NCCN Framework for resource stratification of cervical cancer treatment

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NCCN Framework for resource stratification of cervical cancer treatment:
Goals

• To make NCCN guidelines relevant in a global oncology community

• To provide recommendations of care, adapted from the NCCN institutional standards, for cervical cancer patients in regions where resources are constrained to variable levels
Global Burden of Cervical Cancer

Numbers indicate cases per 100,000 population
Bill & Melinda Gates Foundation (www.gatesfoundation.org)
NCCN Framework for resource stratification of cervical cancer treatment: Process

- Built on methodology developed by the BHGI
- Conceptually introduced at NCCN guidelines panel chair meeting March 2014
- Small working group meeting Oct 2014
- Further development, with review by full cervical guidelines panel Feb 2015
- Original framework presented and web-published Mar 2015
- International review and input
- Updated 2016 version web-published
NCCN Framework for resource stratification of cervical cancer treatment: Development guiding principles

• Current NCCN Guidelines are written for maximum resource settings (NCCN member institutions)

• As one moves from maximum → enhanced → core → basic, there is a decrease in availability of very technical, expensive, and high-maintenance options. For example:
  • Diagnostic modalities – PET/CT, MRI, CT
  • Surgical approaches – pelvic exenteration, sentinel node evaluation, extensive nodal dissection, trachelectomy
  • Radiation facilities, especially brachytherapy
  • Extensive systemic targeted or cytotoxic therapy options
  • Uneven capacity/capability within each resource level – eg good surgeon, no radiotherapy.

• Note that resource-constrained sites may come up with innovative approaches not typically used at NCCN member institutions
NCCN Framework for resource stratification of cervical cancer treatment: Development guiding principles

- Aspirational – sites/providers should seek to provide the highest available level of care. Over time, individual sites may attain higher resource availability

- Pragmatism
  - Critical ‘life-changing’ step(s), versus incremental gain
  - Maintain humility and learn from ‘boots-on-the-ground’ caregivers
  - To avoid ‘dilution’ of recommendations, and prevent justification of convenience/expedience over complex optimal care – eg. brachytherapy
  - Where have you gone, brachytherapy? (Petereit et al, JCO Feb 2015)
• In general, category 3 recommendations are removed (for < maximal level)
• Recognize that the level of resources required to achieve measurable success depends on the stage and extent of disease
  • a specific facility may have variable capability to treat different patients (eg. cone or simple hysterectomy for very early stage tumors, but not for advanced disease)
• Take into account not just the availability of resources, but also how best to allocate such resources
  • Eg. Limited radiotherapy or chemotherapy, and how these can be used for maximal gain/survival benefit
• While there is a general decrease in recommended options, there are ‘new’ options that reflect specific approaches used in resource-constrained setting
## NCCN FRAMEWORK DEFINITIONS*

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic</td>
<td>This level includes essential services needed to provide basic minimal standard of care</td>
</tr>
<tr>
<td>Core</td>
<td>This level includes services provided in the Basic Resources Framework plus additional services that provide major improvements in disease outcomes (e.g. survival) and that are not cost prohibitive.</td>
</tr>
<tr>
<td>Enhanced</td>
<td>This level includes services provided in the Core Resources Framework and additional services that provide lesser improvements in disease outcomes and/or services that provide major improvements in disease outcomes but are cost prohibitive in lower resource settings.</td>
</tr>
<tr>
<td>NCCN Guidelines</td>
<td>The parent NCCN Guidelines® are evidence-based, consensus-driven recommendations made by the NCCN Guidelines panels. They include services from the Enhanced Level and additional services that provide minor improvements in disease outcomes, interventions that are cost prohibitive at lower resource levels, and/or services that do not provide improvement in disease outcomes but are desirable services.</td>
</tr>
</tbody>
</table>

The NCCN Framework™ is represented as follows:

Black Text: Included recommendation
(at each resource level)

Gray Text: Withheld recommendation
(preserving the context of the parent NCCN guidelines)

*Italicized Blue Text: Modified recommendation based on resource level
(including specific/innovative approaches not typically used at NCCN member institutions)*
NCCN Framework for resource stratification of cervical cancer treatment: 2016 updates

• Remove fertility sparing treatment options at basic and core levels

• Simplify management options following incidental finding of invasive cancer after simple hysterectomy at basic and core levels
  • Most are already cured

• Recognize limitations of aggressive interventions and chemotherapy for recurrent/metastatic disease at basic level
WORKUP

- H&P
- Complete blood count (CBC) (including platelets)
- Cervical biopsy, pathologic review
- Cone biopsy as indicated\(^a\)
- LFT/renal function studies
- Imaging\(^b\) (optional for ≤ stage IB1):
  - Chest x-ray
  - CT or PET-CT scan
  - MRI as indicated
- Smoking cessation and counseling intervention if indicated
- Consider HIV testing (category 3)
  - Optional:
    - EUA cystoscopy/proctoscopy\(^c\) (≥ stage IB2)

CLINICAL STAGE

Stage IA1

Stage IA2
Stage IB1

Stage IIA1

Stage IB2
Stage IIA2

Stage IIB
Stage IIIA, IIB
Stage IVA

Incidental finding of invasive cancer at simple hysterectomy → See Treatment (CERV-9)

\(^a\)See Discussion for indications for cone biopsy.

\(^b\)CT and MRI performed with contrast throughout the guidelines unless contraindicated. Contrast not required for screening chest CT.

\(^c\)For suspicion of bladder/bowel involvement, cystoscopy/proctoscopy with biopsy is required.

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

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.
WORKUP

- H&P
- Complete blood count (CBC) (including platelets)
- Cervical biopsy, pathologic review
- Cone biopsy as indicated
- LFT/renal function studies
- Imaging (optional for ≤ stage IB1):
  - Chest x-ray
  - CT or PET-CT scan
  - MRI as indicated
- Smoking cessation and counseling intervention if indicated
- Consider HIV testing (category 3)

Optional:
- EUA cystoscopy/proctoscopy (≥ stage IB2)

CLINICAL STAGE

Stage IA1
- See Primary Treatment (Fertility Sparing) (CERV-2)

Stage IA2
- See Primary Treatment (Non-Fertility Sparing) (CERV-3)
- See Primary Treatment (Fertility Sparing) (CERV-2)

Stage IB1
- See Primary Treatment (Non-Fertility Sparing) (CERV-3) and (CERV-4)

Stage IIA1
- See Primary Treatment (Non-Fertility Sparing) (CERV-4)

Stage IB2
- See Primary Treatment (CERV-4) and (CERV-6)

Stage IIA2
- See Primary Treatment (CERV-4) and (CERV-6)

Stage IIB
- See Primary Treatment (CERV-4)
- See Primary Treatment (CERV-6)

Stage IIIA, IIIB

Stage IVA

Incidental finding of invasive cancer at simple hysterectomy
- See Treatment (CERV-9)

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

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See Discussion for indications for cone biopsy.

CT and MRI performed with contrast throughout the guidelines unless contraindicated. Contrast not required for screening chest CT.

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Note: This is the NCCN Framework for Resource Stratification of NCCN Guidelines. For definitions of the NCCN Framework™, see page FR-1.

All recommendations are category 2A unless otherwise indicated.

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WORKUP

- H&P
- Complete blood count (CBC) (including platelets)
- Cervical biopsy, pathologic review
- Cone biopsy as indicated³
- LFT/renal function studies
- Imagingᵇ (optional for ≤ stage IB1):
  - Chest x-ray
  - CT if available
  - CT or PET-CT scan
  - MRI as indicated
- Smoking cessation and counseling intervention if indicated
- Consider HIV testing (category 3)
- Optional:
  - EUA cystoscopy/proctoscopy⁶ (≥ stage IB2)

CLINICAL STAGE

- Stage IA1
- Stage IA2
- Stage IB1
- Stage IIA1
- Stage IB2
- Stage IIA2
- Stage IIB
- Stage IIIA, IIB
- Stage IVA

- Incidental finding of invasive cancer at simple hysterectomy

See Primary Treatment (Fertility Sparing) (CERV-2)

See Primary Treatment (Non-Fertility Sparing) (CERV-3)

See Primary Treatment (Fertility Sparing) (CERV-2)

See Primary Treatment (Non-Fertility Sparing) (CERV-3) and (CERV-4)

See Primary Treatment (Non-Fertility Sparing) (CERV-4)

See Primary Treatment (CERV-4) and (CERV-6)

See Primary Treatment (CERV-4) and (CERV-6)

See Primary Treatment (CERV-6)

See Treatment (CERV-9)

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

³See Discussion for indications for cone biopsy.
⁶CT and MRI performed with contrast throughout the guidelines unless contraindicated. Contrast not required for screening chest CT.
⁶For suspicion of bladder/bowel involvement, cystoscopy/proctoscopy with biopsy is required.

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WORKUP

- H&P
- Complete blood count (CBC) (including platelets)
- Cervical biopsy, pathologic review
- Cone biopsy as indicated\(^a\)
- LFT/renal function studies
- Imaging\(^b\)
  (optional for ≤ stage IB1):
  - Chest x-ray
  - CT or PET-CT scan
  - MRI as indicated
- Smoking cessation and counseling intervention if indicated
- Consider HIV testing (category 3)
  Optional:
  - EUA cystoscopy/proctoscopy\(^c\)
    (≥ stage IB2)

CLINICAL STAGE

- Stage IA1
- Stage IA2
- Stage IB1
  - See Primary Treatment (Fertility Sparing) (CERV-2)
  - See Primary Treatment (Non-Fertility Sparing) (CERV-3)
- Stage IIA1
- Stage IB2
- Stage IIA2
- Stage IIB
- Stage IIIA, IIIB
  - See Primary Treatment (CERV-4) and (CERV-5)
- Stage IVA
- Incidental finding of invasive cancer at simple hysterectomy
  - See Treatment (CERV-9)

\(^a\)See Discussion for indications for cone biopsy.

\(^b\)CT and MRI performed with contrast throughout the guidelines unless contraindicated. Contrast not required for screening chest CT.

\(^c\)For suspicion of bladder/bowel involvement, cystoscopy/proctoscopy with biopsy is required.

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

**Cervical Cancer**

**NCCN Framework™: Enhanced Resources**

#### Clinical Stage

**Biopsy Results**

- **Negative margins and inoperable**
  - Observe
  - See Surveillance (CERV-10)

- **Negative margins and operable**
  - Extrafascial hysterectomy\(^h\)
  - Extrafascial or modified radical hysterectomy + pelvic lymph node dissection if margins positive for carcinoma\(^h\) (category 2B for node dissection) (Consider SLN mapping [category 2B])\(^h\)
  - or
  - Consider repeat cone biopsy\(^f\) to better evaluate depth of invasion
  - See Surgical Findings (CERV-5)

- **Positive margins for dysplasia or carcinoma**
  - Modified radical hysterectomy + pelvic lymph node dissection\(^h\)
  - ± para-aortic lymph node sampling (category 2B) (Consider SLN mapping [category 2B])\(^h\)
  - or
  - Pelvic RT\(^{ij,k}\) + brachytherapy\(^lm\)
  - See Surveillance (CERV-10)

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**Stage IA1 (no LVS1)**

- Cone biopsy\(^f\)

**Stage IA1 (with LVS1) and Stage IA2**

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\(^f\) 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.

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

\(^i\) Radiation can be an option for medically inoperable patients or those who refuse surgery.

\(^j\) See Principles of Radiation Therapy for Cervical Cancer (CERV-B).

\(^k\) These doses are recommended for most patients based on summation of conventional external-beam fractionation and low-dose rate (40–70 cGy/h) brachytherapy equivalents. Modify treatment based on normal tissue tolerance, fractionation and size of target volume. (See Discussion)

\(^m\) The traditional dose would be 70-80 Gy to total point A dose.

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Note: This is the NCCN Framework for Resource Stratification of NCCN Guidelines. For definitions of the NCCN Framework™, see page FR-1.

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.
**NCCN Guidelines Version 1.2016**  
**Cervical Cancer**  
**NCCN Framework™: Basic Resources**

### CLINICAL STAGE

#### BIOPSY RESULTS

- **Negative margins and inoperable**
  - Observe
  - See Surveillance (CERV-10)

- **Negative margins and operable**
  - Extracervical hysterectomy
    - Extracervical or modified radical hysterectomy
      - + pelvic lymph node dissection if margins positive for carcinoma
        - (category 2B for node dissection)
        - (Consider SLN mapping [category 2B])
      - or
      - Consider repeat cone biopsy to better evaluate depth of invasion
      - See Surgical Findings (CERV-5)

- **Positive margins for dysplasia or carcinoma**
  - Extracervical hysterectomy
    - Modified radical hysterectomy
      - + pelvic lymph node dissection
      - ± para-aortic lymph node sampling (category 2B)
      - (Consider SLN mapping [category 2B])
      - or
      - Pelvic RT
      - + brachytherapy
      - See Surveillance (CERV-10)

#### Stage IA1 (no LVS1)

- Cone biopsy

#### Stage IA1 (with LVS1)

- Stage IA1

#### Stage IA2

- Positive margins for dysplasia or carcinoma

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*Extracervical hysterectomy if resources are unavailable for modified radical hysterectomy.*

*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.*

*See Principles of Evaluation and Surgical Staging (CERV-A).*

*Radiation can be an option for medically inoperable patients or those who refuse surgery.*

*See Principles of Radiation Therapy for Cervical Cancer (CERV-B).*

*These doses are recommended for most patients based on summation of conventional external-beam fractionation and low-dose rate (40–70 cGy/h) brachytherapy equivalents. Modify treatment based on normal tissue tolerance, fractionation and size of target volume. (See Discussion)*

*The traditional dose would be 70-80 Gy to total point A dose.*

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**NCCN Guidelines Version 1.2016**

**Cervical Cancer**

**NCCN Framework™: Enhanced Resources**

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<thead>
<tr>
<th>CLINICAL STAGE</th>
<th>ADDITIONAL WORKUP</th>
<th>PRIMARY TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IB2, IIA2*&lt;sup&gt;*&lt;/sup&gt; (See CERV-4 for alternative recommendations for these patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIB, IIIA, IIIB, IVA</td>
<td>Radiologic imaging only</td>
<td>pelvic RT&lt;sup&gt;k&lt;/sup&gt; + concurrent cisplatin-containing chemotherapy&lt;sup&gt;n&lt;/sup&gt; + brachytherapy&lt;sup&gt;k&lt;/sup&gt; (category 1)</td>
</tr>
</tbody>
</table>
| | Positive adenopathy | Consider needle biopsy  
See Imaging Results (CERV-7) |
| | Negative adenopathy | pelvic RT<sup>k</sup> + concurrent cisplatin-containing chemotherapy<sup>n</sup> + brachytherapy<sup>k</sup> (category 1) |
| | Surgical staging (category 2B): Extraperitoneal or laparoscopic lymph node dissection | |
| | Negative | See Node Status (CERV-8) |
| | Positive | See Node Status (CERV-8) |

*For Stage IB2, Stage IIA2, See CERV-4.

<sup>k</sup>See Principles of Radiation Therapy for Cervical Cancer (CERV-8).

<sup>n</sup>Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.

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Clinical Stage

Stage IB2, Stage IIA2*
(See CERV-4 for alternative recommendations for these patients)
Stage IIB, IIIA, IIB, IVA

Additional Workup

- Negative adenopathy
  - Radiologic imaging only
  - Positive adenopathy

Primary Treatment

- Pelvic RT\(^k\) + concurrent cisplatin-containing chemotherapy\(^n\) + brachytherapy\(^k\)
  (category 1)

  If radiation and/or brachytherapy unavailable:
  - Neoadjuvant chemotherapy\(^f\)
  - Followed by radical hysterectomy (if feasible)\(^h\)
  - Or
  - Neoadjuvant pelvic RT\(^k\) ± concurrent chemotherapy\(^f\) + radical hysterectomy (if feasible)\(^h\)
  - Or
  - If brachytherapy and surgery unavailable:
    - Pelvic RT\(^k\) ± chemotherapy\(^f\)

- Consider needle biopsy

Surgical Staging (category 2B): Extraperitoneal or laparoscopic lymph node dissection

- Negative
  - Pelvic RT\(^k\) + concurrent cisplatin-containing chemotherapy\(^n\) + brachytherapy\(^k\)
    (category 1)

  - See Node Status (CERV-8)

- Positive
  - See Imaging Results (CERV-7)

*For Stage IB2, Stage IIA2, See CERV-4.

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

See Principles of Radiation Therapy for Cervical Cancer (CERV-B).

Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.

See Chemotherapy Regimens for Recurrent or Metastatic Cervical Cancer (CERV-D).

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### SURGICAL FINDINGS

- **Negative nodes, negative margins, negative parametrium**
  
  - Observe
  
  or
  
  - Pelvic RT\textsuperscript{a} if combination of high-risk factors (i.e., primary tumor size, stromal invasion, and/or LVI that meet Sedlis criteria\textsuperscript{a} [category 1])
  
  - \( \pm \) concurrent cisplatin-based chemotherapy\textsuperscript{a}
  
  - category 2B for chemotherapy

- **Positive pelvic nodes and/or Positive surgical margin and/or Positive parametrium**
  
  - Observe
  
  - Pelvic RT\textsuperscript{a} \( \pm \) concurrent cisplatin-containing chemotherapy\textsuperscript{a}
  
  - (category 1)
  
  - \( \pm \) vaginal brachytherapy\textsuperscript{a}

- **Para-aortic lymph node positive by surgical staging**
  
  - Chest CT or PET-CT scan

  - **Negative for distant metastasis**
    
    - Para-aortic lymph node RT\textsuperscript{a} \( \pm \) concurrent cisplatin-containing chemotherapy\textsuperscript{a}
    
    - pelvic RT\textsuperscript{a}
    
    - \( \pm \) brachytherapy\textsuperscript{a}

  - **Positive for distant metastasis**
    
    - **Negative**
      
      - Consider biopsy of suspicious areas as indicated
    
    - **Positive**
      
      - Systemic therapy\textsuperscript{b} \( \pm \) individualized RT\textsuperscript{a}

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\textsuperscript{a}See Principles of Radiation Therapy for Cervical Cancer (CERV-B).

\textsuperscript{b}Concurrent cisplatin-based chemotherapy with RT utilizes cisplatin as a single agent or cisplatin plus 5-fluorouracil.

\textsuperscript{c}Risk factors may not be limited to the Sedlis criteria. See Sedlis Criteria (CERV-C).

\textsuperscript{d}See Chemotherapy Regimens for Recurrent or Metastatic Cervical Cancer (CERV-D).

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Recognize that persistent/recurrent disease is almost never curable, regardless of intervention.
CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC CERVICAL CANCER†
(Strongly consider clinical trial)

First-line combination therapy††
- Cisplatin/paclitaxel/bevacizumab⁵ (category 1)
- Cisplatin/paclitaxel (category 1)²,³
- Topotecan/paclitaxel/bevacizumab⁴ (category 1)
- Carboplatin/paclitaxel⁴,⁵ (Category 1 for patients who have received prior cisplatin therapy)
- Carboplatin/paclitaxel/bevacizumab
- Cisplatin/topotecan⁶
- Topotecan/paclitaxel
  - Cisplatin/gemcitabine (category 3)†

Possible first-line single-agent therapy
- Cisplatin (preferred as a single agent)³
- Carboplatin⁸
- Paclitaxel⁹

Second-line therapy†††
(Agents listed are category 2B unless otherwise noted)
- Bevacizumab
- Albumin-bound paclitaxel
- Docetaxel
- 5-FU (5-fluorouracil)
- Gemcitabine
- Ifosfamide
- Irinotecan
- Mitomycin
- Pemetrexed
- Topotecan
- Vinorelbine

†Cisplatin, carboplatin, docetaxel, and paclitaxel may cause drug reactions (See NCCN Guidelines for Ovarian Cancer—Management of Drug Reactions [OV-C]).
††Cost and toxicity should be carefully considered when selecting an appropriate regimen for treatment.
†††References for second-line therapy are provided in the Discussion.
CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC CERVICAL CANCER

(Strongly consider clinical trial)

First-line combination therapy
- Cisplatin/paclitaxel/bevacizumab\(^1\) (category 1)
- Cisplatin/paclitaxel (category 1)\(^2,3\)
- Topotecan/paclitaxel/bevacizumab\(^1\) (category 1)
- Carboplatin/paclitaxel\(^4,5\) (Category 1 for patients who have received prior cisplatin therapy)
- Carboplatin/paclitaxel/bevacizumab
- Cisplatin/topotecan\(^6\)
- Topotecan/paclitaxel
- Cisplatin/gemcitabine (category 3)\(^7\)

Possible first-line single-agent therapy
- Cisplatin (preferred as a single agent)\(^3\)
- Carboplatin\(^8\)
- Paclitaxel\(^9\)

Second-line therapy\(^{†††}\)
(Agents listed are category 2B unless otherwise noted)
- Bevacizumab
- Albumin-bound paclitaxel
- Docetaxel
- 5-FU (5-fluorouracil)
- Gemcitabine
- Ifosfamide
- Irinotecan
- Mitomycin
- Pemetrexed
- Topotecan
- Vinorelbine

*Other cytotoxic agents may be considered based on availability.
†Cisplatin, carboplatin, docetaxel, and paclitaxel may cause drug reactions [See NCCN Guidelines for Ovarian Cancer—Management of Drug Reactions [OV-C]].
††Cost and toxicity should be carefully considered when selecting an appropriate regimen for treatment.
†††References for second-line therapy are provided in the Discussion.
Emphasis on best supportive care in this situation, at this level
NCCN Framework for resource stratification of cervical cancer treatment: Conclusions

• Widely vetted, and found to be acceptable and useful

• Routine updates, based on
  – Scientific and clinical advances
  – Efforts to increase global resources for cancer care
  – Synchronization with ‘parent’ guidelines

• Opportunity for collaboration, knowledge sharing, and policy development