UPDATE IN THE MANAGEMENT OF INVASIVE CERVICAL CANCER

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Anatomy Review......

Invasive Cervical Cancer- Background

- Third most common gynecologic malignancy in the US
  - Incidence 9/100,000
  - 12,000 new cases with 4300 deaths
- Worldwide, cervical cancer is the most common gynecologic malignancy
  - 17.8/100,000
  - In sub-Saharan Africa, Latin-America and south Asia, it is the LEADING cause of cancer related death
Invasive Cervical Cancer-Background

- Causative agent - the HPV virus
  - Now accounts for >95% of all cervical cancers including both adenocarcinoma and squamous subtypes
- Other risk factors
  - Early age of first coitus
  - History of STD infection
  - Immunosuppression
  - Multiple sexual partners

Invasive Cervical Cancer-Background

- HPV vaccine
  - First time in human history we can an intervention to prevent the onset of a cancer
  - Virus-like protein vaccine which prevents infection by HPV strains 16, 18
  - Prevents 70-80% of cervical cancers
  - Also against strains 6 and 8 which is causative agent of genital warts

Indications for Cervical Cancer Vaccine

<table>
<thead>
<tr>
<th>Bivalent HPV vaccine (9-11)</th>
<th>Quadrivalent HPV vaccine (9-11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female aged 9-18 years for the prevention of</td>
<td>Female aged 9-18 years for the prevention of</td>
</tr>
</tbody>
</table>
  - Cervical cancer caused by HPV types 16 and 18  |  - Cervical cancer caused by HPV types 16 and 18  |
  - Cervical intraepithelial neoplasia (CIN) grade 2 in women and adenocarcinoma in situ  |  - Cervical intraepithelial neoplasia (CIN) grade 2 in women and adenocarcinoma in situ  |
  - CIN grade 3 caused by HPV types 16 and 18  |  - CIN grade 3 caused by HPV types 16 and 18  |
  - CIN grade 2 or 3 and cervical adenocarcinoma in situ caused by HPV types 16, 18, and 31  |  - CIN grade 2 or 3 and cervical adenocarcinoma in situ caused by HPV types 16, 18, and 31  |
  - Vulvar intraepithelial neoplasia (VIN) grade 2 and VIN grade 3 caused by HPV types 16, 18, and 31  |  - Vulvar intraepithelial neoplasia (VIN) grade 2 and VIN grade 3 caused by HPV types 16, 18, and 31  |
  - Precancerous cervical lesions caused by HPV types 16, 18, and 31  |  - Precancerous cervical lesions caused by HPV types 16, 18, and 31  |
  - Malignant melanoma of the vulva caused by HPV types 16, 18, and 31  |  - Malignant melanoma of the vulva caused by HPV types 16, 18, and 31  |
  - Cervical intraepithelial neoplasia caused by HPV types 6 and 11  |  - Cervical intraepithelial neoplasia caused by HPV types 6 and 11  |
  - Vulvar intraepithelial neoplasia caused by HPV types 6 and 11  |  - Vulvar intraepithelial neoplasia caused by HPV types 6 and 11  |
Invasive Cervical Cancer

- Most important question to answer is STAGE!
  - Dictates the management plan of surgery vs. chemotherapy/XRT
  - Cervical cancer is staged clinically, not surgically
  - Allows for accurate prognostication in a low income/resource setting
  - Risk stratifies patients who need adjuvant therapy from those who don’t

Appropriate tests used to stage cervical cancer

- Physical exam
- Colposcopy and directed biopsies
- LEEP or Cold Knife Conization
- Intravenous Pyelogram
- Chest X-ray
- Cystoscopy/Proctoscopy

***Note that CT and PET scan are not on this list***

Imaging for cervical cancer

Havrilesky et al performed a meta analysis of 25 studies looking at the sensitivity and specificity of PET scan to detect occult retroperitoneal LN metastases in early stage cervical cancer

- Pooled sensitivity was 84% and specificity was 95% for para-aortic LN metastases
- Pooled sensitivity was 77% and specificity was 99% for pelvic LN metastases

Staging of Cervical Cancer

**TABLE 1. STAGING OF CERVICAL CANCER**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Extent of the disease</th>
<th>Prognosis – 5 yr survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Invasive carcinoma: diagnosed by microscopy</td>
<td>90%</td>
</tr>
<tr>
<td>1a1</td>
<td>Invasion no greater than 3mm depth and 7mm in horizontal spread</td>
<td>80%</td>
</tr>
<tr>
<td>1a2</td>
<td>Invasion more than 3mm and no more than 7mm, depth and 7mm in horizontal spread</td>
<td>70%</td>
</tr>
<tr>
<td>1b</td>
<td>Clinically visible lesion confined to the cervix or microscopically greater than 7mm</td>
<td>60%</td>
</tr>
<tr>
<td>1a1</td>
<td>Clinically visible lesion present in the cervix in greatest dimension</td>
<td>60%</td>
</tr>
<tr>
<td>1b2</td>
<td>Clinically visible lesion present in the cervix in greatest dimension</td>
<td>50%</td>
</tr>
<tr>
<td>2a</td>
<td>Carcinoma extends to the uterus but does not extend to the pelvic wall</td>
<td>40%</td>
</tr>
<tr>
<td>2a1</td>
<td>As above but without parametral spread</td>
<td>30%</td>
</tr>
<tr>
<td>2a2</td>
<td>As above, with parametral spread</td>
<td>20%</td>
</tr>
<tr>
<td>3a</td>
<td>Tumour invades lower third of vagina; no extension to pelvic side wall</td>
<td>10%</td>
</tr>
<tr>
<td>3a1</td>
<td>Tumour extends to pelvic side wall and/or causes hydronephrosis or non-functioning kidney</td>
<td>5%</td>
</tr>
<tr>
<td>3a2</td>
<td>Tumour invades urethra or bladder to rectum or extends beyond pelvis</td>
<td>0%</td>
</tr>
<tr>
<td>4a</td>
<td>Tumour invades urethra or bladder to rectum or extends beyond pelvis</td>
<td>0%</td>
</tr>
<tr>
<td>4b</td>
<td>Tumour invades urethra or bladder to rectum or extends beyond pelvis</td>
<td>0%</td>
</tr>
</tbody>
</table>

Source: Lauren and Herrero (2005)

Invasive Cervical Cancer

- Two general broad categories
  - Nonoperative Candidates
    - Patients with disease > stage IIB
  - Operative candidates
    - Patients with disease < stage IIB

Approach to Early Stage Cervical Cancer

- Microscopic disease (IA1, IA2)
- IA1 disease (<3mm of stromal invasion, <7mm lateral spread)
  - Fertility sparing: Cold knife conization
  - Definitive treatment: Simple hysterectomy
Approach to Early Stage Cervical Cancer

- IA2 disease (between 3-5mm stromal invasion, <7mm lateral spread)
- Radical hysterectomy with pelvic lymph node dissection
- Radical hysterectomy with LND may be performed up to stage IIA (down to upper vagina but not parametrium)

Critical question to ask is whether or not to do surgery?

Critical question to ask is will patient need adjuvant radiotherapy after surgery?

Risks of bowel, bladder complications is significantly higher if patient receives both surgery and radiotherapy.

Is surgery or radiotherapy better?

Landmark trial, Landoni et al
- Randomized 343 patients, IB-IIA to either
  - Radical hysterectomy
  - External beam radiotherapy (pelvic RT)
- 5-year outcome: no difference; Non-bulky: OS surgery 87% vs. RT 90% (NS), DFS surgery 80% vs. 82% (NS)
- AdenoCA: significantly better outcomes with surgery: OS (70% vs. 59%), DFS (66% vs. 47%)
- Complications (Grade 2-3): Surgery 28% vs RT 12% (SS). Severe leg edema surgery 0%, RT 1%, surgery + RT 9%

Approach to Early Stage Cervical Cancer

- If you do surgery, do patients need post operative adjuvant therapy
- And if yes, what do they need?
  - Chemotherapy
  - Radiation
  - Chemotherapy + radiation

Approach to Early Stage Cervical Cancer

- Which patients are at risk for recurrence?
- GOG 49 established certain factors which predisposed patients to recurrence
  - Lymphvascular space invasion
  - Tumor size
  - Depth of stromal invasion

Approach to early stage cervical cancer

- Sedlis et al determined that having 2 of 3 of these increased risk of recurrence to 22% and randomized these patients to observation versus pelvic RT
  - Recurrences in 15% (RT) vs 28% (no RT). 2-year recurrence free rate 88% vs 79%. Hazard ratio=0.53. Grade 3/4 adverse effects were 6% vs 2.1% Distant mets 2% (RT) vs 7% (no RT).

Approach to early stage cervical cancer

- Rotman et al performed a secondary survival analysis for these patients
- Decreased rate of recurrence by 46%; local recurrence 13.9% (RT) vs 20.7% (no RT), distant 2.9% vs 8.6%.
- Improved PFS by 42%. Decreased death rate by 30% (28.6% vs 19.7%) but not S.S. (p=0.07).
- RT has improved benefit for adenocarcinoma or adenosquamous histologies (8.8% vs 44% recurrence).


Adjuvant Therapy for Early Stage Cervical Cancer

- What about adding chemotherapy?
- Peters et al identified post surgical patients who are at risk for recurrence
  - Positive surgical margins
  - Parametrial involvement
  - Positive lymph nodes

Adjuvant Therapy for Early Stage Cervical Cancer

- Peters et al determined that the addition of platinum based chemotherapy (cisplatin) to adjuvant radiotherapy in these patients offered a significant benefit
  - Randomized to RT vs RT+CT. Chemotherapy consisted of cisplatin and 5-FU every 3 weeks x four cycles and adjuvant pelvic RT with peri-aortic boost as needed
  - 4-year OS RT 71% vs CRT 81% (SS); 4-year PFS 63% vs 80%, HR=2.0 (SS). Local failure 17% vs 6%.
  - No difference in outcome based on histology (squamous vs adeno) for patients who underwent chemo-RT

Adjuvant Therapy for Early Stage Cervical Cancer

• Monk et al further validated this in a post-hoc analysis of the Peters trial
• Found a significant benefit to adjuvant chemo+RT but decreased benefit if tumor was <2cm or if only 1 LN was positive

Conclusions

• For IA1 disease proceed with simple hysterectomy
• For IA2-IB1- radical hysterectomy with LND after imaging/pathology precludes the need for adjuvant RT
• IB2-IIA- surgery is feasible but due to bulky disease risk of adjuvant therapy is high—would likely opt for treatment with chemo +RT

Advanced Cervical Cancer

• Generally for stage II and above treatment of choice is chemo+RT
• Chemotherapy consists of Cisplatin 40mg/m2 as radiosensitizer weekly with concomitant pelvic radiotherapy
• For stage IVB disease (distant metastases)
  • Pelvic RT to control symptoms
  • Systemic therapy with carboplatin and taxol
Recurrent Cervical Cancer

- Recurrent cervical cancer is generally NOT curable with survival rates post diagnosis of only 9-12 months
- Although uncommon at initial diagnosis, metastatic disease will develop in 15 to 61 percent women with cervical cancer, usually within the first two years of completing treatment.
- Most important in the recurrent setting is the site of recurrence
  - PET, physical exam and minor operative procedures are vital
  - Local, central recurrence
  - Distant metastases

Recurrent Cervical Cancer

- The only curative procedure for patients with recurrent disease is total pelvic exenteration
  - Removal of all pelvic structures including bladder, uterus, adnexae, rectosigmoid
  - Creation of urostomy with ileal conduit and colostomy
  - Significant morbidity is associated with this procedure—only 50% are successful.

Chemotherapy for Recurrent Cervical Cancer

- For patients who are not surgical candidates and have received radiotherapy; chemotherapy offers some hope
- Monk et al randomized patients to taxol + one of four other drugs to obtain an “optimum doublet” (GOG 204)
  - Cisplatin
  - Vinorelbine
  - Gemcitabine
  - Topotecan

Recurrent Cervical Cancer

- 513 patients randomized to doublets of PC, VC, GC or TC
  - The experimental-to-PC hazard ratios of death were
    - 1.15 (95% CI, 0.79 to 1.67) for VC,
    - 1.32 (95% CI, 0.91 to 1.92) for GC,
    - 1.26 (95% CI, 0.86 to 1.82) for TC.
  - Response rates (RRs) for PC, VC, GC, and TC were
    - 29.1%, 25.9%, 22.3%, and 23.4%,
  - Conclusion:
    - VC, GC TC are not superior to PC for OS analysis. Trend in RR and PFS favors PC.

Current trends in management

- Some preliminary data has shown that adding bevacizumab to current treatment regimens many improve survival in recurrent cervical cancer
  - This intervention, while expensive, may be life saving in patients with recurrent disease not amenable to radiotherapy or surgery

Current trends in management

- Tewari et al designed a study to answer this question
  - 452 patients were randomized in a 1:1 fashion to either receive
    - Cisplatin + Taxol with or without Avastin
    - Taxol +Topotecan with or without Avastin
  - Inclusion criteria were patients with recurrent, progressive or persistent cervical cancer who were NOT candidates for curative surgical therapy
  - Study was powered to show a 30% reduction in risk of death over the non-Avastin arm
Current trends in treatment

• Results
  • Cisplatin + taxol (+/- bev) had a longer progression free survival as compared to Topotecan+ taxol (+/- bev) (HR=1.39, 95% CI 1.09-1.77, p=.01)
  • There was no significant difference in OS
  • With regards to the addition of bevacizumab
    • The addition of bevacizumab to either arm significantly increased OS from 13.3 to 17.7 months (HR=.71, 95% CI .54-.95)
    • Treatment with the platinum based regimen was the most associated with improved overall survival

Conclusions

• The worldwide burden of cervical cancer continues to be high with a significant portion being in the developing world.
• The advent of screening with the Pap test and the development of a vaccine against cervical cancer represents the biggest breakthrough in fighting this disease.
• Early stage cervical cancer (<IIB) should be treated surgically.
• Advances stage cancers should be managed with chemo-radiation.
• There may be a benefit to the addition of bevacizumab to current regimens in the treatment of recurrent or progressive disease.