Evolving Treatment Strategies for Cervical Cancer

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Memorial Sloan Kettering Cancer Center

National Comprehensive Cancer Network®

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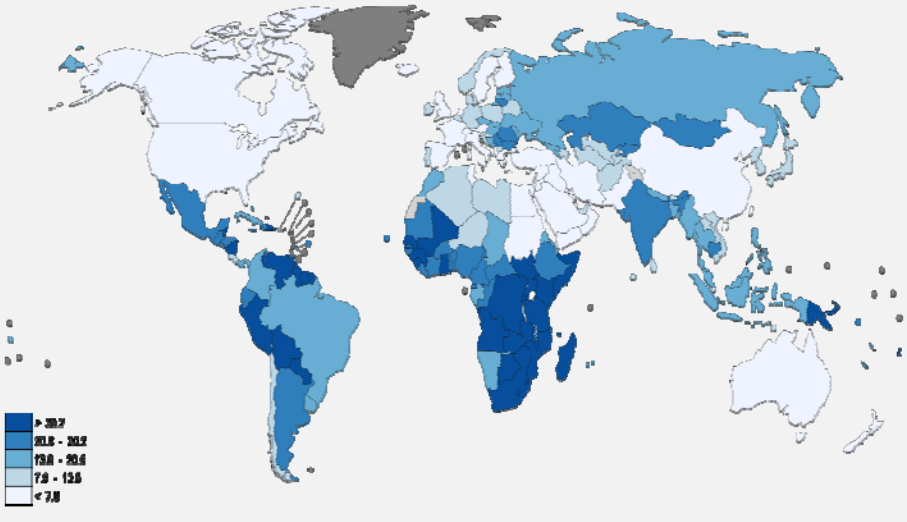
Evolving Treatment Strategies

1. Surgery
2. Radiation
3. Chemotherapy

Incidence of cervix cancer

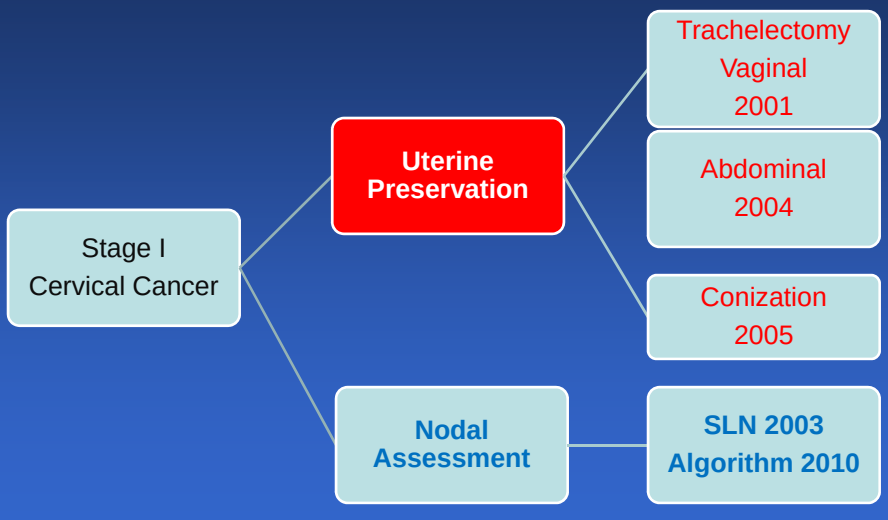


Surgery Generally for Stage I Cervical Cancer
FIGO stage IB1 (2-3cm adenoca)

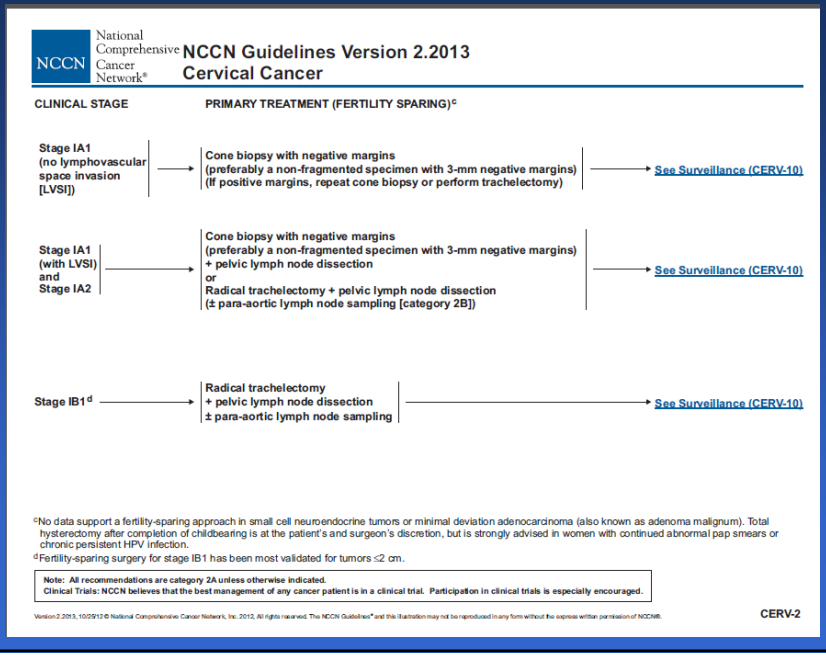
Surgical Questions in Cervical Cancer 2016

1. Decrease radicality of resections
2. Sentinel lymph node (SLN) mapping
3. Neoadjuvant chemotherapy (area of active research not in NCCN guidelines)
   - Pre-Fertility sparing surgery
   - Pre-Radical hysterectomy
4. Improving QOL
   - Nerve Sparing Radical Hysterectomy
   - Minimally invasive surgery vs. Open
5. Surgical Staging in Advanced Stage

Changes in Surgical Approach Stage I 2001-2016



2013 NCCN Guidelines



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NCCN Guidelines Version 2.2013
Cervical Cancer

CLINICAL STAGE	PRIMARY TREATMENT (FERTILITY SPARING)[c]	
Stage IA1 (no lymphovascular space invasion [LVSI])	Cone biopsy with negative margins (preferably a non-fragmented specimen with 3-mm negative margins) (If positive margins, repeat cone biopsy or perform trachelectomy)	See Surveillance (CERV-10)
Stage IA1 (with LVSI) and Stage IA2	Cone biopsy with negative margins (preferably a non-fragmented specimen with 3-mm negative margins) + pelvic lymph node dissection or Radical trachelectomy + pelvic lymph node dissection (± para-aortic lymph node sampling [category 2B])	See Surveillance (CERV-10)
Stage IB1[d]	Radical trachelectomy + pelvic lymph node dissection ± para-aortic lymph node sampling	See Surveillance (CERV-10)

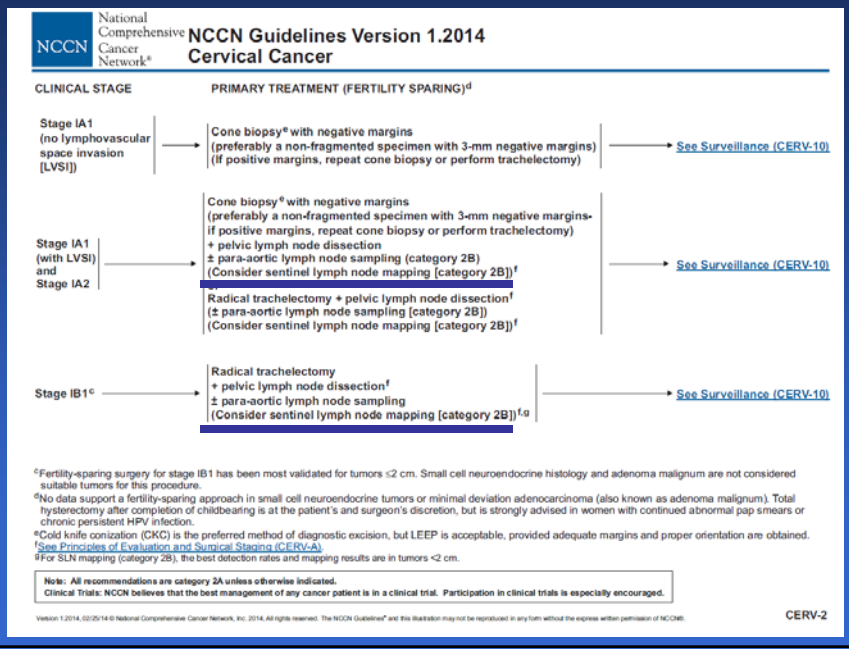
[c]No data support a fertility-sparing approach in small cell neuroendocrine tumors or minimal deviation adenocarcinoma (also known as adenoma malignum). Total hysterectomy after completion of childbearing is at the patient's and surgeon's discretion, but is strongly advised in women with continued abnormal pap smears or chronic persistent HPV infection.

[d]Fertility-sparing surgery for stage IB1 has been most validated for tumors ≤2 cm.

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.

CERV-2

2014 NCCN Guidelines



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NCCN Guidelines Version 1.2014
Cervical Cancer

CLINICAL STAGE	PRIMARY TREATMENT (FERTILITY SPARING)[d]	
Stage IA1 (no lymphovascular space invasion [LVSI])	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)	See Surveillance (CERV-10)
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 mapping [category 2B])[f] or Radical trachelectomy + pelvic lymph node dissection[f] (± para-aortic lymph node sampling [category 2B]) (Consider sentinel lymph node mapping [category 2B])[f]	See Surveillance (CERV-10)
Stage IB1[c]	Radical trachelectomy + pelvic lymph node dissection[f] ± para-aortic lymph node sampling (Consider sentinel lymph node mapping [category 2B])[f,g]	See Surveillance (CERV-10)

[c]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.

[d]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.

[e]Cold knife conization (CKC) is the preferred method of diagnostic excision, but LEEP is acceptable, provided adequate margins and proper orientation are obtained.

[f]See Principles of Evaluation and Surgical Staging (CERV-A)

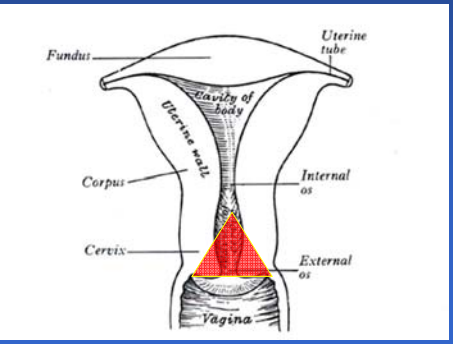
[g]For SLN mapping (category 2B), the best detection rates and mapping results are in tumors <2 cm.

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.

CERV-2

Stage IA1 No Lymphovascular Invasion (LVI)

- Can be treated with Cone
- Review Pathology



Abu-Rustum. Atlas of Procedures in Gynecologic Oncology

Stage IA1 with LVI

SLN Mapping & Conization

SLN mapping is Category 2B recommendation

"Less is more…."

Sentinel lymph node (SLN)

Abu-Rustum. Atlas of Procedures in Gynecologic Oncology

SENTICOL Study

- 139 patients
- Intraoperative radioisotope-blue dye mapping detected at least one SLN in 98%, 23 of whom had true-positive results and two who had false-negative results, yielding 92.0% sensitivity and 98.2% NPV.
- No false-negative results were observed in the 104 patients (76.5%) in whom SLN were identified bilaterally.
- SLN biopsy was fully reliable only when SLNs were detected bilaterally.

Lecuru F. JCO 2011

MSKCC SLN Mapping Algorithm (Category 2B)

- 122 patients were included. Median SLN count was 3 and median total LN count was 20.
- At least one SLN was identified in 93%
- Optimal (bilateral) mapping was achieved in 75% of cases.
- SLN correctly diagnosed 21 of 25 patients with nodal spread.
- When the algorithm was applied, all patients with LN metastasis were detected
- With optimal mapping, bilateral pelvic LND could have been avoided in 75% of cases.

Cormier B. et al. Gynecol Oncol 2011

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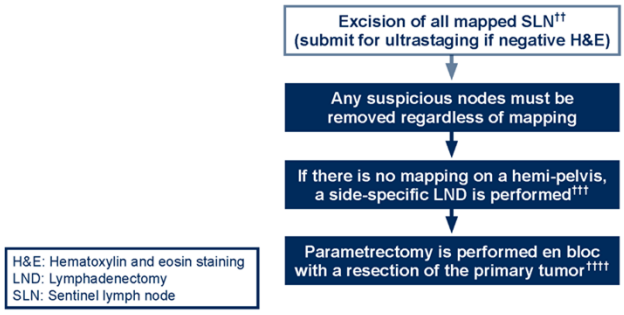
Cervical Cancer

PRINCIPLES OF EVALUATION AND SURGICAL STAGING WHEN SLN MAPPING IS USED

The key to a successful SLN mapping (category 2B) is the adherence to the SLN algorithm, which requires the performance of a side-specific nodal dissection in cases of failed mapping and removal of any suspicious or grossly enlarged nodes regardless of mapping (Figure 3).

Figure 3: Surgical/SLN Mapping Algorithm for Early-Stage Cervical Cancer†



†Reproduced with permission from Cormier B, Diaz JP, Shih K, et al. Establishing a sentinel lymph node mapping algorithm for the treatment of early cervical cancer. Gynecol Oncol. 2011 Aug;122:275-280.
††Intracervical injection with dye, 99m technetium, or both.
†††Including interiliac/subaortic nodes.
††††Exceptions made for select cases (see CERV-A 1 of 7).

CERV-A
4 of 7

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NCCN Guidelines Version 1.2016
Cervical Cancer

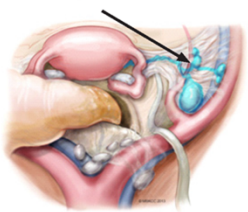
PRINCIPLES OF EVALUATION AND SURGICAL STAGING

Sentinel Lymph Node Mapping for Cervical Cancer:

- **SLN mapping as part of the surgical management of select stage I cervical cancer is considered in gynecologic oncology practices worldwide. While this technique has been used in tumors up to 4 cm in size, the best detection rates and mapping results are in tumors less than 2 cm. This simple technique utilizes a direct cervical injection with dye or radiocolloid Technetium-99 (99Tc) into the cervix, usually at 2 or 4 points as shown in Figure 1 (below). The SLNs are identified at the time of surgery with direct visualization of colored dye, a fluorescent camera if indocyanine green (ICG) was used, or a gamma probe if 99Tc was used. SLNs following a cervical injection are commonly located medial to the external iliac vessels, ventral to the hypogastric vessels, or in the superior part of the obturator space (Figure 2). SLNs usually undergo ultrastaging by pathologists, which allows for higher detection of micrometastasis that may alter postoperative management.**

Figure 1: Options of SLN Cervical Injection Sites†

Figure 2: SLNs (blue, arrow) After Cervical Injection Are Commonly Located Medial to the External Iliac, Ventral to the Hypogastric, or in the Superior Part of the Obturator Space†

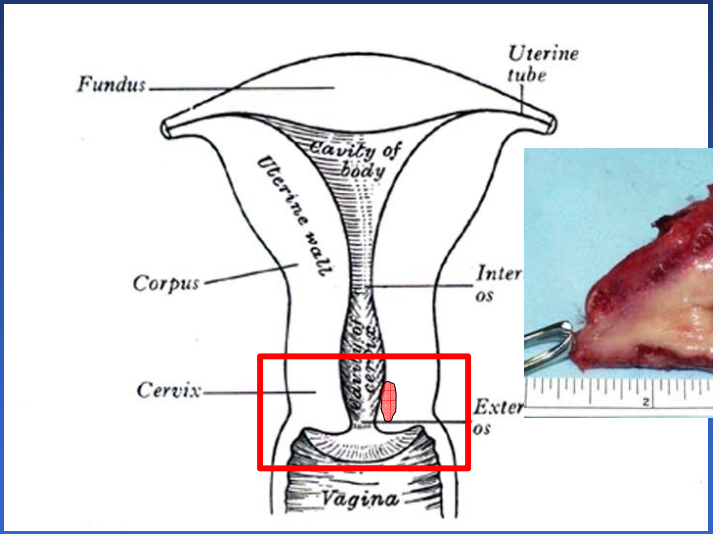


†Figures 1 and 2 are reproduced with permission from Memorial Sloan Kettering Cancer Center. © 2013 Memorial Sloan Kettering Cancer Center.

CERV-A
3 of 7

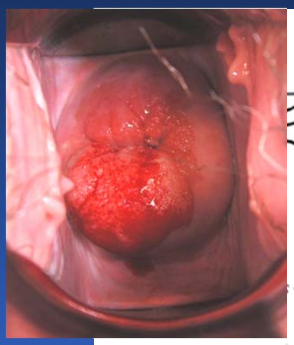
Stage IA2

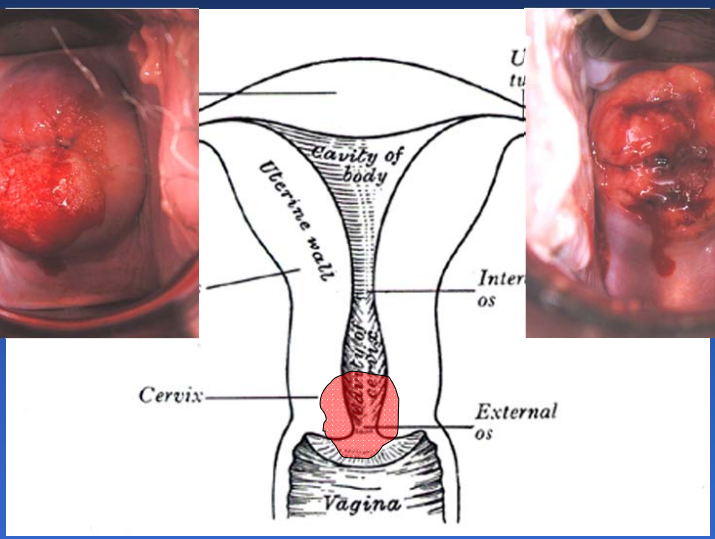
cancer invasion is 3-5 mm deep and < 7 mm wide

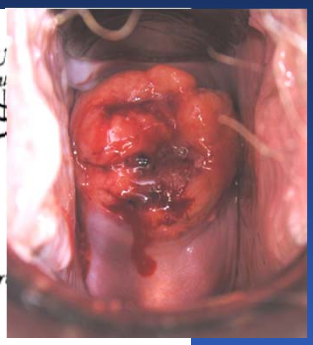


Abu-Rustum. Atlas of Procedures in Gynecologic Oncology

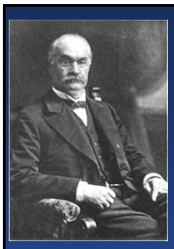
Stage IB1



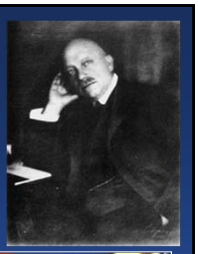


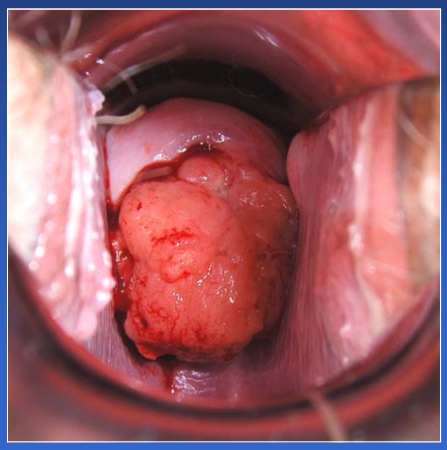


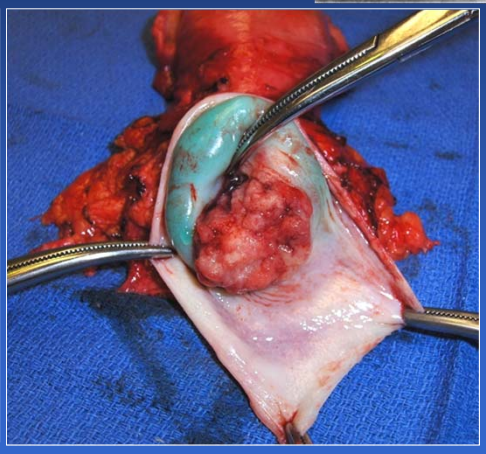
Abu-Rustum. Atlas of Procedures in Gynecologic Oncology



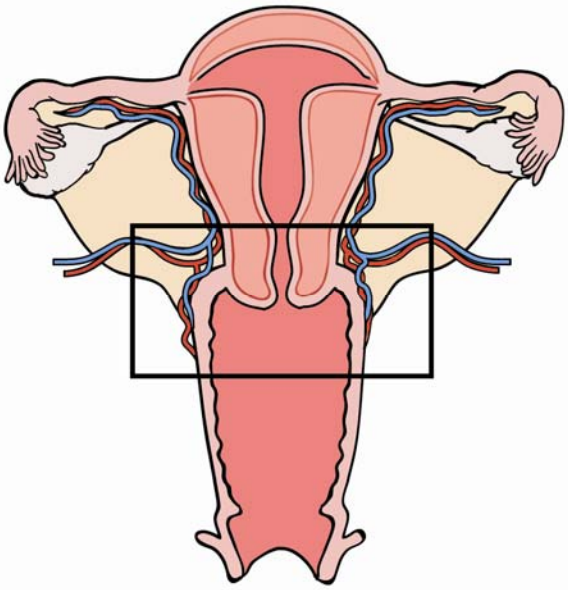
- Radical Abdominal (Wertheim) Hysterectomy
- Radical Vaginal (Schauta) Hysterectomy
- Complete Bilateral Pelvic Lymphadenectomy
  +/- Paraaortic Lymph Node Sampling



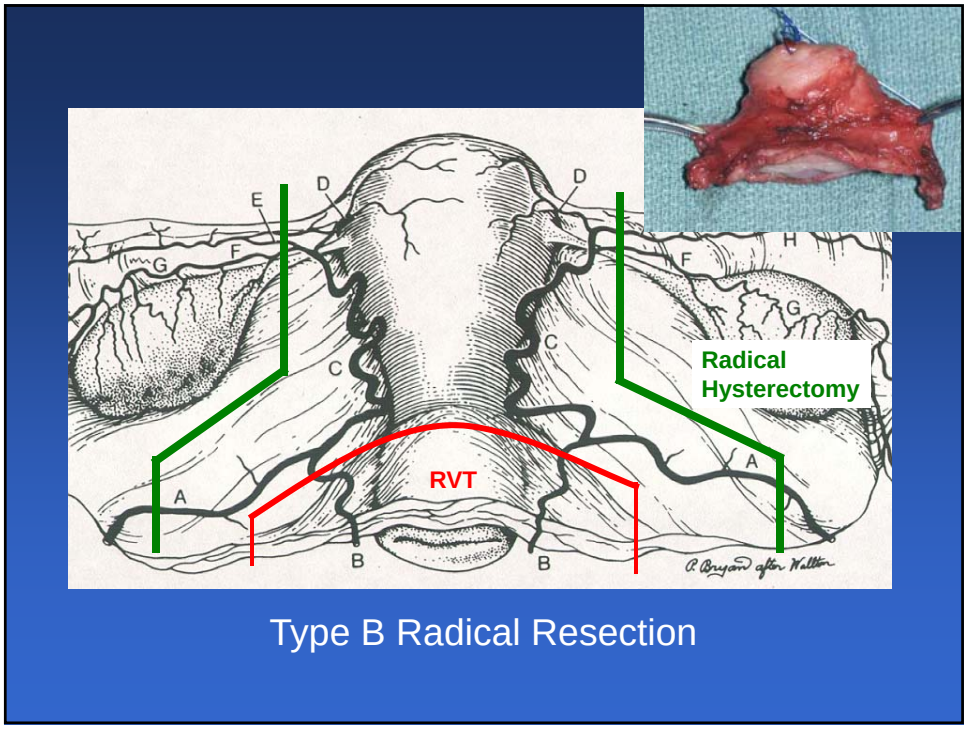




Abu-Rustum. Atlas of Procedures in Gynecologic Oncology



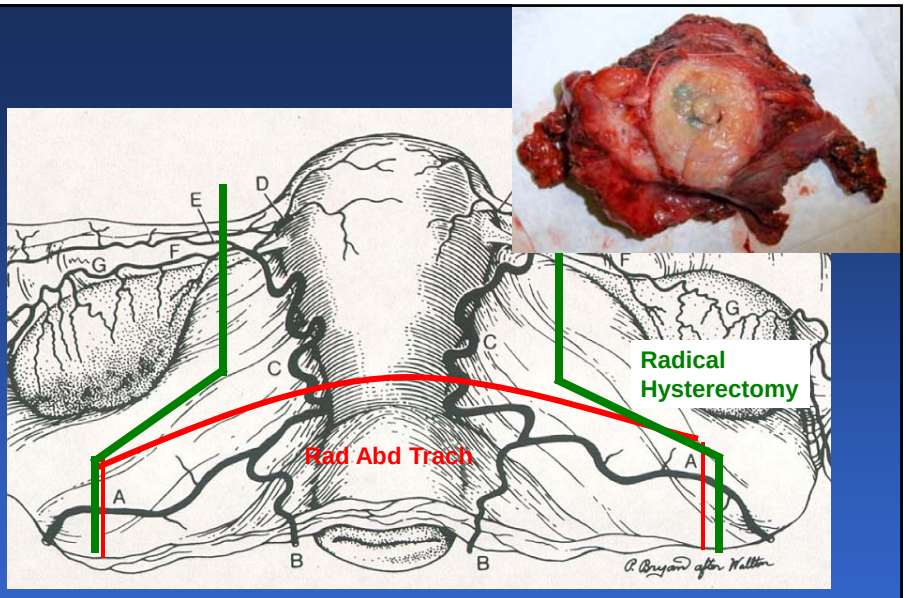
© MSKCC 2006



Type B Radical Resection

Endocervical Margin Vaginal Trachelectomy

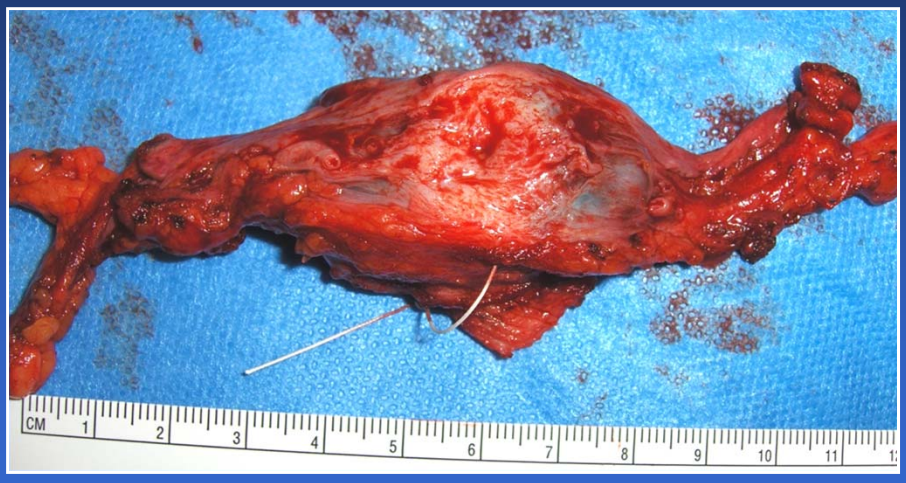
Abu-Rustum. Atlas of Procedures in Gynecologic Oncology



Type C Radical Resection

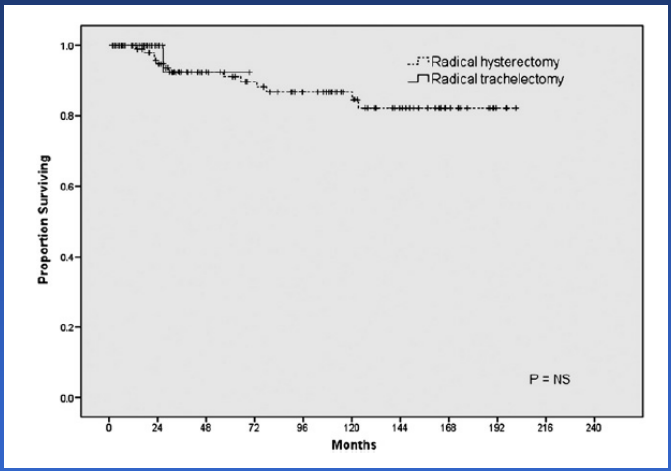
Parametrectomy

We recommend exercising caution when considering abbreviation of parametrectomy and based on our data we continue to include this procedure in our surgical algorithm for the majority of stage IB1 cervical cancers



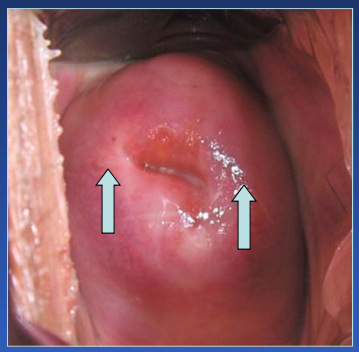
Park KJ, Soslow RA, Sonoda Y, Barakat RR, Abu-Rustum NR. Gynecol Oncol 2008

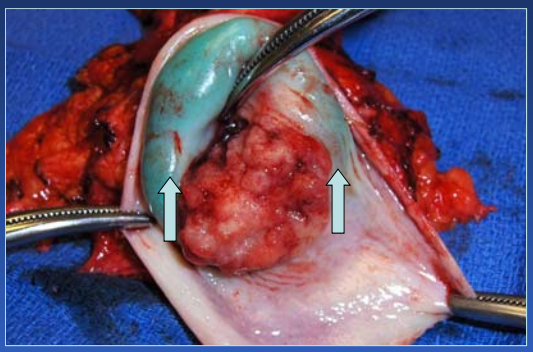
Oncologic Outcome of Radical Trachelectomy vs. Radical Hysterectomy for Stage ***IB1*** Cervical Cancer
MSKCC Survival Data



Diaz JP, et al. Gynecol Oncol 2008

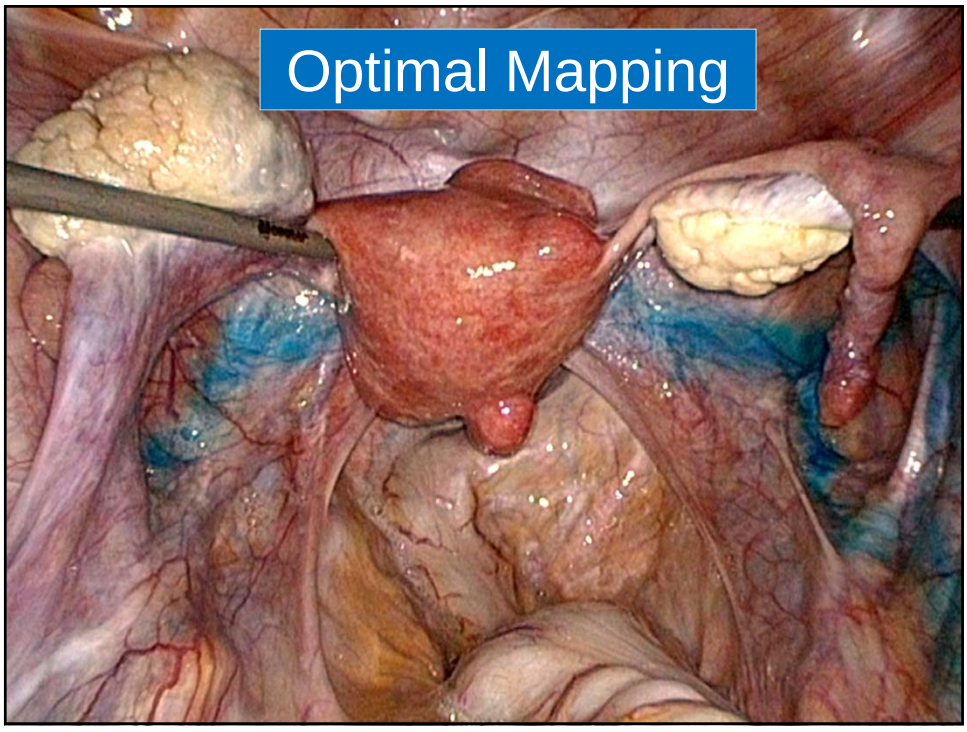
3 & 9 O'clock: 1cc superficial on each side



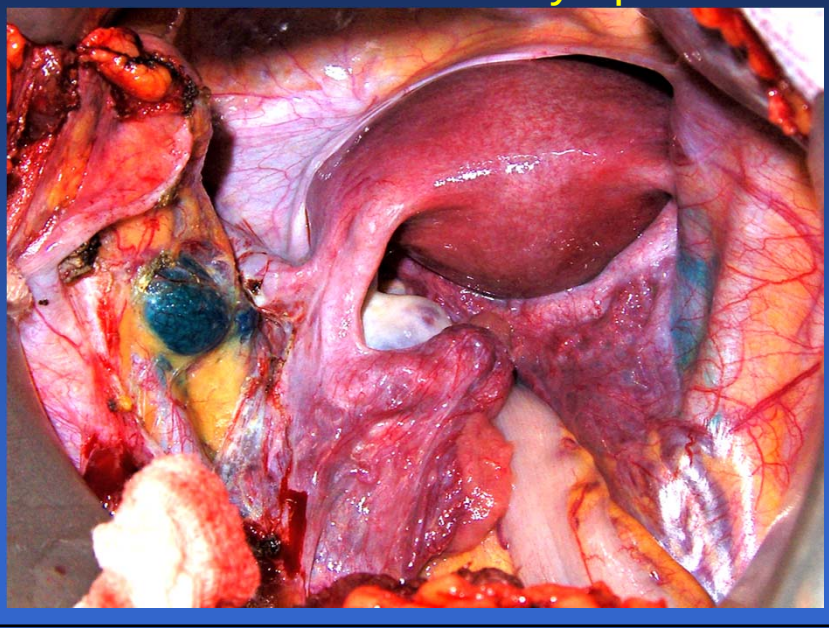


Abu-Rustum. Atlas of Procedures in Gynecologic Oncology

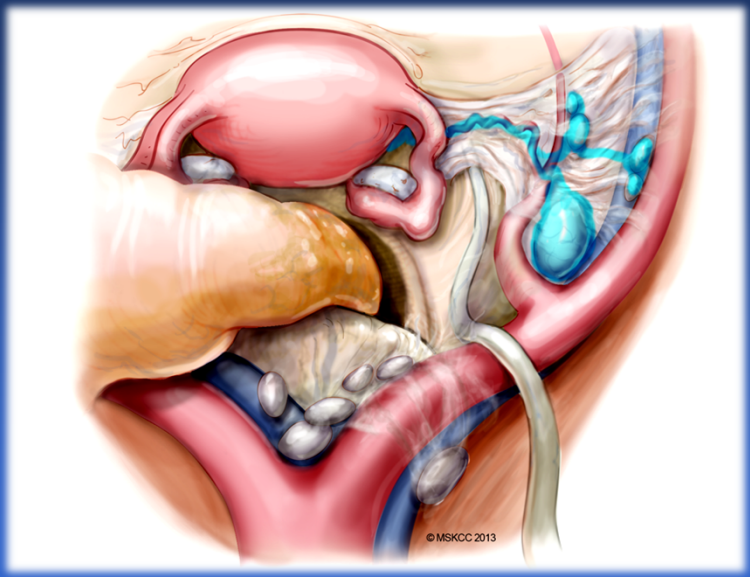
Colored Dye: Simple Setup

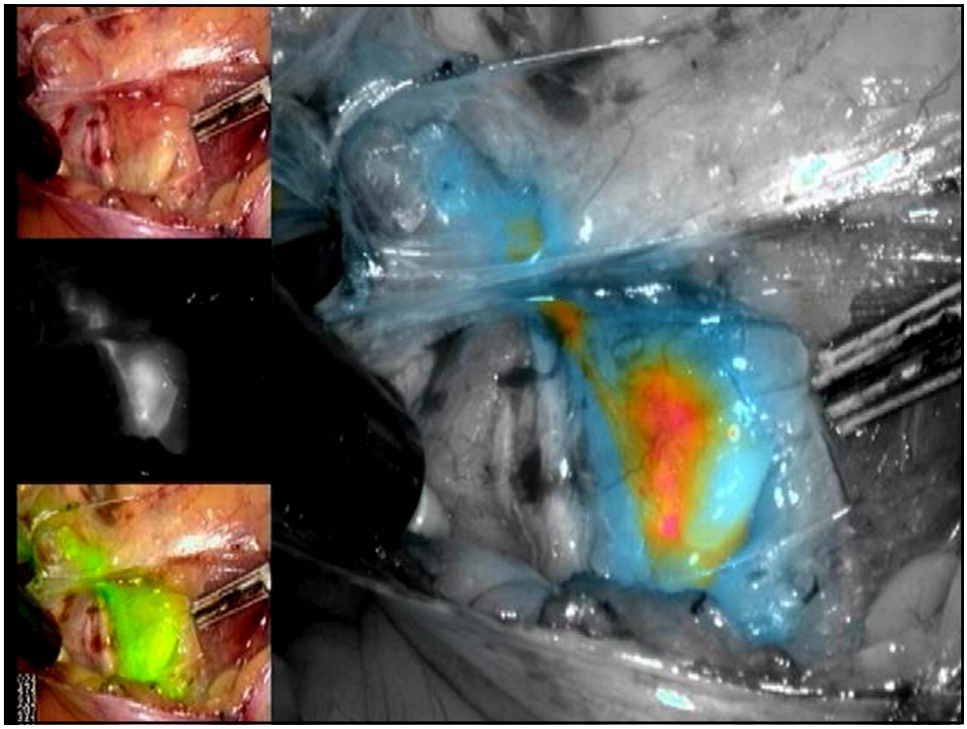


SLN Left External Iliac Lymph Node

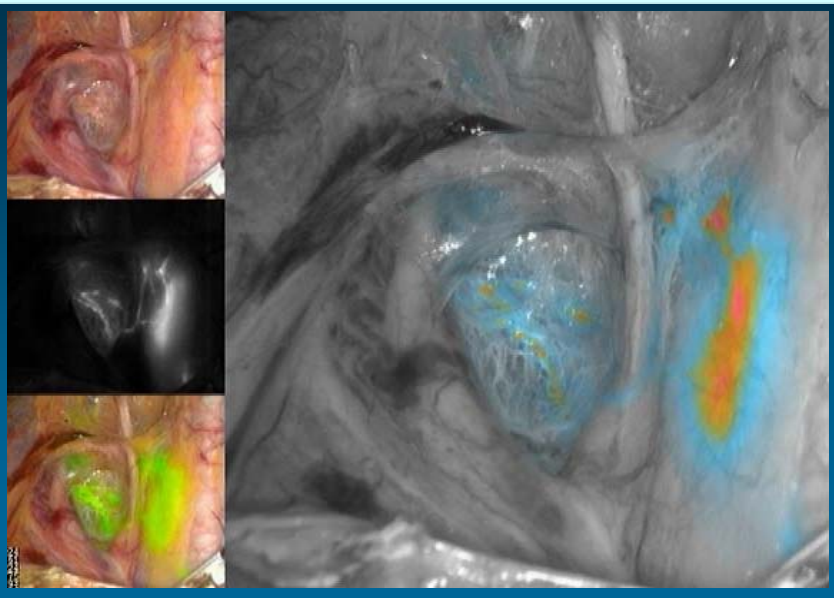


Most Common Drainage





ICG – Color Segmented Fluorescence



SLN Future Directions

Fertility-Sparing Surgery in Stage I Cervical Ca

- For bigger lesions with no obvious metastasis by imaging:
  - SLN Algorithm
  - If (-)SLN ⟹ Neoadjuvant chemotherapy followed by radical trachelectomy or conization
- For smaller lesions:
  - SLN Algorithm
  - if (-) SLN ⟹ conization or simple trachelectomy
- For high-risk resected lesions:
  - Adjuvant chemotherapy, instead of radiation+chemo

Challenges in Surgical Research

Availability of Expertise - Feasibility

- Nerve sparing surgery
- Trachelectomy
- SLN
- Laparoscopy & Robotic in developing world

Patient Access & Funding

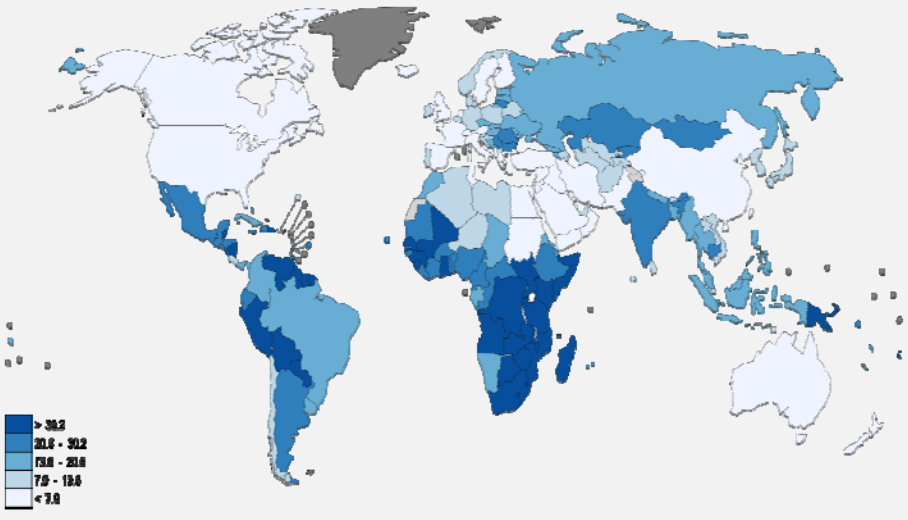
- Majority of cervical cancers in developing world

Select Current Surgical Studies

1) GOG #278-Physical Function and Quality of Life Before and After Surgery in Patients With Stage I Cervical Cancer
2) GCIG Shape Trial- Radical Versus Simple Hysterectomy and Pelvic Node Dissection in Patients With Low-risk Early Stage Cervical Cancer
3) Uterus11- Surgical Staging in Cervical Cancer Prior to Chemoradiation
4) LACC- Laparoscopic Approach to Cervical Cancer

NCCN Framework for Resource Stratification of NCCN Guidelines (NCCN Framework™)

Incidence of cervix cancer



NCCN Framework for Resource Stratification of NCCN Guidelines (NCCN Framework™)

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Cervical Cancer
NCCN Framework™: Basic Level

NCCN FRAMEWORK DEFINITIONS*	
The NCCN Framework™ outlines a rational approach for building cancer management systems to provide the highest achievable level of cancer care by applying available and affordable services in a logical sequence. Each level builds on the one before it, providing a framework for improving cancer care with incremental changes to the allocation of resources. Treatment recommendations applicable to each level of the NCCN Framework™ can be viewed within the context of the parent NCCN Guidelines®.	
Basic Level	This level includes essential services needed to provide basic minimal standard of care.
Limited Level	This level includes services from the Basic Level and additional services that provide major improvements in disease outcomes, eg, survival, that are not cost prohibitive.
Enhanced Level	This level includes services from the Limited Level and additional services that provide lesser improvements in disease outcomes and/or services that provide major improvements in disease outcomes but are cost prohibitive at lower resource levels.
NCCN Guidelines	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.
NCCN believes that if higher-level resources are available, providers should use the higher level. If basic level cancer treatments or higher are unavailable, palliative and best supportive care should be provided.	
*Modified from Anderson BO and Carlson RW. Guidelines for improving breast health care in limited resource countries: the Breast Health Global Initiative. J Natl Compr Canc Netw 2007;5:349-356.	

THE NCCN FRAMEWORK FOR RESOURCE STRATIFICATION IS REPRESENTED AS FOLLOWS:
Black Text: Included recommendation
Gray Text: Withheld recommendation
Italicized Blue Text: Modified recommendation based on resource level

Note: Drugs and Biologics included in the NCCN Framework™ are approved by the United States Food and Drug Administration. Alternate agents based on the local regulations and availability may be substituted provided evidence supports their efficacy and safety. Generic drugs should be used only when studies have proven bioequivalence and the drugs have met the same standards for identity, strength, purity, and quality as the innovator drugs. The WHO essential medicines list can be found here: http://www.who.int/medicines/publications/essentialmedicines/en/.

Note: This is the NCCN Framework for Resource Stratification of NCCN Guidelines. For definitions of the NCCN Framework™ levels, 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.

FR-1

NCCN Framework™ For Resource Stratification of NCCN Guidelines

Includes essential services needed to provide basic minimal standard of care.

NCCN Framework™ For Resource Stratification of NCCN Guidelines

Includes services that provide major improvements in disease outcomes, eg, survival, that are not cost prohibitive.

NCCN Framework™ For Resource Stratification of NCCN Guidelines

This level includes additional services that provide lesser improvements in disease outcomes and/or services that provide major improvements in disease outcomes but are cost prohibitive at lower resource levels.

Chemotherapy & Radiation Trials

Primary Treatment

- Chemoradiation:
  - Chemoradiation & cisplatin schedule
  - Chemoradiation + Adjuvant chemo
  - Neoadjuvant chemo + Chemoradiation
- Adjuvant Radiation:
  - Post op high risk
  - Post op intermediate risk

Palliative RT

NACT (Neoadjuvant Chemotherapy)

Not currently an NCCN Guideline

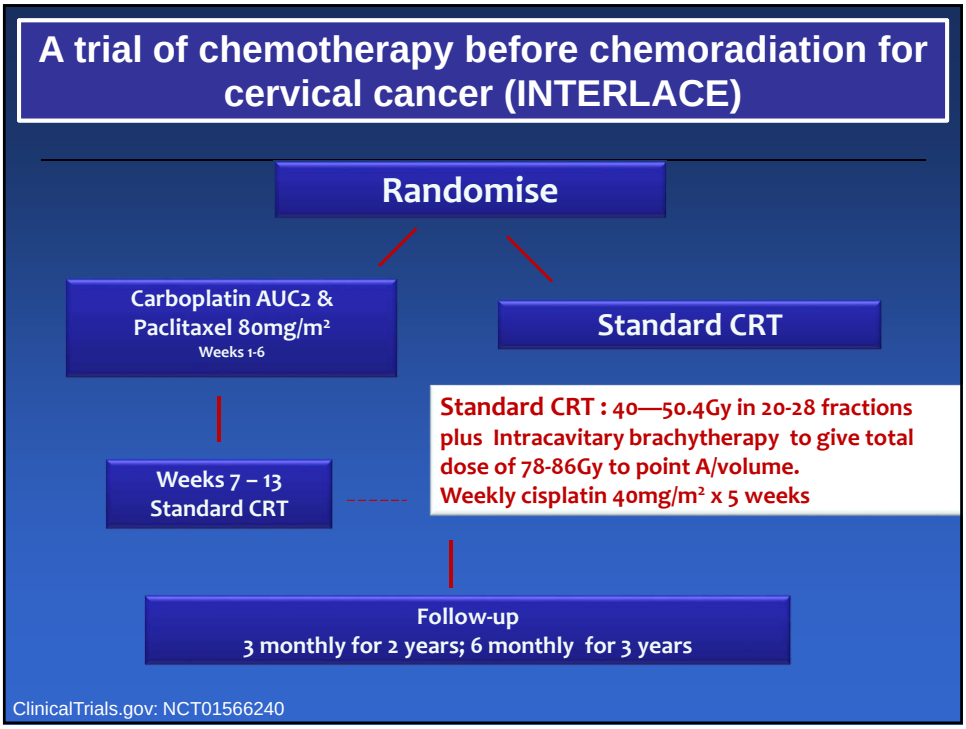
1. Induction Chemotherapy Plus Chemoradiation as First Line Treatment for Locally Advanced Cervical Cancer **(INTERLACE)** UK
2. Neoadjuvant Chemotherapy Followed by Surgery Vs. Chemoradiation in Carcinoma of the Cervix (NACTcervix) India
3. Neoadjuvant Chemotherapy Followed by Radical Hysterectomy Vs. Primary Chemo-radiation in FIGO Stage IB2 - IIB (NACOPRAD) Germany
4. Neoadjuvant Chemotherapy and Radical Surgery in Stage IIB Cervical Cancer (SYSGO002) China
5. Induction Chemotherapy With Cisplatin and Gemcitabine Followed by Chemoradiation or Definitive Chemoradiation in Invasive Locally Advanced Carcinomas of Uterine Cervix. (CIRCE) Brazil

A trial of chemotherapy before chemoradiation for cervical cancer (INTERLACE)

- This trial is looking at giving carboplatin and paclitaxel before chemoradiation for cervical cancer that cannot be removed with surgery.
- This trial is supported by Cancer Research UK.

ClinicalTrials.gov: NCT01566240

A trial of chemotherapy before chemoradiation for cervical cancer (INTERLACE)



ClinicalTrials.gov: NCT01566240

INTERLACE Trial

Current status:

- 27 sites open to recruitment
- 83 patients recruited
- Target recruitment =770

ClinicalTrials.gov: NCT01566240

IMRT (Intensity-Modulated Radiation Therapy)

- Standard vs. IMRT in Endometrial or Cervical Cancer (Ann Klopp, USA)
- IMRT for Locally Advanced Cervical Cancer (Melanie Powell, UK)
- IMRT With Cisplatin Stage I-IVA Cervical Cancer (Loren Mell, USA)
- IMRT With Cisplatin and Gemcitabine to Treat Locally Advanced Cervical Ca (Loren Mell, USA)

Hypofractionated Radiation Therapy (CCRN)

- Radiation treatment total dose is divided into larger doses/day and treatments are given once a day or less often.
- Radiation is delivered over a shorter period of time than standard therapy.
- Goal is to improve care delivery
- More practical
- Integration with chemo to be determined
- Toxicity to be determined

Adjuvant Chemotherapy after Chemoradiation

1. A Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone (**OUTBACK,** Linda Mileshkin, AU)
2. ChemoRT with and without adjuvant chemotherapy in high risk cervix cancer after hysterectomy

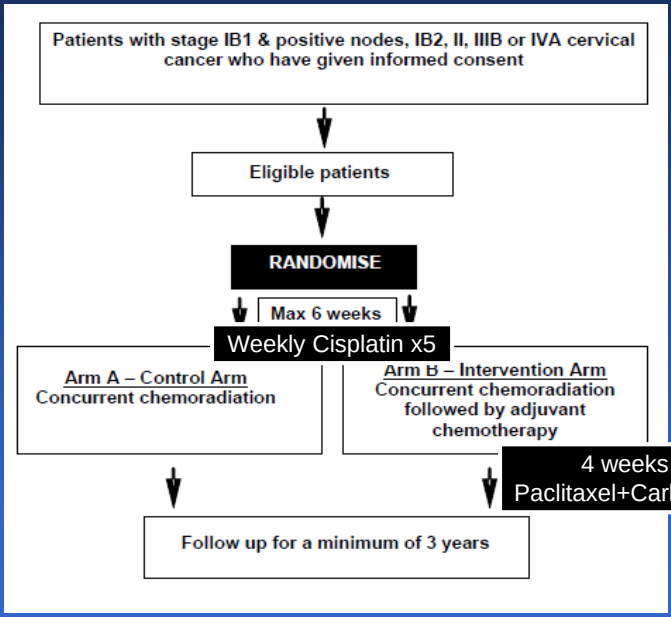
   RTOG-0724 (GOG William Small)
3. Adjuvant Chemotherapy (TPx3) for Locally Advanced Cervical Cancer (Siriwan and Vichan, Thailand)
4. A Multicenter Trial of Benefits of Adding Post-surgery Chemotherapy (TP 2x2) for Cervical Cancer (Jihong Liu, China)

OUTBACK Trial

(ANZGOG 0902 / GOG 0274 / RTOG 1174)
NCT01414608
A Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone

Principal Investigator: Prof Linda Mileshkin

OUTBACK Study Schema



ClinicalTrials.gov: NCT01414608

Chemoradiation

Adjuvant:

- Randomized Phase III Clinical Trial of Adjuvant Radiation vs. Chemoradiation In Intermediate Risk, Stage I/IIA Cervical Cancer Treated With Initial Radical Hysterectomy and Pelvic Lymphadenectomy ;Sang Young Ryu, GOG 263-KGOG

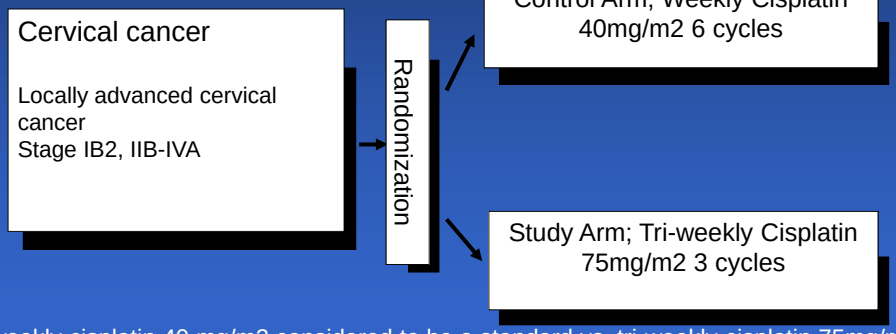
Curative:

- Tri-weekly Cisplatin Based Chemoradiation in Locally Advanced Cervical Cancer (**TACO)** (Sang Young Ryu, Korea)

TACO

(Tri-weekly Administration of Cisplatin in LOcally Advanced Cervical Cancer)

"the optimal cisplatin dose and dosing schedule are still undetermined"



weekly cisplatin 40 mg/m2 considered to be a standard vs. tri-weekly cisplatin 75mg/m2 that may have lower toxicities and better outcomes

ClinicalTrials.gov: NCT01561586

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2016
Cervical Cancer

CHEMOTHERAPY REGIMENS FOR RECURRENT OR METASTATIC CERVICAL CANCER
(Strongly consider clinical trial)

First-line combination therapy
- Cisplatin/paclitaxel/bevacizumab (category 1)
- Cisplatin/paclitaxel (category 1)
- Topotecan/paclitaxel/bevacizumab (category 1)
- Carboplatin/paclitaxel (Category 1 for patients who have received prior cisplatin therapy)
- Carboplatin/paclitaxel/bevacizumab
- Cisplatin/topotecan
- Topotecan/paclitaxel
- Cisplatin/gemcitabine (category 3)

Possible first-line single-agent therapy
- Cisplatin (preferred as a single agent)
- Carboplatin
- Paclitaxel

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

CERV-D
1 of 2

Targeted Therapy

- Radiation Therapy and Cisplatin With or Without Triapine in Treating Patients With Newly Diagnosed Stage IB2, II, or IIIB-IVA Cervical Cancer or Stage II-IVA Vaginal Cancer
- A Study of Nelfinavir Added to Cisplatin Chemotherapy Concurrent With Pelvic Radiation for Locally Advanced Cervical Cancer (II-IVA)
  - Fiona Simpkins, USA
- The Potential for Metformin to Improve Tumor Oxygenation in Locally Advanced Cervix Cancer: A Phase II Randomized Trial
  - Kathy Han, Canada
- Pembrolizumab and Chemoradiation Treatment for Advanced Cervical Cancer
  - Linda Duska, USA
- 3 Weekly Carboplatin/Paclitaxel With or Without Nintedanib (BIBF 1120) in Cervix Cancer. Ignace Vergote, Belgium
- Cisplatin-based Chemotherapy Combined With P16_37-63 Peptide Vaccination in Patients With HPV-positive Cancers (VICORYX-2) Elke Jager, Germany

Targeted Therapy (completed)

- A Phase I/II Study of Cisplatin and Radiation in Combination With Sorafenib in Cervical Cancer
- Mapatumumab, Cisplatin and Radiotherapy for Advanced Cervical Cancer
- Cisplatin and Radiation Therapy With or Without Tirapazamine in Treating Patients With Cervical Cancer
- Triapine, Cisplatin, and Radiation Therapy in Treating Patients With Cervical Cancer or Vaginal Cancer
- Cetuximab, Cisplatin, and Radiation Therapy in Treating Patients With Stage IB, Stage II, Stage III, or Stage IVA Cervical Cancer

Future Trials

- Checkpoint Inhibitors/Immune Modulators
  - Ipilimumab, an anti-CTLA-4 antibody
  - MEDI6469, an OX40 immune
  - MEDI4736, a PD-L1-targeting
  - Urelumab (BMS-663513), an anti-4-1BB/CD137 antibody
  - Lirilumab (BMS-986015), an anti-KIR
  - MK-4166, an anti-GITR antibody
  - MOXR0916, an anti-OX40 agonist antibody
  - MEDI6383, an OX40 agonist
- Therapeutic Vaccines
  - ADXS11-001, a vaccine against the E7 protein
  - pNGVL4a/E7 (Detox)/HSP70 DNA vaccine
- Adoptive T Cell Therapy