

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Age-standardized mortality (per 100000 women-years) (Arbyn et al 2018 Lancet 2019)

| Age-standardized mortality (per 100000 women-years) (Arbyn et al 2018 Lancet 2019) |
Cervical carcinoma, a global problem

- There have been giant strides in the global effort to reduce the burden of cervical cancer with WHO announcing a call for elimination.
- In over 80 countries, HPV vaccination is now included in the national program. Screening has also seen major advances with implementation of HPV testing on a larger scale.
- Papaniclaou (pap) smear is considered a very cost-effective cancer screening program.

US Preventive Services Task Force
Pap smear - guidelines

- Women 18 to 65 years, in combination with HPV testing:
  - Every 5 years for women age 30-65 years with screening with a combination of cytology and HPV testing.

- Women < 30 years, HPV testing:
  - No screening for cervical cancer with HPV testing, alone or in combination with cytology, in women younger than age 30 years.

- Women < 21 years:
  - No screening for cervical cancer in women younger than age 21 years.

- Women > 65 years, who have had adequate prior screening:
  - No screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer.

- This recommendation statement applies to women who have a cervix, regardless of sexual history.
- This recommendation statement does not apply to women who have received a diagnosis of a high-grade precancerous cervical lesion or cervical cancer, women with in utero exposure to diethylstilbestrol, or women who are immunocompromised (such as those who are HIV positive).

Epidemiologic factors

- Peak incidence between ages 45 and 55.
- More prevalent in African American women
- Vaginal bleeding (mainly post coital) is one of the main presenting symptoms.
- Squamous cell carcinoma in about 85% associated with HPV.
- Adenocarcinoma in 10% and may be associated with DES exposure
Human papillomavirus (HPV)

- 70% of cervical cancer
- 20% of cervical cancer
- 90% of anogenital warts
- 90% of anal cancer
- 70% vaginal cancer
- 45% vulvar cancer
- 50% oropharyngeal
- 25% of oral cavity
- 20% of laryngeal cancers
- 40% of penile cancer

HPV vaccines

- Bivalent vaccine (Cervarix)
  - 16
  - 18
  - 31
  - 33
  - 45
  - 52
  - 58
- Quadrivalent vaccine (Gardasil)
  - 6
  - 11
- 9-valent vaccine (Gardasil 9)
  - 6
  - 11

HPV infection and progression
Work-up for invasive cervical cancer

■ Vaginal examination with a speculum.
■ Biopsy if any visible
■ If biopsy is positive, then staging work-up to rule metastatic disease:
  ▶ PET/CT scan (whole body)
  ▶ OR CT of the chest, abdomen and pelvis
■ Examination under anesthesia (EUA) for locally advanced disease with a cystoscopy and or sigmoidoscopy

Pre treatment 18-FDG PET/CT scan

Cervical cancer staging (2018)
Management of cervical carcinoma

- Surgery (radical, MR or simple hysterectomy) based on the FIGO stage (stages IA-IB2)
  - Fertility sparing surgical procedure such as trachelectomy in a very selected group of women with cervical carcinoma.
- Definitive radiation treatment with concurrent cisplatin chemotherapy for FIGO stages (IB3-IVA).
- Chemotherapy with palliative radiation treatment in stage IVB.
  - In a very selected women with stage IVB, definitive radiation treatment with cisplatin chemotherapy may be considered.

Management of cervical carcinoma

- Hysterectomy (radical, modified radical or simple) based on the stage of the disease.
  - Emerging data for fertility preserving surgery
  - Growing interest in minimally invasive hysterectomy
- Some women will need postoperative radiation treatment with chemotherapy after hysterectomy (positive nodes, positive margins, positive parametrial involvement ... etc.).

Radiation treatment for cervical cancer

- Curative with concurrent cisplatin chemotherapy
  - External beam pelvic RT +/- paraaortic RT
  - Internal radiation treatment (brachytherapy)
    - Intracavitary or interstitial
Requirements for image-based brachytherapy

- Imaging (CT in the treatment position fused with MRI (better) and/or PET scan.
- CT/MRI compatible applicators
  - Most of the LDR brachytherapy applicators are metal (non-CT compatible).
  - The metal applicators are very good to use with old X-ray machine for imaging.
- Treatment planning system (VariSource or Nucleatron)
Management of uterine cancer

Epidemiology

- Mainly in postmenopausal white females (75%).
- Mainly present at early stages (stage I in 75%, II in 10%, III in 10% and IV in 5%)
- Baby boomer women (1946-1964) are doing better compared to pre boomers (1926-1945)
Histopathologic types
- Epithelial (95%) and mesenchymal (5%)
- Endometroid adenocarcinoma 87% of all epithelial carcinomas (Type I)
- Serous carcinoma in 10% and clear cell in 3% (Type II)
- Uterine sarcomas or malignant mixed Mullerian tumor (MMMT) in 5%.

Risk factors
- Obesity
- Early menarche, late menopause or nulliparity
- Endogenous unopposed estrogen e.g. polycystic ovarian syndrome or estrogen-producing tumors such as granulosa cell tumors.
- Tamoxifen treatment for breast cancer
- Familial such as Lynch syndrome
- It is associated with hypertension and diabetes mellitus.

Work-up
- Endometrial biopsy
- Dilatation and curettage (D&C) +/- hysteroscopy
- CT scan of the abdomen and pelvis for selected cases.
- PET scan in selected patients
- Pelvic MRI in selected patients
Surgical staging (2009)
International J of Gyn and Obstet 104: 103, 2009

Stage I
- Tumor confined to the corpus uteri
  - IA Disease limited to the endometrium and/or < half of the myometrium
  - IB Disease invades > half of myometrium

Stage II
- Tumor invades cervical stroma but does not extend beyond the uterus

Stage III
- Local and/or regional spread
  - IIA Serosa or adnexal involvement
  - IIB Vaginal or parametrial involvement
  - IIC Metastases to pelvic and/or para-aortic lymph nodes
    - IIC1 Positive pelvic lymphadenopathy
    - IIC2 Positive paraaortic lymphadenopathy without pelvic LN

Stage IV
- IV A Bladder or rectal mucosal involvement
- IV B Distant metastases

* Endocervical glandular involvement only should be considered as stage I and no longer stage II.
** Positive cytology has to be reported separately without changing the staging.

Management

- Surgical staging; hysterectomy, salpingo-ophorectomy, lymph node evaluation (controversial for stage I) and peritoneal cytology.
- Omentectomy for uterine serous carcinoma.
- Adjuvant treatment (external beam RT, brachytherapy, chemotherapy or combination) in selected patients with adverse prognostic factors

Prognostic factors in endometrial carcinoma

- Older age
- African American race
- Pathologic type (serous or endometrioid)
- Histological grade
- Lymphovascular space invasion
- Depth of myometrial invasion
- FIGO stage
- Tumor size
- Microcystic, elongated, and fragmented (MELF) pattern
- Loss of function PTEN mutation
- PI3K/AKT/mTOR pathway aberrations
- TP53 mutation
- NR2
- Activating HER2 mutation
- Angiogenesis markers
- Activating HRAS mutation
- L1CAM expression

- Obesity
- DNA ploidy
- Metformin use

Rather than looking at risk grouping, individualized risk stratification incorporating available clinicopathologic factors is critical in counseling individual patient about adjuvant management options.
Henry Ford Cancer Institute adjuvant recommendation for FIGO stages I-II (Assuming adequate surgical staging. LVSI should be considered)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Grade I</th>
<th>Grade II</th>
<th>Grade III</th>
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<tbody>
<tr>
<td>IA</td>
<td>Observe</td>
<td>VB</td>
<td>VB</td>
</tr>
<tr>
<td>IB</td>
<td>VB</td>
<td>VB</td>
<td>VB</td>
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<tr>
<td>II</td>
<td>VB</td>
<td>VB</td>
<td>VB</td>
</tr>
<tr>
<td>Serous, clear</td>
<td>VB + chemother.</td>
<td>VB + chemother.</td>
<td>VB chemother.</td>
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Pelvic, PA and vaginal cuff coverage

Post treatment potential vaginal narrowing, prevention

Vaginal dilators (two sizes) with lubricants and instructions
The evolving role of genomics, proteomics, transcriptomic, in uterine carcinoma

Integrated genomic characterization of endometrial carcinoma (373 patients)

- POLE ultramutated
- Microsatellite instability hypermutated
- Copy number, low
- Copy number, high

The cancer genome atlas, uterine endometrioid carcinoma

<table>
<thead>
<tr>
<th>POLE ultramutated</th>
<th>MSI hypermutated</th>
<th>Copy-number low</th>
<th>Copy-number high</th>
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<tbody>
<tr>
<td>4% of endometrioid carcinoma</td>
<td>39% of endometrioid carcinoma</td>
<td>49% of endometrioid carcinoma</td>
<td>8% of endometrioid carcinoma</td>
</tr>
<tr>
<td>High frequency of mutations in the domain of POLE</td>
<td>High microsatellite instability (MSI)</td>
<td>Low copy number alterations</td>
<td>High copy number alterations</td>
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<tr>
<td>High expression of POLE</td>
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POLE: DNA polymerase epsilon, catalytic subunit; MSI: microsatellite instability; PTEN: phosphatase and tensin homolog; KRAS: Kirsten rat sarcoma viral oncogene; SOX17: a member of the SOX (SRY-related HMG-box) family of transcription factors; RAD50: double-strand break repair protein.

Management of vulvar cancer
Epidemiology
- About 6000 new patients in 2019 (0.3% of all new cancers) in USA.
- About 2000 deaths
- <5% of gynecologic malignancies
- Median age for invasive carcinoma is ~ 70 years
- HPV-negative (classic type) in older patients
- HPV-positive (16, 18 and 33)(atypical) in younger patients

Anatomy
- Labia (majora and minora) 80%
- Clitoris (10%)
- Perineum
- Forchette
- Vulvar vestibule
- Mons pubis
- Bartholin’s and Skene’s glands.

Histopathologic types
- Squamous cell carcinoma in more than 89%
- Melanoma
- Adenocarcinoma (Bartholin and Skene’s glands)
Surgical management

- Historically: Radical vulvectomy with a single large incision (en bloc resection).
- Adequate and timely wound healing was a major challenge in women with vulvar cancer after this surgery.

Surgical management

- Hacker et al., Obstet. Gyn, 1981 showed that multiple incisions (3) were less morbid than single large incision.
- Multiple institutional experiences have confirmed that multiple incisions did not appear to adversely affect outcome and had lower rates of complications.

The revised 2009 FIGO staging

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<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>T1a</td>
<td>Confined to epidermis, size ≤1 mm, clinical invasion ≤1 mm, MO</td>
</tr>
<tr>
<td>T1b</td>
<td>Confined to epidermis, size ≤1 mm, clinical invasion &gt;1 mm, MO</td>
</tr>
<tr>
<td>T2</td>
<td>Any site or invasion to 1/3 lower vagina, 1/3 lower urethra, or any site, MO</td>
</tr>
<tr>
<td>T3</td>
<td>Any site or invasion to 1/3 lower vagina, 1/3 lower urethra, or any site, MO with positive inguinal lymph nodes</td>
</tr>
<tr>
<td>N1a</td>
<td>1 LN &gt; 5 mm, or 2-3 LN ≤5 mm</td>
</tr>
<tr>
<td>N1b</td>
<td>4 or more LN &gt; 5 mm, or 5 or more LN ≤5 mm</td>
</tr>
<tr>
<td>N2a</td>
<td>Positive LN with extracapsular extension</td>
</tr>
<tr>
<td>N2b</td>
<td>Positive LN with extracapsular extension</td>
</tr>
<tr>
<td>M1</td>
<td>Any distant metastasis including pelvic LN</td>
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~30% of patients present with stage IIIb.
Predictive factors for LR recurrence

- Inguinal lymphadenopathy
- Positive or close margins
  - An 8-mm margin in fixed tissue, corresponding to a clinical margin of ~10 mm in vivo.
  - Close margin < 1 cm is associated with higher vulvar recurrence rates.
- Extensive angiophatic infiltration

Radiotherapeutic options

- Postoperative after vulvectomy
- Preoperative for marginally resected tumors
- Definitive radiation with concurrent chemotherapy for locally advanced disease
- Salvage for local recurrence
- For palliation (metastatic or recurrent tumors)

The rarity of vulvar carcinoma precludes phase III randomized studies to compare survival endpoint between different treatment approaches.
The impact of HPV on prognosis

- Some studies suggest that women with HPV-associated vulvar cancer have improved disease outcomes with radiotherapy compared with those whose tumors are not associated with HPV as determined by p16 immunostaining (about 50% reduction in recurrence rates at 5-year.

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Treatment-related morbidity

- Lymphedema (43%)
- Skin desquamation and necrosis
- Delayed wound healing
- Pelvic relaxation and organ prolapse
- Urinary and/or fecal incontinence
- Vaginal stenosis
- Sexual dysfunction (dyspareunia).
- Femoral head avascular necrosis
- Psychological issues

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Stages of lymphedema

- Stage I: Mild, resolves overnight
- Stage II: Always present but varies in severity
- Stage III: Persistent, moderate to severe

Consequences of lymphedema: Financial, altered daily activities and change of clothing.
National Lymphedema Network recommendations:

**Avoid constriction**
- Wear properly fitted shoes, socks and knee highs
- Avoid crossing legs
- Ambulate at intervals
- Elevate legs if swelling occurs

**Avoid infection/inflammation**
- Keep skin clean and dry
- Use an emollient cream to keep skin soft
- Use taped bands
- Use sunscreen
- Cut toenails straight across
- Use an electric shaver

**Avoid factors increase to lymphatic circulation**
- Gradually increase exercise
- Deep breathing exercises will help the flow of lymph
- Avoid temperature extremes, such as saunas and hot tubs

**Use caution during air travel**
- Consider use of personally fitted compression stockings
- If lymphedema is present, use personally fitted compression stockings
- Hydrate during flight
- Ambulate during flight
- Request a seat assignment with adequate leg room

**Call your call provider (lymphedema clinic) when you have**
- Swelling
- Fever
- Erythema or warmth

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**GOG 244: Prospective lymphedema study (PI: Barakat)**

- To prospectively determine the incidence and potential risk factors for women with endometrial, cervical and vulvar malignancies who received surgery with a lymphadenectomy as primary treatment.
- Serial circumferential measurements (baseline, 4-6 weeks postoperative and then every 3 months for the first year and then every 6 months for the second year.
- Patient-reported quality of life data were also collected at regular intervals.

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**Measurements of lymphedema**
GOG 244 (Carlson et al Gyn Oncol 2019)

- The incidence of limb volume change > 10% was 34% in endometrial cancer patients, 35% for cervical cancer patients and 43% for vulvar cancer patients.
- Independent prognostic factors for developing lymphedema included:
  - Young age
  - Dissected number of lymph nodes > 8 (in EC cohort)
- There was no association between lymphedema and radiation treatment or other risk factors

Take home messages

- More than 90% of cervical cancer tumors are HPV-related.
- HPV vaccination, early diagnosis and treatment are strategies to reduce cervical cancer burden.
- Radiation treatment is effective for women with advanced stage cervical carcinoma.
- For women with endometrial cancer, hysterectomy is the cornerstone of treatment. Some women will need postoperative radiation treatment or chemotherapy if they adverse prognostic factors.
- Small vulvar lesions can be treated with wide local excision +/- adjuvant RT (based on adverse pathologic factors).
- Patients with locally advanced vulvar disease benefit from preoperative radiation and surgery or definitive radiation treatment with concurrent chemotherapy.

Thanks for your attention

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