Tumor Board

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Charlotte, NC

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VERBAL DISCLOSURE

• Rob Coleman: research grant support from AstraZeneca, Merck, Genentech/Roche, Clovis, Novartis, Oncomed, NCCN, NCI

• Erin Crane: No disclosures
Douglas A. Levine, MD
Head, Gynecology Research Laboratory
Attending Surgeon
Memorial Sloan Kettering Cancer Center
VERBAL DISCLOSURE

• I will try not to refer to too many MSK studies when discussing primary debulking surgery (PDS).
Case 1

A 60 year-old presents to you with an CA-125 >1,000, CT scan shows large amount of ascites with bilateral adnexal masses (6 cm and 8 cm). Exam shows extensive disease in the cul de sac. She has no known family history of breast or ovarian cancer.
Case 1 (cont’d)

How would you confirm diagnosis?

(1) Biopsy prior to neoadjuvant chemotherapy
(2) Primary cytoreduction
(3) Diagnostic laparoscopy to assess tumor extent followed by surgery versus chemo based on intraoperative findings
Primary surgical cytoreduction is superior to neoadjuvant chemotherapy and remains the standard of care for women with advanced ovarian cancer.

<table>
<thead>
<tr>
<th></th>
<th>EORTC PDS</th>
<th>EORTC NACT</th>
<th>CHORUS PDS</th>
<th>CHORUS NACT</th>
<th>GOG-182 PDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>336</td>
<td>334</td>
<td>276</td>
<td>274</td>
<td>4312</td>
</tr>
<tr>
<td>Residual (\leq 1) cm</td>
<td>42%</td>
<td>81%</td>
<td>-</td>
<td>-</td>
<td>70%</td>
</tr>
<tr>
<td>No gross residual</td>
<td>19%</td>
<td>51%</td>
<td>15%</td>
<td>35%</td>
<td>23%</td>
</tr>
<tr>
<td>PFS (mos)</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>OS (mos)</td>
<td>29</td>
<td>30</td>
<td>25</td>
<td>23</td>
<td>44</td>
</tr>
</tbody>
</table>

All debulking is not equal: Survival not increase when optimal / CGR rates do after NACT.
NACT will always be required for a subset of patients based on medical co-morbidity or extent of disease, both of which are highly subjective to the board-certified gyn oncologist.

40-50% LAR in optimal PDS

NACT rates should approximate 20-30%
Primary surgical cytoreduction is not possible for all patients and NACT will be required for some.

If you, with or without a little help from your friends (surgical consultants), can remove all disease, in a healthy enough patient, then do it.
Complete gross resection is the goal of primary surgical cytoreduction, but optimal (<1cm) residual disease has a significant survival benefit.

Reproducible and statistically significant 20% increase in PFS and OS between suboptimal and optimal with gross residual disease.
Proper diagnosis is critical to proper treatment and tissue biopsy should be obtained by core needle or laparoscopy if cytoreduction is not performed.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoembryonic antigen elevation and the cancer antigen 125/carcinoembryonic antigen ratio among ovarian versus non-ovarian cancer patients.</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>CA 125 = cancer antigen 125; CEA = carcinoembryonic antigen; CI = 95% confidence interval; NPV = negative predictive value; PPV = positive predictive value.</td>
</tr>
<tr>
<td>CEA &lt; 5 ng/ml</td>
</tr>
<tr>
<td>CA-125/CEA &gt; 25</td>
</tr>
<tr>
<td>CA-125/CEA &gt; 100</td>
</tr>
</tbody>
</table>

2-4% of diagnoses incorrect in EORTC and CHORUS NACT trials.

CA-125/CEA ratio > 25 helpful.

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2016 Annual Winter Meeting

Dan Med Bul 58/11
November 2011
Pre-operative diagnostic laparoscopy can be useful for treatment stratification (PDS/NACT) but is likely dependent on local cytoreduction rates and preference for NACT.

Success of staging LSC is dependent on overall cytoreductive rates and use of NACT.
Case 1 (cont’d)

Would you recommend germline BRCA testing in this patient?
(1) Yes
(2) No
All women with ovarian cancer should be tested for \textit{BRCA1} and \textit{BRCA2} germline mutations.
We have been successful in identifying women at very high risk for ovarian cancer.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group at study entry, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 40</td>
<td>0.30</td>
<td>0.19 to 0.49</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>41-50</td>
<td>0.24</td>
<td>0.17 to 0.33</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>51-60</td>
<td>0.27</td>
<td>0.18 to 0.38</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>≥ 61</td>
<td>0.49</td>
<td>0.31 to 0.76</td>
<td>.002</td>
</tr>
<tr>
<td>Total</td>
<td>0.31</td>
<td>0.26 to 0.38</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Previous breast cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.32</td>
<td>0.26 to 0.39</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>No</td>
<td>0.23</td>
<td>0.13 to 0.39</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Additional ovarian cancer susceptibility genes are being identified but incorporation into clinical practice remains challenging at present.

*BRIP1*: Prevalence in ovarian cancer ~1%
Lifetime risk ~6%
Median age at diagnosis: 64 years

Other risk genes include *RAD51C, RAD51D, BRIP1*
Putative genes include *PALB2* and *BARD1*, but age at onset and lifetime risk are unclear
Case 1 (cont’d)

She undergoes primary optimal tumor reductive surgery consisting of:

- Exploratory laparotomy
- TAH/BSO
- Peritonectomy
- Sigmoid resection and EEA

She has no visible residual disease (R0) at the end of surgery
Case 1 (cont’d)

Postoperatively, what treatment would you recommend?
(1) Dose dense paclitaxel/carboplatin
(2) IP paclitaxel/platinum
(3) Paclitaxel/carboplatin/bevacizumab q 21d
(4) Paclitaxel/carboplatin q 21 day dosing
(5) HIPEC followed by chemotherapy
(6) Other
After primary surgery, women with optimally-debulked FIGO stage III ovarian cancer should be counseled about the clinical benefit associated with combined IV and IP administration of chemotherapy [and] ..... Strong consideration should be given to a regimen containing IP cisplatin [NCI Clinical Alert – 2006].

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Details</th>
<th>Path CR</th>
<th>OS</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 104</td>
<td>IV cyclophosphamide + IV or IP CDDP</td>
<td>36%</td>
<td>41 mos</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>49 mos</td>
<td></td>
</tr>
<tr>
<td>GOG 114</td>
<td>IV Pac + IV CDDP or IV carbo then IV Pac + IP</td>
<td>47%</td>
<td>22.5 mos</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27.6 mos</td>
<td></td>
</tr>
<tr>
<td>GOG 172</td>
<td>IV Pac + IV CDDP or IV/IP Pac + IP CDDP (100)</td>
<td>47%</td>
<td>19.3 mos</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24.3 mos</td>
<td></td>
</tr>
</tbody>
</table>

Courtesy of Paul Sabbatini, MD
Impressive outcomes initially reported for weekly taxol by JGOG, but confirmatory US studies are more difficult to interpret.

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Treatment gp</th>
<th>n</th>
<th>Median PFS (Mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Bev</td>
<td>ddP + Carbo</td>
<td>55</td>
<td>14.2</td>
</tr>
<tr>
<td></td>
<td>q3wkP + Carbo</td>
<td>57</td>
<td>10.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stratum</th>
<th>Tx gp</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Bev</td>
<td>Weekly :Q3wk</td>
<td>0.596</td>
<td>0.369 – 0.958</td>
<td>0.033</td>
</tr>
</tbody>
</table>

Lancet Oncol 2013; 14: 1020–26
Bevacizumab has reproducibly been shown to extend PFS by ~4-6 months with no benefit in OS.

GOG-218

<table>
<thead>
<tr>
<th>Arm</th>
<th>Event, n (%)</th>
<th>Median PFS, months</th>
<th>Stratified analysis HR (95% CI)</th>
<th>One-sided p-value (log rank)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm I</td>
<td>423 (67.7)</td>
<td>10.3</td>
<td>0.908 (0.759–1.040)</td>
<td>0.080&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Arm II</td>
<td>418 (66.9)</td>
<td>11.2</td>
<td>0.717 (0.625–0.824)</td>
<td></td>
</tr>
<tr>
<td>Arm III</td>
<td>360 (57.8)</td>
<td>14.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Control Research

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Median, months</th>
<th>Log-rank test</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>464 (61)</td>
<td>17.4</td>
<td>p=0.039</td>
<td>0.87 (0.77–0.99)</td>
</tr>
<tr>
<td>470 (62)</td>
<td>19.8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Case 1 (cont’d)

Would you recommend maintenance therapy?
(1) Yes
(2) No
Case 1 (cont’d)

If you recommended maintenance therapy, what regimen would you choose?

(1) Maintenance bevacizumab
(2) Maintenance PARPi
(3) Maintenance with a immune-oncology agent (e.g. vaccine or checkpoint inhibitor)
(4) Maintenance monthly paclitaxel
(5) I don’t recommend maintenance therapy as standard of care (and this number better be the same as the last question or you have to go tree skiing with Coleman for half a day)
Most first remission maintenance therapies have historically failed.

<table>
<thead>
<tr>
<th>Intervention</th>
<th>N</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 vs 10 CAP(^1)</td>
<td>78</td>
<td>No benefit OS</td>
</tr>
<tr>
<td>6 vs 12 CAP(^2)</td>
<td>202</td>
<td>No benefit OS</td>
</tr>
<tr>
<td>Epirubicin X 4 vs obs(^3)</td>
<td>162</td>
<td>No benefit OS</td>
</tr>
<tr>
<td>IP CDDP vs obs(^4)</td>
<td>153</td>
<td>No benefit PFS/OS</td>
</tr>
<tr>
<td>IFN-α 3 X week vs obs(^5)</td>
<td>300</td>
<td>No benefit PFS/OS</td>
</tr>
<tr>
<td>Erlotinib(^6)</td>
<td>243</td>
<td>No benefit PFS, OS</td>
</tr>
<tr>
<td>(^{32})IP vs. Obs(^7)</td>
<td>202</td>
<td>No benefit PFS/OS</td>
</tr>
<tr>
<td>CT-2103 vs obs(^8)</td>
<td></td>
<td>Results pending</td>
</tr>
<tr>
<td>Paclitaxel 3 vs 12(^9)</td>
<td>287</td>
<td>7 mos PFS, no OS</td>
</tr>
<tr>
<td>Olaparib vs. obs(^{10})</td>
<td>265</td>
<td>3.6 mos PFS, no OS</td>
</tr>
</tbody>
</table>
Taxol and olaparib appear to be exceptions with reasonable toxicity.

Checkpoint blockade has limited experience in ovarian cancer and limited activity to date.

Recurrent ovarian cancer trials of PD-1 and PD-L1 antibodies
But Doctor...

Which of the following would be your preference for a maintenance strategy on trial?

(1) Angiogenesis
(2) PARP
(3) Vaccine
(4) PD-1/PD-L1
(5) Chemotherapy
(6) Other (and you know we’re going to pick on you)
Case 1 (cont’d)

Would you give maintenance therapy if you had known about the BRCA2 mutation?

(1) Yes
(2) No
Case 1 (cont’d)

If so, what would you have chosen as maintenance in setting of a **BRCA2** mutation?

(1) Maintenance bevacizumab
(2) Maintenance PARPi
(3) Maintenance with a immune-oncology agent (e.g. vaccine or checkpoint inhibitor)
(4) Maintenance monthly paclitaxel
(5) I don’t recommend maintenance therapy as standard of care (and this number better be the same as the last question or you have to go CLIFF skiing with Coleman for half a day)
PARP inhibitors work well in tumors with germline and somatic BRCA1 and BRCA2 tumors through synthetic lethality.
BRCA1 IHC antibodies are notoriously difficult to work with and require biologic positive and negative controls.
There is no good evidence to suggest that patients with BRCA1 loss respond uniquely better to IP chemo.

BRCA mutation carriers consistently have better outcome, before and during the era of IP chemo.

BRCA1 pts were not younger and did not have a better OS with IV chemo.

BRCA1 IHC not well validated or interpreted.

Case 1 (cont’d)

She develops recurrent disease. With regards to molecular profiling (NGS), you would order it:

(1) At the initial time of diagnosis
(2) At the time of recurrence, regardless of platinum sensitivity
(3) At the time of recurrence with platinum-resistant disease
(4) Only having exhausted standard treatment
(5) Never
Molecular profiling for HGSC may be beneficial when clinical trials with targeted agents or off-label use is considered.

Don’t confuse the fancy science of precision medicine with expensive hype.
Do not confuse faith and evidence; nor prognostic and predictive biomarkers.

Stolen from Lisa McShane, PhD
Molecular profiling can take many forms and for HGSC it is generally useless in the clinic, but in the laboratory it is awesome.

Normal (germline) sample is important to determine tumor (somatic) mutations

Data extrapolated from different tumor settings and not validated are not likely to help in clinical care
There are few recurrent somatic mutations in HGSC, but selection through chemotherapy treatment will enrich for resistant subclones.

cDNA has the potential to provide a more rich framework to assess tumor heterogeneity.
In conclusion, PDS remains the standard of care and IP chemotherapy has consistently shown a dramatic survival benefit for resected pts.

Due to intratumoral heterogeneity, molecular profiling should be performed from the most recent (or fresh) sample possible.

All newly diagnosed patients with ovarian cancer should have germline genetic testing for BRCA mutations (SGO position statement; March 2014)

Be wary of molecular profiling for clinical use that has not been properly or fully validated for the intended purpose

Questions?
Case 2

A 28 yo G1 is referred to you for a stage IB1 grade 2 cervical adenocarcinoma on a cone biopsy. Margins are negative, tumor size is 1.5 cm, and LVSI is equivocal. She wants to have another child but wants to do what is best for her.
Case 2 (cont’d)

What treatment would you recommend for her?
(1) Radical hysterectomy + pelvic nodes
(2) Radical trachelectomy + pelvic nodes
(3) Laparoscopic pelvic nodes only
(4) Imaging with no treatment if negative
(5) Surveillance only
Would you refer her to a reproductive endocrinologist?

(1) Yes, regardless of treatment plan
(2) Yes, if offered trachelectomy
(3) Yes, if offered radical hysterectomy
(4) Yes, only if adjuvant radiation was needed
(5) No, because it would not change my recommendation
Case 2 (cont’d)

At the time of lymphadenectomy she is found to have a grossly enlarged pelvic node. Frozen section is positive for carcinoma.
Case 2 (cont’d)

What would you do in the setting of a **positive** node discovered intraoperatively?

1. Proceed with radical hysterectomy, perform oophoropexy
2. Proceed with radical hysterectomy, leave ovaries alone
3. Proceed with radical trachelectomy
4. Abandon surgery, perform oophoropexy
5. Abandon surgery, leave ovaries alone, refer to REI post-op
Fertility Sparing Treatment of Cervical Carcinoma

Stephanie V. Blank, MD
NYU Langone Medical Center
New York, NY
VERBAL DISCLOSURE

• No disclosures
Fertility Sparing Treatment of Cervical Cancer: Rationale

• Almost half of cervical cancer patients are under 45 years of age
• Will be successfully treated and live to experience survivorship
• ASCO: discussion of future fertility is an oncologist’s responsibility
Fertility preservation assessment and discussion algorithm for patients with cancer.

**Assessment of risk for infertility**
Communication with patient

**Patient at risk for treatment-induced infertility**
Patient interested in fertility preservation options*

Refer to specialist with expertise in fertility preservation methods

**Eligible for proven fertility preservation methods**

**Male**
Sperm cryopreservation†

**Female**
Embryo or oocyte cryopreservation
Conservative gynecologic surgery

**Investigational fertility preservation techniques**
Cryopreservation of ovarian or testicular tissue
Others

*Alison W. Loren et al. JCO 2013;31:2500-2510
Radical Trachelectomy

“…dramatic shift from skepticism to acceptance”

Wethington et al, IJCS, 23(6) 2013
#### Cervical Cancer

<table>
<thead>
<tr>
<th>CLINICAL STAGE</th>
<th>PRIMARY TREATMENT (FERTILITY SPARING)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IA1 (no lymphovascular space invasion [LVS1])</td>
<td>Cone biopsy with negative margins (preferably a non-fragmented specimen with 3-mm negative margins) (if positive margins, repeat cone biopsy or perform tracheectomy)</td>
</tr>
<tr>
<td>Stage IA1 (with LVS1) and Stage IA2</td>
<td>Cone biopsy with negative margins (preferably a non-fragmented specimen with 3-mm negative margins) (if positive margins, repeat cone biopsy or perform tracheectomy) + pelvic lymph node dissection ± para-aortic lymph node sampling (category 2B) (Consider sentinel lymph node [SLN] mapping [category 2B])</td>
</tr>
<tr>
<td>Stage IB1</td>
<td>Radical tracheectomy + pelvic lymph node dissection ± para-aortic lymph node sampling</td>
</tr>
</tbody>
</table>

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**Footnotes:**
- **d** Fertility-sparing surgery for stage IB1 has been most validated for tumors ≤2 cm. Small cell neuroendocrine histology and adenoma malignum are not suitable tumors for this procedure.
- **e** No data support a fertility-sparing approach in small cell neuroendocrine tumors or minimal deviation adenocarcinoma (also known as adenoma malignum) or small cell neuroendocrine tumors. Hysterectomy after completion of childbearing is at the patient’s and surgeon’s discretion, but is strongly advised in women with continued abnormal pap smear, positive HPV infection, positive margins and proper orientation are obtained.
- **g** Negative for invasive disease or histologic high-grade squamous intraepithelial lesion (HSIL) at margins.
- **h** See Principles of Evaluation and Surgical Staging (CERV.A)
Radical Trachelectomy

- Ability to retain fertility
- Removal of cervix, parametrium, pelvic lymph nodes while sparing the fundus
- Lower uterine segment reconnected to vagina
- Cerclage may be placed
Radical Trachelectomy Candidates

• Desire to retain fertility
  – age cut off (?)
• Stage IA2 or IB1
• Tumors ≤ 2 cm
  – Larger tumors (?)
• NED beyond cervix
• No high risk histology (?)

Wethington et al, IJGC 2013
Preoperative Assessment

Pelvic MRI if macroscopic tumor

- T2-weighted sagittal view
- Speak with your radiologist
- Nodes, extracervical disease
- Assess length of endocervical canal
- Assess endocervical extension of tumor
- Relationship proximal margin of tumor to isthmus
Preoperative Assessment

REI evaluation for realistic expectations

• Current fertility potential
• Future fertility potential
• Frank discussion about pregnancy risk
• Alternatives
Intraoperative Assessment

• Notify pathology preoperatively
• Frozen section on nodes
• Frozen section on specimen
  – longitudinal measurements
  – 10 mm (5mm?)
• Frozen section on ECC
• Separate endocervical margin
Should we measure the success of fertility sparing surgery via oncologic or fertility outcomes?
Radical Trachelectomy Outcomes

- Recurrence rate same as for comparably-sized lesions treated with radical hysterectomy
- Factors associated with recurrence: lesion size >2cm, LVSI but not adenocarcinomas
- Fertility outcomes are in fertility language

Marchiole P et al, Gyn Onc, 2007
Plante M IJGC 2013
Radical Trachelectomy: Oncologic Outcomes

Vaginal Approach

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Fertility Not Preserved</th>
<th>Recurrences</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanowiska et al (2011)</td>
<td>225</td>
<td>13 (6%)</td>
<td>8 (3.8%)</td>
<td>4 (1.9%)</td>
</tr>
<tr>
<td>Shepherd et al (2012)</td>
<td>208</td>
<td>24 (11.5%)</td>
<td>8 (3.8%)</td>
<td>5 (2.4%)</td>
</tr>
<tr>
<td>Covens et al (2013)*</td>
<td>180</td>
<td>17 (9.4%)</td>
<td>9 (2.7%)</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Helpman et al (2011)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plante et al (2011)</td>
<td>140</td>
<td>15 (10.7%)</td>
<td>6 (4.8%)</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>Marchiolo et al (2007)</td>
<td>135</td>
<td>17 (12.6%)</td>
<td>7 (5.7%)</td>
<td>5 (4.2%)</td>
</tr>
<tr>
<td>Kim et al (2012)</td>
<td>51</td>
<td>9 (17.6%)</td>
<td>2 (3.9%)</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>924</td>
<td>95 (10.2%)</td>
<td>40 (4.4%)</td>
<td>19 (2.1%)</td>
</tr>
</tbody>
</table>

*Personal communication, updated information, January 2013.

Abdominal Approach

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Fertility Not Preserved</th>
<th>Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wethington et al (2012)*</td>
<td>101</td>
<td>30 (30%)</td>
<td>4 (4%)†</td>
</tr>
<tr>
<td>Nishio et al (2009)</td>
<td>71</td>
<td>10 (14%)</td>
<td>6 (10%)‡‡</td>
</tr>
<tr>
<td>Li et al (2011)*</td>
<td>64</td>
<td>12 (19%)</td>
<td>0</td>
</tr>
<tr>
<td>Muraji et al (2012)*</td>
<td>23</td>
<td>3 (13%)</td>
<td>0</td>
</tr>
<tr>
<td>Saso et al (2012)*</td>
<td>30</td>
<td>0</td>
<td>3 (10%)††</td>
</tr>
<tr>
<td>Pareja et al (2008)*</td>
<td>15</td>
<td>1 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Ungar et al (2005)*</td>
<td>33</td>
<td>3 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>337</td>
<td>59 (17%)</td>
<td>13 (3.7%)</td>
</tr>
</tbody>
</table>

†Two patients alive with disease, 2 no evidence of disease (NED).
‡Three patients NED, 3 lost to follow-up.
§Five of 6 recurrences: lesions ≥2 cm.
||Two patients died of disease, 1 NED.

Includes series already published from Memorial Sloan-Kettering Cancer Center (Abu-Rustum), the Czech Republic (Cibula) and the Massachusetts General Hospital (Duska).
Radical Trachelectomy: Fertility Outcomes

Vaginal Approach

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>&lt;32 wk</th>
<th>32-36.6 wk</th>
<th>&gt;37 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shepherd et al (2012)</td>
<td>125</td>
<td>27</td>
<td>18</td>
<td>73</td>
<td>14</td>
<td>26</td>
<td>33</td>
</tr>
<tr>
<td>Plante et al (2011)</td>
<td>106</td>
<td>21</td>
<td>3</td>
<td>77</td>
<td>11</td>
<td>15</td>
<td>58</td>
</tr>
<tr>
<td>Covens*</td>
<td>86</td>
<td>14</td>
<td>7</td>
<td>65</td>
<td>11</td>
<td>11</td>
<td>43</td>
</tr>
<tr>
<td>Helpman et al (2011)</td>
<td>60</td>
<td>5</td>
<td>3</td>
<td>45</td>
<td>12</td>
<td>10</td>
<td>43</td>
</tr>
<tr>
<td>Speiser et al (2003)</td>
<td>56</td>
<td>9</td>
<td>8</td>
<td>34</td>
<td>2</td>
<td>3</td>
<td>29</td>
</tr>
<tr>
<td>Mathevet et al (2003)</td>
<td>19</td>
<td>1</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>452</td>
<td>77</td>
<td>39</td>
<td>309</td>
<td>43</td>
<td>67</td>
<td>199</td>
</tr>
</tbody>
</table>

The percentage in bold represents the percentage of term delivery of patients reaching the third trimester.
*Personal communication, January 2013.

Abdominal Approach

- About 1/3 of 337 attempted pregnancy
- 44 pregnancies = 13% of trachelectomy pts or 39% of trach pts pursuing fertility

Plante M et al, IJGC 2013
Conservative Surgery?

- 60-65% of radical trachelectomy specimens have no residual disease after a diagnostic cone

- In patients with favorable pathologic characteristics, <1% have parametrial involvement on radical hysterectomy specimens
Parametrial Involvement

- 350 patients who underwent radical hysterectomy
- 27 patients (7.7%) had parametrial involvement
- Subgroup of 125 patients:
  - Tumor < 2 cm
  - No LVSI
  - Negative pelvic lymph nodes
  - Parametrial involvement = 0%

Frumovitz M et al. Obstet Gynecol 2009
Could we get away with a cone and lymph nodes?

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Low-risk criteria</th>
<th>N</th>
<th>Parametrial involvement in low-risk group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinney [13]</td>
<td>1995</td>
<td>Squamous histology only, tumor &lt; 2 cm, no LVSIs**</td>
<td>83</td>
<td>0.0%</td>
</tr>
<tr>
<td>Covens [14]</td>
<td>2002</td>
<td>All histologies, tumor &lt; 2 cm, DOI** &lt; 10 mm, negative pelvic lymph nodes</td>
<td>536</td>
<td>0.6%</td>
</tr>
<tr>
<td>Stegeman [15]</td>
<td>2007</td>
<td>Squamous, adenocarcinoma, adenosquamous or clear cell histology, tumor &lt; 2 cm, DOI** &lt; 10 mm, no LVSIs**, negative pelvic lymph nodes</td>
<td>103</td>
<td>0.0%</td>
</tr>
<tr>
<td>Wright [16]</td>
<td>2008</td>
<td>All histologies, tumor &lt; 2 cm, no LVSIs**, negative pelvic lymph nodes</td>
<td>270</td>
<td>0.4%</td>
</tr>
<tr>
<td>Frumovitz [19]</td>
<td>2009</td>
<td>Squamous, adenocarcinoma or adenosquamous histology, tumor &lt; 2 cm, no LVSIs**</td>
<td>125</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

*LVSIs: lymphvascular space involvement
**DOI: depth of invasion

Italian series- 2/37 recurred

Maneo et al Gyn Onc 2011
Schmeler et al Gyn Onc 2011
ConCerv Trial

- Patients desiring future fertility undergo cone and pelvic lymph node dissection
- Patients not desiring future fertility undergo simple hysterectomy and pelvic lymph node dissection

NCT01048853
**ConCerv Trial**

**Inclusion Criteria:**
- Stage IA2 or IB1 cervical cancer
- Tumor diameter ≤ 2 cm
- No LVSI
- ≤ 10 mm stromal invasion
- Squamous cell histology (any grade) or adenocarcinoma (grade 1 or 2 only)
- Cone margins and ECC negative for malignancy or CIN/AIS (one repeat cone/ECC permitted)
SHAPE Trial

Simple Hysterectomy And Pelvic node dissection in Early cervix cancer

Comparing radical hysterectomy and pelvic node dissection against simple hysterectomy and pelvic node dissection in patients with low risk cervical cancer

Chair: Marie Plante
University of Laval, Quebec City

Gynecological Cancer Inter Group
(GCIG)
Patient Population
Stage IA2-IB1 Cervix cancer
Squamous, Adeno & Adenosquamous ca
< 2cm and < 50% stromal invasion
Grades 1, 2 & 3
MR/ CT node negative

RANDOMIZATION

Stratification
Centers (SN mapping vs not)
Mode of surgery (abd vs vaginal)
Stage (IA2 vs IB1)
Histology (squamous vs adenocarcinoma)
Grade (1-2 vs 3)

Control Arm
Radical Hysterectomy & PLND* +/- SLN Mapping**

Experimental Arm
Simple Hysterectomy with Upper Vaginectomy & PLND* +/- SLN Mapping**

Post surgical quality of life & disease outcomes measured 3 monthly X 2 years, and 6 monthly for further 3 yrs

* PLND – Pelvic lymph node dissection
**SLN – Sentinel lymph node mapping optional
Should we measure the success of fertility sparing surgery via oncologic or fertility outcomes? QOL?
Gynecologic Oncologists and Oncofertility

1. Do we answer the whole question or just one part?
2. Counseling is everything.
3. How do we counsel patients with these type of data knowing that counseling is everything?