Gynecologic Malignancies

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4/20/18
Outline

• Female Cancer Statistics
• Uterine Cancer
• Adnexal Cancer
• Cervical Cancer
• Vulvar Cancer
## Estimated New Cancer Cases* in the US in 2016

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>841,390</td>
<td>843,820</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>21%</td>
<td>29%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>8%</td>
<td>13%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>6%</td>
<td>7%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>All other sites</td>
<td>22%</td>
<td>21%</td>
</tr>
</tbody>
</table>

*Breast: 13%  Lung & bronchus: 8%  Colon & rectum: 7%  Uterine corpus: 6%  Thyroid: 4%  Non-Hodgkin lymphoma: 3%  Melanoma of skin: 3%  Leukemia: 3%  Pancreas: 3%  Kidney & renal pelvis: 3%  All other sites: 21%

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.
<table>
<thead>
<tr>
<th>Site</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites*</td>
<td>1 in 3</td>
</tr>
<tr>
<td>Breast</td>
<td>1 in 8</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>1 in 17</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>1 in 23</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>1 in 36</td>
</tr>
<tr>
<td>Melanoma of the skin†</td>
<td>1 in 52</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1 in 53</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1 in 58</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1 in 67</td>
</tr>
<tr>
<td>Ovary</td>
<td>1 in 77</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1 in 82</td>
</tr>
</tbody>
</table>

*All sites exclude basal cell and squamous cell skin cancers and in situ cancers except urinary bladder. †Statistic for white females.

Estimated Cancer Deaths in the US in 2016

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>27%</td>
<td>26%</td>
</tr>
<tr>
<td>Prostate</td>
<td>8%</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>All other sites</td>
<td>24%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Lung & bronchus, Breast, Colon & rectum, Pancreas, Ovary, Uterine corpus, Leukemia, Liver & intrahepatic bile duct, Non-Hodgkin lymphoma, Brain & other nervous system, All other sites
Uterine Cancer
Endometrial Cancer
Uterine Sarcoma
Endometrial Cancer

- Epidemiology and Risk Factors
- Histology
- Presentation
- Diagnosis
- Staging
- Therapy
  - Early
  - Locally Advanced
  - Metastatic
  - Recurrent
- Follow-Up
- Future Therapy
Epidemiology

- 60,500 cases expected in 2016
  - 25.3 per 100,000 women
- 10,470 deaths expected in 2016
Epidemiology

Increased Risk
• Age
• Unopposed Estrogens
  • Exogenous
  • Tamoxifen
  • Obesity
• Genetic Risk
  • Lynch Syndrome
  • Cowden Syndrome

Decreased Risk
• Progestational Agents
  • Oral Contraceptive Pills
  • Levonorgestrel IUS
• Physical Activity
• Pregnancy
• Breastfeeding
Histology

• **Type I**
  - Endometrioid, well differentiated
  - Less aggressive
  - Usually localized
  - Good Prognosis

• **Type II**
  - Clear cell, papillary serous, MMMT (carcinosarcoma), poorly differentiated
  - More aggressive
  - Likely to spread
  - Worse Prognosis
Histology – Molecular Features

Type I
• Diploid
• K-ras overexpression
• PTEN mutations
• Microsatellite instability

Type II
• Aneuploid
• K-ras overexpression
• P53 overexpression
Clinical Presentation

- Abnormal Uterine Bleeding
- Postmenopausal Uterine Bleeding
- Abnormal Vaginal Discharge
- Endometrial cells on a pap smear
- Bloating/pelvic pressure/pain (if advanced disease)
Diagnosis

- Ultrasound
- Endometrial Biopsy
- Hysteroscopy
- Dilation and Curettage

- Hysterectomy +/- BSO +/- Lymph node sampling
Staging

Stage 1A cancer has spread into the ovary

Stage 1B cancer has spread into the vagina

Stage 2: The cancer has grown into the cervix

Stage 3A: The cancer has spread into the ovary

Stage 3B: The cancer has spread into the vagina

Stage 3C: The cancer has spread into the lymph nodes

Stage 4A: The cancer is in the bladder or bowel

Stage 4B: The cancer is in other organs
Endometrial Carcinoma

**CLINICAL FINDINGS**

<table>
<thead>
<tr>
<th>Stage IA (&lt;50% myometrial invasion)</th>
<th>Stage IB (≥50% myometrial invasion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgically staged: Stage Ia</td>
<td></td>
</tr>
<tr>
<td>Adverse risk factors not present</td>
<td>Adverse risk factors not present</td>
</tr>
<tr>
<td>Adverse risk factors present</td>
<td>Adverse risk factors present</td>
</tr>
</tbody>
</table>

**ADVERSE RISK FACTORS**

- Adverse risk factors not present
- Adverse risk factors present

**HISTOLOGIC GRADE/ADJUVANT TREATMENT**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Observe or Vaginal brachytherapy</td>
</tr>
<tr>
<td>G2</td>
<td>Observe or Vaginal brachytherapy and/or EBRT (category 2B for EBRT)</td>
</tr>
<tr>
<td>G3</td>
<td>Observe or Vaginal brachytherapy and/or EBRT</td>
</tr>
</tbody>
</table>

*All staging in guideline is based on updated 2010 FIGO staging. (See ST-1)*

*EBRT and/or Vaginal brachytherapy ± chemotherapy (category 2B for chemotherapy)*
### Therapy – Locally advanced disease

**NCCN Guidelines Version 2.2016**

**Endometrial Carcinoma**

All staging in guideline is based on updated 2010 FIGO staging. *(See ST-1)*

<table>
<thead>
<tr>
<th>CLINICAL FINDINGS</th>
<th>HISTOLOGIC GRADE/ADJUVANT TREATMENT⁶,g,n,o</th>
</tr>
</thead>
</table>
| Surgically staged:⁴  
Stage IIq,r           | Vaginal brachytherapy and/or EBRT         | Vaginal brachytherapy and/or EBRT         | EBRT ± vaginal brachytherapy ± chemotherapy⁵  
(c category 2B for chemotherapy) |
| Surgically staged:⁴  
Stage IIIA      | Chemotherapy ± RT  
or Tumor-directed RT  
± chemotherapy  
or EBRT  
± vaginal brachytherapy | Chemotherapy ± RT  
or Tumor-directed RT  
± chemotherapy  
or EBRT  
± vaginal brachytherapy | Chemotherapy ± RT  
or Tumor-directed RT  
± chemotherapy  
or EBRT  
± vaginal brachytherapy |
Therapy – Metastatic disease

Endometrial Carcinoma

All staging in guideline is based on updated 2010 FIGO staging. (See ST-1)

CLINICAL FINDINGS

Stage IIIB

Stage IIIC1

Pelvic node positive

Stage IIIC2

Para-aortic node positive ± pelvic node positive

Surgically staged: Stage IIIB, IIIC, IV

Debulked¹ and with no gross residual disease or microscopic abdominal disease

Stage IVA, IVB

ADJUVANT TREATMENT⁰,⁹,ⁿ

Chemotherapy and/or tumor-directed RT

Chemotherapy and/or tumor-directed RT

Chemotherapy ± RT
Therapy - Recurrence

- Re-excision
- Radiation
- Systemic Therapies:

**HORMONE THERAPY**
- Megestrol/tamoxifen (alternating)
- Progestational agents
- Aromatase inhibitors
- Tamoxifen

**CHEMOTHERAPY REGIMENS**
- Multi-agent chemotherapy regimens preferred, if tolerated
  - Carboplatin/paclitaxel
  - Cisplatin/doxorubicin
  - Cisplatin/doxorubicin/paclitaxel
- Single agents
  - Cisplatin
  - Carboplatin
  - Doxorubicin
  - Liposomal doxorubicin
  - Paclitaxel
  - Topotecan
  - Bevacizumab
  - Temsirolimus
  - Docetaxel (category 2B)
  - Ifosfamide (for carcinosarcoma)

- Carboplatin/docetaxel
- Ifosfamide/paclitaxel (category 1 for carcinosarcoma)
- Cisplatin/ifosfamide (for carcinosarcoma)
Follow-up

- Regular pelvic examinations
- Symptom awareness
- No role for routine imaging/vaginal cytology
Emerging Therapies

• Sentinel Node Mapping
• Fertility Preservation
• Targeted Therapies
New classification of endometrial cancers - TCGA (endometrioid, serous, mixed)
New classification of endometrial cancers- TCGA (carcinosarcoma)
<table>
<thead>
<tr>
<th>Overall</th>
<th>Immediate?</th>
<th>Future Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reproducible categorization</td>
<td>Characterization of tumours with two or more molecular features</td>
</tr>
<tr>
<td></td>
<td>Stratification of trials: past and future, e.g. GOG 210, PORTEC4a</td>
<td>Modeling: which features (clinical, pathological, IHC)* can be added to molecular classification to improve the ability to discern outcomes</td>
</tr>
<tr>
<td>MMR-D</td>
<td>Referred for hereditary cancer counselling and testing</td>
<td>Health economic implications</td>
</tr>
<tr>
<td></td>
<td>Options in immunotherapy</td>
<td>QoL and patient reported outcomes</td>
</tr>
<tr>
<td>POLE EDM</td>
<td>Options in immunotherapy (for rare recurrence or advanced disease unresponsive to conventional Rx)</td>
<td>Further characterization of predictive and prognostic differences within MMR-D: specific mutations, germline vs. somatic, and epigenetic</td>
</tr>
<tr>
<td>p53 wt</td>
<td>Lower likelihood metastatic disease: hysterectomy/BSO, managed in community (?)</td>
<td>Can adjuvant therapy be withheld? Determination of role of treatment in tumors with POLE EDMs: are favorable outcomes independent of therapy?</td>
</tr>
<tr>
<td>p53 abn</td>
<td>Fertility sparing Rx not recommended</td>
<td>Possible hormonal management/fertility sparing Rx in young women desiring childbearing</td>
</tr>
<tr>
<td></td>
<td>Complete/aggressive surgical staging</td>
<td>What additional parameters* can further direct management within this subgroup?</td>
</tr>
<tr>
<td></td>
<td>High likelihood will require adjuvant chemotherapy +/- radiation</td>
<td>Stratification of clinical trials within molecular subgroup</td>
</tr>
</tbody>
</table>
Uterine Sarcoma

• Epidemiology and Risk Factors
• Histology
• Presentation
• Diagnosis/Staging
• Therapy
• Follow-Up
• Future Therapy
Epidemiology

• Median age ranges is 40s to 50s based on histologic type
• Leiomyosarcomas are more common in black women than white women (age adjusted risk is 1.5 vs 0.9 per 100,000)
Risk Factors

• Prior radiation exposure
• Hormone exposure
  • ESS is the only true contraindication to hormone replacement after surgery for a gynecologic malignancy
• Tamoxifen Use
• Hereditary Predisposition
  • HNPCC/Lynch syndrome
Histology

- Leiomyosarcoma
  - Fleshy
  - Nuclear Atypia
  - Tumor Necrosis

- Endometrial stromal sarcoma
  - Low Grade
  - “Bland”
  - Single mass
  - ER/PR positive
Histology

- Undifferentiated Uterine Sarcoma
  - VERY atypical cells
Presentation

• Abnormal vaginal bleeding
• Abdominopelvic mass
• Incidental diagnosis at the time of hysterectomy
## Diagnosis/Staging

### Staging for uterine sarcomas (leiomyosarcomas, endometrial stromal sarcomas, adenosarcomas, and carcinosarcomas)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor limited to uterus</td>
</tr>
<tr>
<td>IA</td>
<td>&lt; 5 cm</td>
</tr>
<tr>
<td>IB</td>
<td>&gt; 5 cm</td>
</tr>
<tr>
<td>II</td>
<td>Tumor extends to the pelvis</td>
</tr>
<tr>
<td>IIA</td>
<td>Adnexal involvement</td>
</tr>
<tr>
<td>IIB</td>
<td>Tumor extends to extrauterine pelvic tissue</td>
</tr>
<tr>
<td>III</td>
<td>Tumor invades abdominal tissues (not just protruding into the abdomen)</td>
</tr>
<tr>
<td>IIIA</td>
<td>One site</td>
</tr>
<tr>
<td>IIIB</td>
<td>&gt; one site</td>
</tr>
<tr>
<td>IIIC</td>
<td>Metastasis to pelvic and/or para-aortic lymph nodes</td>
</tr>
<tr>
<td>IV</td>
<td>Tumor invades bladder and/or rectum</td>
</tr>
<tr>
<td>IVA</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

### Endometrial stromal sarcomas (ESS) and adenosarcomas

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumor limited to uterus</td>
</tr>
<tr>
<td>IA</td>
<td>Tumor limited to endometrium/endocervix with no myometrial invasion</td>
</tr>
<tr>
<td>IB</td>
<td>Less than or equal to half myometrial invasion</td>
</tr>
<tr>
<td>IC</td>
<td>More than half myometrial invasion</td>
</tr>
<tr>
<td>II</td>
<td>Tumor extends to the pelvis</td>
</tr>
<tr>
<td>IIA</td>
<td>Adnexal involvement</td>
</tr>
<tr>
<td>IIB</td>
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<tr>
<td>III</td>
<td>Tumor invades abdominal tissues (not just protruding into the abdomen)</td>
</tr>
<tr>
<td>IIIA</td>
<td>One site</td>
</tr>
<tr>
<td>IIIB</td>
<td>&gt; one site</td>
</tr>
<tr>
<td>IIIC</td>
<td>Metastasis to pelvic and/or para-aortic lymph nodes</td>
</tr>
<tr>
<td>IV</td>
<td>Tumor invades bladder and/or rectum</td>
</tr>
<tr>
<td>IVA</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>
Therapy

- Endometrial Stromal Sarcoma
  - Observation
  - Hormonal Therapy
  - Consider Radiotherapy

- LMS/UUS
  - Chemotherapy
  - Radiotherapy

- Lots of negative trials... disappointing results
- Most trials have slow accrual due to rarity of tumors
Therapy

Uterine Sarcoma

SYSTEMIC THERAPY FOR UTERINE SARCOMA
(Clinical trials strongly recommended)

Combination regimens:
- Docetaxel/gemcitabine
  (preferred for leiomyosarcoma)
- Doxorubicin/ifosfamide
- Doxorubicin/dacarbazine
- Gemcitabine/dacarbazine
- Gemcitabine/vinorelbine

Single-agent options:
- Dacarbazine
- Doxorubicin
- Epirubicin
- Eribulin
- Gemcitabine
- Ifosfamide
- Liposomal doxorubicin
- Pazopanib
- Temozolomide
- Trabectedin
- Vinorelbine (category 2B)
- Docetaxel (category 3)

HORMONE THERAPY
(For Low-grade ESS or Hormone Receptor Positive (ER/PR) uLMS):
- Medroxyprogesterone acetate
  (category 2B for ER/PR positive uLMS)
- Megestrol acetate
  (category 2B for ER/PR positive uLMS)
- Aromatase inhibitors
- GnRH analogs
  (category 2B for low-grade ESS and ER/PR positive uLMS)
Follow-Up

- Recurrence is common
- Routine exams
- Routine CT scans
- Patient symptom monitoring
Emerging Therapies

• Continued chemotherapy trials
• Biologic therapies
• Numerous genetic mutations in these tumors
  • Targeted therapies
    • Anti-VEGF
    • Multi-kinase inhibitors
    • mTOR inhibitors
Cervical Cancer
Cervical Cancer

- Epidemiology and Risk Factors
- Histology
- Presentation
- Diagnosis
- Staging
- Therapy
  - Early
  - Locally Advanced
  - Metastatic
  - Recurrent
- Follow-Up
- Future Therapy
Epidemiology

- 12,990 cases expected in 2016
  - 7.7 per 100,000 women
- 4,120 deaths expected in 2016
Epidemiology - Global

• In 2015, 526,000 women developed cervical cancer worldwide

• Cervical cancer caused 239,000 deaths
Epidemiology

- HPV infection
- High parity
- Increased number of sexual partners
- Young age at time of first sexual intercourse
- Low socioeconomic status
- History of smoking
- Long-term use of oral contraceptives
- Physical inactivity
Histology

- Squamous
- Adenocarcinoma
- Rare histologies
  - Clear cell
  - Serous
  - Glassy Cell
  - Neuroendocrine
  - Mesenchymal tumors
Pathogenesis
Pathogenesis - HPV

Growth Inhibited Normal Cell

HPV 16/18 Infected Cell
Pathogenesis- HPV

- Cervical cancers arise due to viral inactivation of TP53 and RB tumor suppressors by the HPV E6 and E7 oncoproteins
- TP53 inactivation $\rightarrow$ genomic instability $\rightarrow$ secondary genetic alterations $\rightarrow$ intratumoral heterogeneity
- MYC and RAS play a significant role in cervical cancer
  - Mutant RAS genes are capable of cooperating with HPV in transforming cells
  - Overexpression of MYC has been demonstrated in one-third of early invasive carcinomas and some cervical intraepithelial neoplasia (CIN) 3 lesions
- CDK inhibitor p16 is strikingly upregulated in most cervical dysplasias and cancers
Clinical Presentation

• Post-coital bleeding
• Abnormal uterine bleeding
• Abnormal Pap smear
• Pelvic pain
• Flank pain
• Uncontrolled leakage of urine/stool from vagina
Diagnosis

- Pelvic examination/biopsies
- Cone biopsy
- Chest x-ray
- IVP
- Cystoscopy
- Proctoscopy
Staging

- Clinically staged
- PET CT often used in western countries but not available in the highest prevalence regions of the world

Figure 1. Staging of uterine cervix carcinoma according to FIGO.

http://dx.doi.org/10.1590/S0100-39842007000300014
Therapy

- Stage IA1 – Cone biopsy, hysterectomy
- Stage IA2 – modified radical hysterectomy
- Stage IB and IIA – radical hysterectomy OR pelvic RT
  - Add chemotherapy to RT in IB2 and IIA2
  - Can add to RT in IB1 and IIA1
- Stage IIB to IVA – pelvic RT with chemotherapy
- Stage IVB – systemic chemotherapy/clinical trials
Follow-up

• Psychosocial Support
• Routine exams
• Cytologic testing
Emerging Therapies

• Sentinel Node Mapping
• Fertility Preservation
• Targeted Therapies
Vulvar Cancer
Vulvar Cancer

• Epidemiology and Risk Factors
• Histology
• Presentation / Diagnosis
• Staging
• Therapy
  • Early
  • Locally Advanced
  • Metastatic
• Follow-Up
Epidemiology

- 5,950 cases expected in 2016
- 1,110 deaths expected in 2016
Epidemiology

- Condyloma
- History of squamous dysplasia
- HPV infection in basaloid or warty types
- Common risk factors with cervical cancer
  - Multiple sex partners
  - Early age at initiation of sexual intercourse
  - History of abnormal Pap smears
- HPV associated more common in women < 50 years
- Non-HPV is more common in older women
Histology
Presentation – Early disease

Persistent Irritation
Discoloration
Bleeding
Presentation – Late disease

Severe Pain
Bleeding
Pressure from enlarged masses
Foul odor
Disfigurement
Staging

# Staging

## Table 19.2: Integrated 2009 FIGO and AJCC Staging System for Squamous Cell Carcinoma of the Vulva

<table>
<thead>
<tr>
<th>FIGO</th>
<th>AJCC</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Tumor confined to the vulva</td>
<td></td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>1A</td>
<td>Lesions ≤ 2 cm in size, confined to vulva or perineum and with stromal invasion ≤ 1.0 mm, no nodal metastasis</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>1B</td>
<td>Lesions &gt; 2 cm in size or with stromal invasion &gt; 1.0 mm, confined to the vulva or perineum, with negative nodes</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>II</td>
<td>Tumor of any size with extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus), with negative nodes</td>
<td>T1 or T2</td>
<td>N1-N3</td>
<td>M0</td>
</tr>
<tr>
<td>III</td>
<td>Tumor of any size with or without extension to adjacent perineal structures (1/3 lower urethra, 1/3 lower vagina, anus), with positive inguinal/femoral lymph nodes</td>
<td>T1 or T2</td>
<td>N1a = (i) N1b = (ii)</td>
<td>M0</td>
</tr>
<tr>
<td>IIIA</td>
<td>(i) 1–2 lymph node metastasis(es) (&lt; 5 mm), or (ii) 1 lymph node metastasis (≥ 5 mm)</td>
<td>T1 or T2</td>
<td>N2a = (i) N2b = (ii)</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>(i) 3 or more lymph node metastases (&lt; 5 mm) or (ii) 2 or more lymph node metastases (≥ 5 mm)</td>
<td>T1 or T2</td>
<td>N2c</td>
<td>M0</td>
</tr>
<tr>
<td>IIIC</td>
<td>Positive nodes with extracapsular spread</td>
<td>T1 or T2</td>
<td>N3 = inguinal skin ulceration or fixed nodes</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Tumor invades other regional (2/3 upper urethra, 2/3 upper vagina), or distant structures</td>
<td>T3 = any size, involves upper urethra, bladder, rectum, bone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVA</td>
<td>Tumor invades: (i) upper urethral and/or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bdie, or (ii) fixed or ulcerated inguinal/femoral lymph nodes</td>
<td>T3</td>
<td>M0</td>
<td></td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastasis: includes pelvic nodes</td>
<td>T1, T2 or T3</td>
<td>M1</td>
<td></td>
</tr>
</tbody>
</table>
Therapy – Early

- Local excision (simple or radical)
Therapy – Locally Advanced
Therapy – Metastatic

- Systemic cytotoxic therapy is disappointing
- Targeted therapies are under development
Follow-up

- Psychosocial Support
- Routine exams
Summary

• Risk can be reduced by modifying risk factors
• Most cancers are responsive to front-line therapy
• Management of recurrent disease varies by site of origin/histology but is often sub-optimal
• More discoveries are needed to overcome these diseases