Neo-adjuvant chemotherapy and fertility sparing surgery for stage IB1 cervix cancer (2-4 cm)

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Jeffrey Goh & Vivek Arora (ANZGOG)
**NCCN Guidelines Version 2.2015**

**Cervical Cancer**

### CLINICAL STAGE

<table>
<thead>
<tr>
<th>Stage IA1 (no lymphovascular space invasion [LVSI])</th>
<th>Cone biopsy(^e) with negative margins (preferably a non-fragmented specimen with 3-mm negative margins) (If positive margins, repeat cone biopsy or perform trachelectomy)</th>
<th>See Surveillance (CERV-10)</th>
</tr>
</thead>
</table>

| Stage IA1 (with LVSI) and Stage IA2 | Cone biopsy\(^e\) with negative margins (preferably a non-fragmented specimen with 3-mm negative margins; if positive margins, repeat cone biopsy or perform trachelectomy) + pelvic lymph node dissection ± para-aortic lymph node sampling (category 2B) (Consider sentinel lymph node [SLN] mapping [category 2B])\(^f\) or Radical trachelectomy + pelvic lymph node dissection\(^f\) (± para-aortic lymph node sampling [category 2B]) (Consider SLN mapping [category 2B])\(^f\) | See Surveillance (CERV-10) |

| Stage IB1\(^c\) | Radical trachelectomy + pelvic lymph node dissection\(^f\) ± para-aortic lymph node sampling (Consider SLN mapping [category 2B])\(^f\) | See Surveillance (CERV-10) |

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\(^d\) Fertility-sparing surgery for stage IB1 has been most validated for tumors ≤2 cm. Small cell neuroendocrine histology and adenoma malignum are not considered 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). Total hysterectomy after completion of childbearing is at the patient’s and surgeon’s discretion, but is strongly advised in women with continued abnormal pap smears or chronic persistent HPV infection.

\(^f\) Cold knife conization (CKC) is the preferred method of diagnostic excision, but loop electrosurgical excision procedure (LEEP) is acceptable, provided adequate margins and proper orientation are obtained.

\(^g\) See Principles of Evaluation and Surgical Staging (CERV-A).

\(^h\) For SLN mapping (category 2B), the best detection rates and mapping results are in tumors <2 cm.

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**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
NACT and Fertility Sparing

How to best manage women with larger size lesions / bulky IB1-IB2 (2-4 cm)

- Preservation of fertility and ovarian function
- Oncologic outcome
- Obstetrical outcome
NACT and Fertility Sparing

Management options for patients with larger size lesions

• Upfront Radical Trachelectomy
• NACT followed by fertility-preserving surgery (FPS)
## Upfront ART: lesions > 2 cm

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Fertility spared</th>
<th>Node Positivity</th>
<th>Recurrences</th>
<th>Pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wethington, 2013</td>
<td>29</td>
<td>9 (31%)</td>
<td>13 (45%) *</td>
<td>1/29 (11%)</td>
<td>1/3</td>
</tr>
<tr>
<td>Lintner, 2013</td>
<td>45</td>
<td>31 (69%)</td>
<td>13 (29%)</td>
<td>4/31 (13%) **</td>
<td>4/8</td>
</tr>
<tr>
<td>Liu, 2013</td>
<td>62</td>
<td>55 (89%)</td>
<td>6 (9.8%)</td>
<td>0</td>
<td>3/9</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>136</td>
<td>95 (70%)</td>
<td>32 (24%)</td>
<td>5/122 (5.3%)</td>
<td>8/20 (40%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8/95 (8.9%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8/136 (5.8%)</td>
</tr>
</tbody>
</table>

**MSKCC:** SLN mapping and ultra staging

**Hungarian series:** 14 ptes who had rad hyst excluded from analysis

**Plante M. Internat J Gynecol Cancer 2015 May;25(4):722-8.**
Indications for adjuvant RT

<table>
<thead>
<tr>
<th>LVSI</th>
<th>Stromal Invasion</th>
<th>Tumor Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Deep 1/3</td>
<td>Any</td>
</tr>
<tr>
<td>Positive</td>
<td>Middle 1/3</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Negative</td>
<td>Superficial 1/3</td>
<td>&gt; 5</td>
</tr>
<tr>
<td>Negative</td>
<td>Deep or Middle 1/3</td>
<td>&gt; 4</td>
</tr>
</tbody>
</table>

Sedlis criteria: needing 2 or more of these factors
- LVSI involvement
- Deep stromal invasion (middle or deep third)
- Size > 4 cm
Abdominal Trachelectomy

- Upfront ART technically feasible in bulky stage I cervical cancer
- Oncologic outcome good
- Obstetric outcome limited
- High rate of adjuvant Tx post trachelectomy
  - Impact on fertility and ovarian function
  - Impact on QoL
NACT + FPS

NACT option followed by fertility-preserving surgery (FPS)
Neoadjuvant chemotherapy

Pre-chemo

Post-chemo
## NACT + fertility preserving surgery

<table>
<thead>
<tr>
<th>Patient</th>
<th>Chemotherapy Regimen</th>
<th>Procedure</th>
<th>Optimal Response to NACT (CR + OPR)</th>
<th>Node Positivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maneo</td>
<td>TIP x 3</td>
<td>LPLND + cone</td>
<td>17/21 (81%)</td>
<td>2</td>
</tr>
<tr>
<td>Plante</td>
<td>TIP x 3</td>
<td>LPLND + RVT</td>
<td>3/3 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Marchiole</td>
<td>TIP/TEP x 3</td>
<td>LPLND + RVT</td>
<td>4/7 (57%)</td>
<td>0</td>
</tr>
<tr>
<td>Lanowska</td>
<td>TIP/TP x 2-3</td>
<td>LPLND + RVT</td>
<td>14/18 (78%)</td>
<td>2</td>
</tr>
<tr>
<td>Robova</td>
<td>CI q 10d x 3, CA q 10d x 3</td>
<td>LPLND + SVT</td>
<td>17/28 (61%)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>77</strong></td>
<td></td>
<td><strong>55/77 (71%)</strong></td>
<td><strong>6/77 (7.8%)</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Recurrences</th>
<th>Death</th>
<th>Fertility Preserved</th>
<th>Pregnancy/Attempted</th>
<th>Pregnancy Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maneo</td>
<td>0</td>
<td>0</td>
<td>16/21 (76%)</td>
<td>10/9</td>
<td>1 FTM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 preterm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 SVD (term)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 CS (term)</td>
</tr>
<tr>
<td>Plante</td>
<td>0</td>
<td>0</td>
<td>3/3 (100%)</td>
<td>4/3</td>
<td>1 FTM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 preterm , 2 term</td>
</tr>
<tr>
<td>Marchiole</td>
<td>0</td>
<td>0</td>
<td>6/7 (86%)</td>
<td>1/1</td>
<td>1 ongoing</td>
</tr>
<tr>
<td>Lanowska</td>
<td>1/18 (5.5%)</td>
<td>0</td>
<td>17/18 (94%)</td>
<td>7/5</td>
<td>1 FTM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 ectopic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 ongoing</td>
</tr>
<tr>
<td>Robova</td>
<td>4/20 (20%)</td>
<td>2/20 (10%)</td>
<td>20/28 (71%)</td>
<td>13/10</td>
<td>1 FTM</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 STM</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>2 ongoing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 preterm, 2 term</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All in suboptimal responders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5/69 (7.2%)</td>
<td>2/69 (2.9%)</td>
<td>62/77 (80%)</td>
<td>35/28</td>
<td>11 FT loss (31%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11 preterm (31%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13 term (37%)</td>
</tr>
</tbody>
</table>

NACT + fertility preserving surgery

- Substantial response to NACT
  - CR/OPR: 71%
- Recurrence rate
  - Worrisome in suboptimal responders
- Fertility preservation high: 80%
- Obstetrical outcome: good
Unresolved issues

未经授权 lymph node dissection prior to NACT？
未经授权 Radical vs simple trachelectomy vs cone post NACT？
未经授权 Best chemotherapy regimen？
NACT + fertility preserving surgery

Should a staging lymph node evaluation be done prior to NACT?
NACT + fertility preserving surgery

Advantage of LN staging

- Allows triaging of pts with metastatic disease
- Option of non-surgical treatment (CT/RT)

Disadvantage of LN staging

- Exclude some patients with minimal LN involvement who might have cleared the LN metastasis with NACT
NACT + fertility preserving surgery

Should a radical or a simple trachelectomy (cone) be done post NACT?
NACT + fertility preserving surgery

Simple / radical trachelectomy / cone

- Very little data available
- Trend towards less radical surgery in small volume cervical cancer (< 2 cm)
NACT + fertility preserving surgery

In good chemotherapy responders

- Node negative patients
- Minimal / no residual disease post NACT
  - Gyn exam & MRI
- The chances of finding occult parametrial infiltration are probably very low
- Simple trach / cone sufficient?
NACT + fertility preserving surgery

Optimal chemotherapy regimen
Optimal chemotherapy regimen

☞ Taxol / Ifosfamide / Platinum (TIP)
  - Most widely used regimen
  - Toxicity of triple chemo regimen
  - Ifosfamide (alkylating agent)
    - gonadotoxicity
Optimal chemotherapy regimen

🔗 Systematic review

- 17 studies / 1181 patients
- Recurrent or metastatic cervical cancer
- Comparing cisplatin and carbo + taxol
- Conclusion: carboplatin represents a valid and less toxic alternative compared to cisplatin

Optimal chemotherapy regimen

A randomized, phase III trial of paclitaxel plus carboplatin (TC) versus paclitaxel plus cisplatin (TP) in stage IVb, persistent or recurrent cervical cancer: Japan Clinical Oncology Group study (JCOG0505) (n=253)

Taxol 175 & Carbo AUC 5 q 3 wks
- Non-inferior in terms of OS
- More feasible
- Less toxic

Kitagawa R et al. J Clin Oncol. 2015 Mar
Optimal chemotherapy regimen

- Dose-dense NACT chemo regimen
  - Weekly Taxol/Carbo
    - Taxol 60-80 mg/m2 and Carbo AUC 2
  - Locally advanced cervical cancer
  - Objective response rate (complete & partial)
    - Ranges from 68-87%

Optimal chemotherapy regimen

Another dose-dense chemo regimen

- Taxol 80mg/m2 weekly (d 1, 8, 15)
- Carbo AUC 6 q 3 weeks (d 1)
- JGOG 3016 trial in ovarian cancer

Chemotherapy regimen

- Taxol
- Ifosfamide
- Cis Platinum

- Taxol
- Cis Platinum

- Taxol
- Carbo Platinum

- Dose Dense Taxol-Carbo
  - Weekly TC
  - Weekly Taxol/3W Carbo
Optimal chemotherapy regimen

Adding GnRHa during chemo?

- Breast cancer data suggest a benefit of adding goserelin with chemotherapy
- Protect against ovarian failure
- Reduce the risk of early menopause
- Improve prospects for fertility

Cervical cancer size 2-4 cm
MRI - corpus negative, node negative
Pathology - Squamous and adenocarcinoma
LYSI - negative or positive
Patient age < 40 years
Desires of preserving fertility
Baseline QLQ-C30, QLQ-CX24 (baseline and 6 months post treatment)

Laparoscopy
transperitoneal / extraperitoneal
pelvic lymph node dissection

SLN mapping
(optional)

Node positive

Node negative

Chemoradiation

Baseline AMH, FSH,
E2 levels (baseline and 6 / 12 months post Rx)

3 cycles of NACT
Carboplatin / Cisplatin +
Paclitaxel weekly

After 3 cycles
Clinical assessment
and pelvic MRI

No response / progression

Complete response
after 3 cycles

Partial response >50% after 3 cycles

Suboptimal response
< 50% after 3 cycles or residual tumor > 2 cm

Chemoradiation

Trachelectomy
Simple / modified radical
glandular / abdominal / laparoscopic

Trachelectomy
Modified radical
glandular / abdominal / laparoscopic

Consider chemoradiation

Adjuvant chemoradiation
Positive margins
Stromal involvement in outer 1/2
≥ 5 mm stromal invasion
< 10 mm margin
Outcome measures

- **Primary end point**
  - Successful *fertility preservation* defined as intact uterine corpus with no adjuvant XRT

- **Secondary end points**
  - Response rates to chemotherapy
  - Toxicity
  - Proportion requiring trimodality treatment
  - QoL indices / Ovarian function indices
  - 3 and 5 year disease free survival
Phase II: Sample Size

- **All cases**
  - N = 100
  - 20% nodes +

- **NACT**
  - N = 80
  - 30% SO response

- **FPS**
  - N = 56