Management of Cervical Cancer

Abigail Winder, MD, FACOG
Assistant Professor
Dept OBGYN, Gynecologic Oncology

- No disclosures

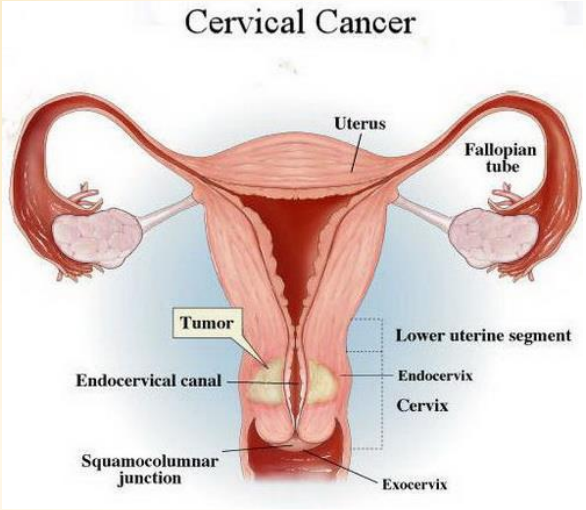
Outline

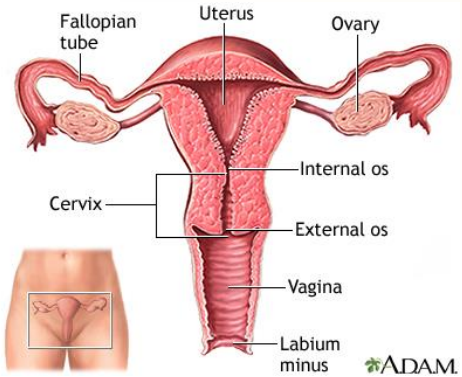
LOYOLA UNIVERSITY HEALTH SYSTEM

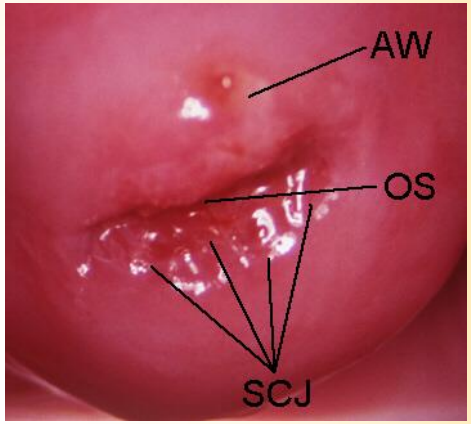
- The Problem
- Management of Early Stage Cervical Cancer
- Prevention
- The hysterectomy
- Fertility Sparing
- Ovaries
- Sentinel lymph nodes

Cervical Cancer

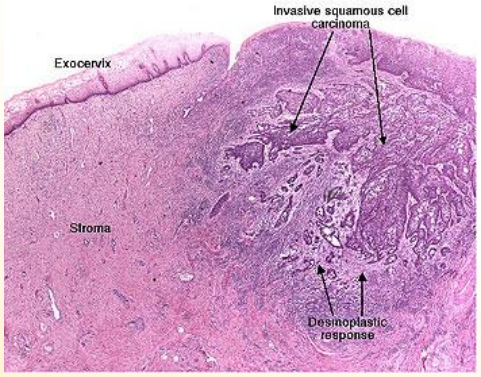
LOYOLA UNIVERSITY HEALTH SYSTEM



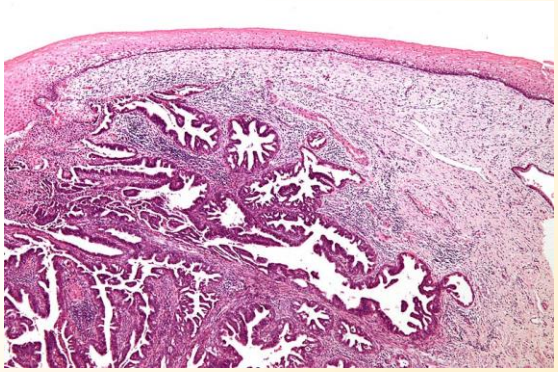




Squamous Cell Carcinoma



Adenocarcinoma



Cervical cancer – USA stats

LOYOLA UNIVERSITY HEALTH SYSTEM

- 2019 American Cancer Society estimates:
  - 13,170 new cases (13,240 in 2018)
  - 4,250 deaths (4,170 in 2018)

- 0.68% lifetime risk (1/147 women in USA)

5 year survival				
	All stages	Local	Regional	Distant
Cervix	68	**91**	57	**16**
Uterine	82	95	68	17
Ovary	44	92	72	27

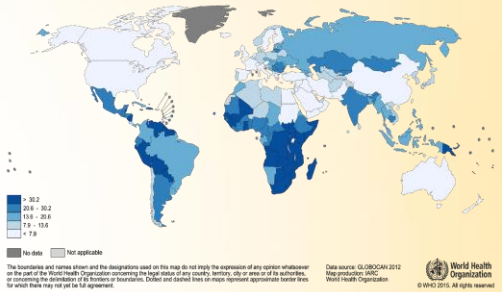
The Global Problem

LOYOLA UNIVERSITY HEALTH SYSTEM

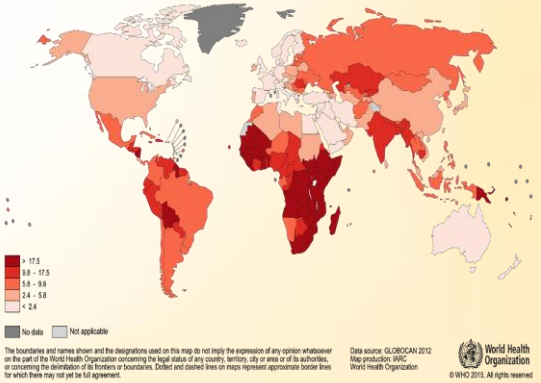
"It is unacceptable that every two minutes one woman dies of cervical cancer in a world where we have the proven solutions to prevent and treat this disease" says WHO Assistant Director-General for Noncommunicable Diseases and Mental Health, Dr Svetlana Axelrod

feb4, 2019: One World Cancer Day WHO launched a new toolkit or collection

- WHO **Worldwide** stats (2012)
  - 4th Most common *cancer in women*
    - Breast > Colorectal > Lung > **Cervical** >Stomach
    - 7.9% of femal cancers
    - 530,000 new cases



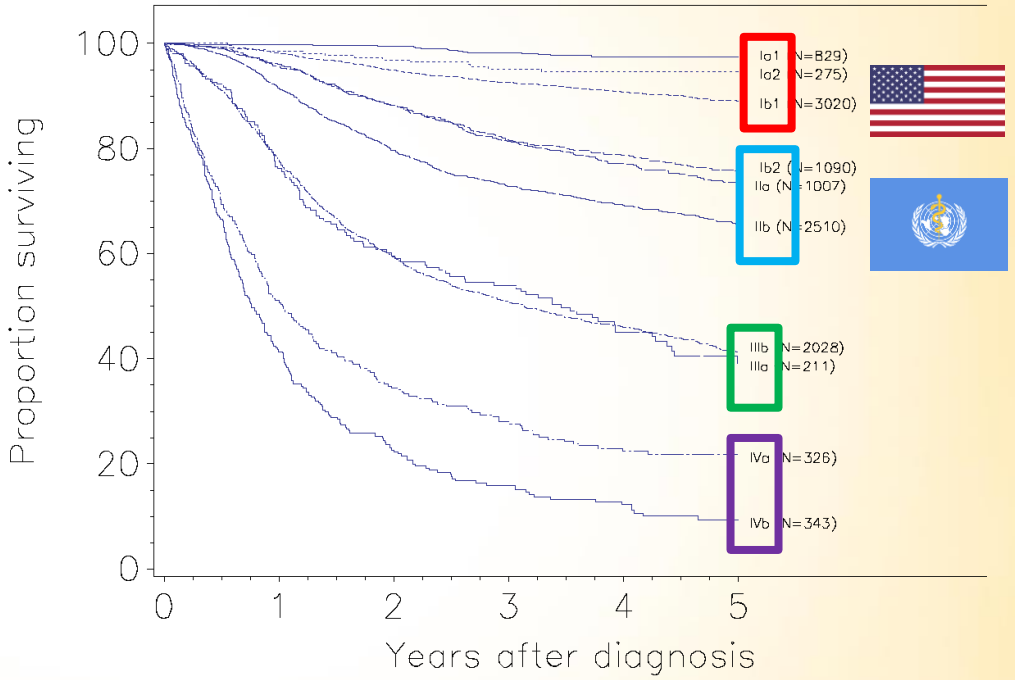
  - 4th leading cause of *cancer death in women*
    - Breast > Lung > Colorectal > **Cervical** > Stomach
    - >300,000 deaths
    - 85% in low to middle income countries



Why is it such a problem? Early detection is key!

LOYOLA UNIVERSITY HEALTH SYSTEM

Stage	5 Year OS (%)
IA1	97.5
IA2	94.8
IB1	89.1
IB2	75.7
IIA	73.4
IIB	65.8
IIIA	39.7
IIIB	41.5
IVA	22.0
IVB	9.3



Quinn *et al.* Int J Gynaecol Obstet. 2006 Nov;95 Suppl 1:S43-103. Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer.

Risk Factors for Cervical Cancer:

LOYOLA UNIVERSITY HEALTH SYSTEM

- Demographic Factors
  - Age
  - Race (black, Hispanic, American Indian)
  - **Low socioeconomic status**
  - Low educational level
- Behavioral and Sexual Factors
  - Number of sexual partners
  - **Early age at first coitus**
  - **Cigarette Smoking**
  - Long-term contraceptive use
  - Diet low in folate, carotene
- Medical/Gynecological
  - **Infection with High-risk HPV**
  - Multiparity
  - **Early age at first pregnancy**
  - **History of sexually transmitted disease** (HSV/HPV-associated lesions)
  - **Lack of routine cytologic screening**
  - **Immunosuppression** (HIV, steroids, Fanconi anemia, transplant)
  - Specific HLA-DR hapotypes

Symptoms of Cervical Cancer

LOYOLA UNIVERSITY HEALTH SYSTEM

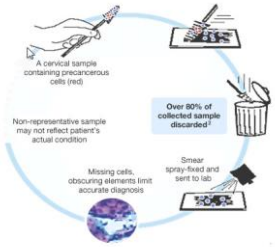
- Most common presentation of invasive cervical cancer:
  - **Abnormal vaginal bleeding**
  - **Post-coital bleeding**
  - Vaginal discharge
- Advanced disease symptoms
  - Pelvic pain
  - Difficulty urinating/defecating
  - Metastatic: back pain, leg swelling (unilateral)
- PE: abnormal lesion on cervix, necrotic/friable.
  - Staging is clinical, include RVE
  - **Biopsy** confirmation

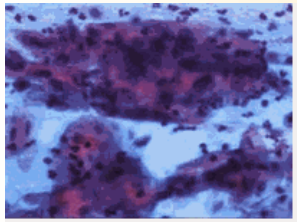
Early detection = The Pap Smear

LOYOLA UNIVERSITY HEALTH SYSTEM

- Drs. Papaniculaou & Traut (published 1941)
  - Became available in many countries in 1950s
  - Research showed treating precancerous lesions prevented development of cancer
  - USA incidence cervical cancer in 1975 was14.8/100K → 6.5/100K (2006)

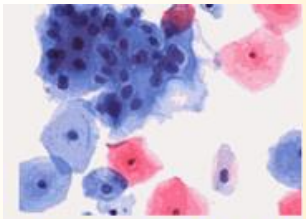
- Conventional:
  - Sensitivity HSIL: >90%





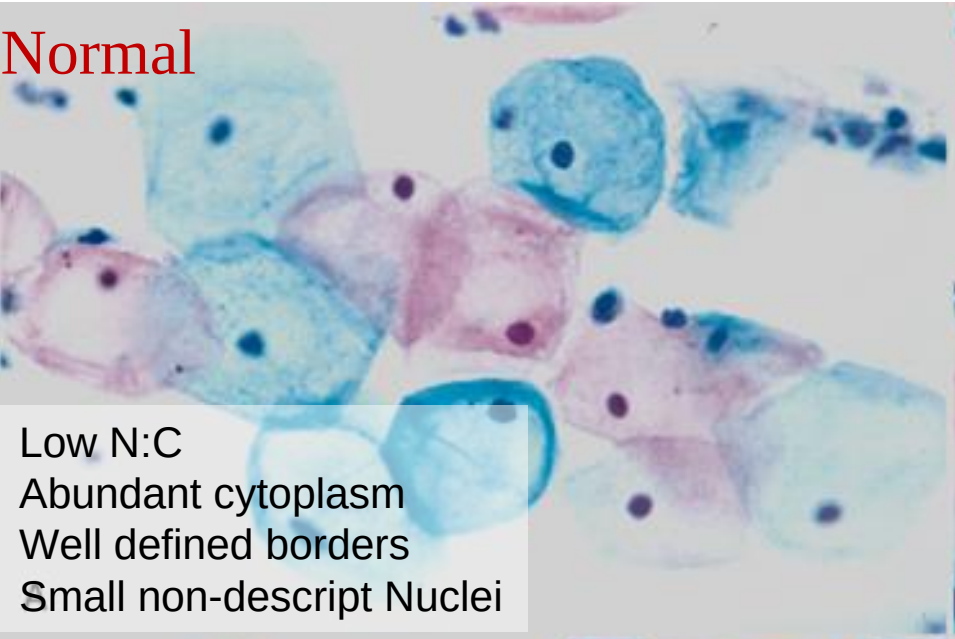
Conventional Pap Smear

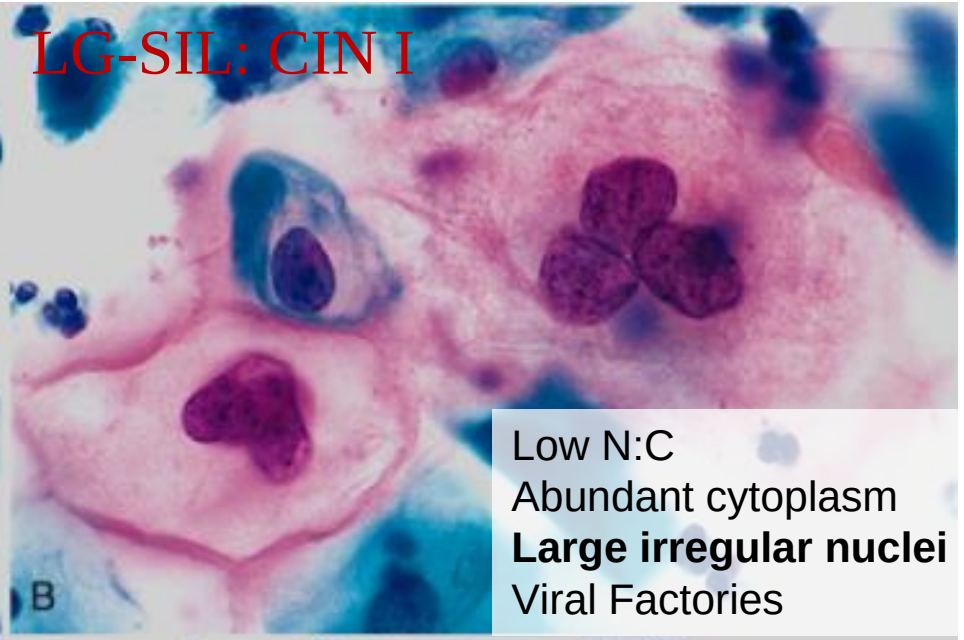
- **Liquid-based:**
  - **Sensitivity HSIL: >95%**
  - **Allows for reflex HPV testing**
  - Disadvantage higher cost

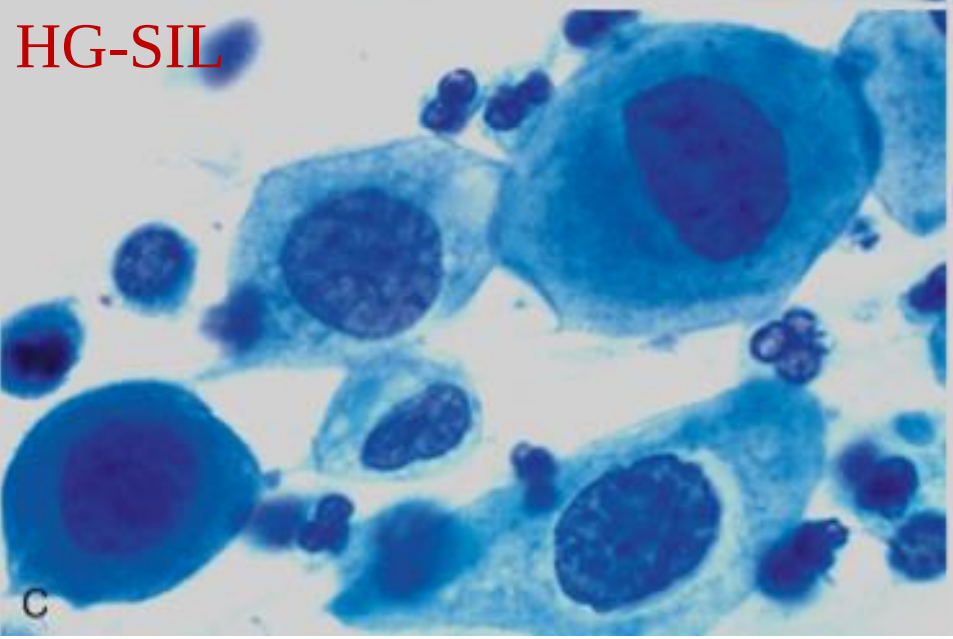


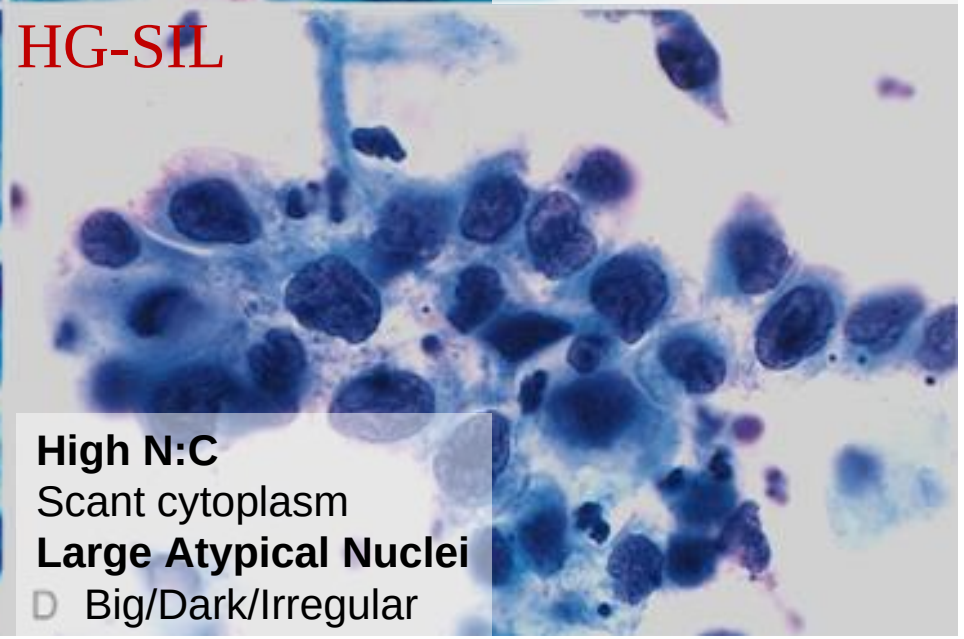
ThinPrep Pap Test Slide

- Future: HPV testing → reflex PAP



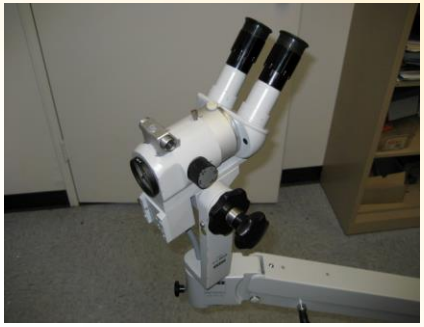






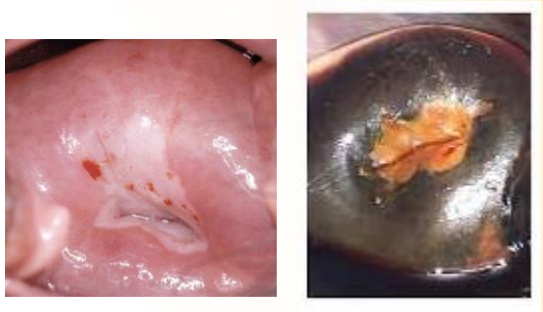
Slide Courtesy of Dr. Ajit Paintal

Abnormal PAP → Colposcopy



LOYOLA UNIVERSITY HEALTH SYSTEM

- Low-power (3x-15x) binocular
- Evaluate Cervix/Vulva/Vagina
- Focus on Transformation Zone (TZ)
  - Area between normal columnar epithelium & mature squamous epithelium
- **Acetic Acid (3-5%)**
  - Look for areas of **acetowhite change**
- **Lugol Iodine Solution**
  - Look for areas that **do not absorb iodine**
- **Satisfactory colposcopy**
  - Complete visualization of TZ and entire lesion
  - **BAD things:**
    - **raised, gray, non-arborizing blood vessels , extension beyond TZ**



- **Biopsy**: Taken to confirm colposcopist impression
- Colposcopic **Sensitivity to detect CIN 3** approx 70%. (ALTS)
  - Increased when 2 or more biopsies taken
  - Did not matter level of training: NP, Generalist, Gyn Onc Fellow, Gyn Onc

Primary Prevention: the best management of early stage cervical cancer!

LOYOLA UNIVERSITY HEALTH SYSTEM

- HPV Vaccination: HPV most common STD
  - HPV 16,18 → 80% cervical cancer cases
  - HPV 31,33, 45, 52, 58 also oncogenic
  - HPV 6,11 → 90% genital warts
- Who: everyone age 9-45 years old, CDC recommends age 11-12
- What: 2 shots <15years old, 3 shots >15 years old

The HPV Vaccine

LOYOLA UNIVERSITY HEALTH SYSTEM

- Recombinant Non-infectious Viral Like Particle
  - Capsid alone (L1) → neutralizing antibody response
- Gardasil (Merck)
  - HPV 6,11,16,18 → Garadasil 9 (31, 33, 45, 52, 58)
  - Immunity 10 years → at least 6 years with Gardasil 9
  - CIN3/AIS prevention efficiency > 93%
- Cervarix (GlaxoSmithKline)
  - HPV 16,18
  - Immunity at least 9 years
  - CIN3/AIS prevention efficiency > 93%
- WHO supports use of either
- Treatment CIN3 and ok to get if h/o HPV

Early Stage Cervical Cancer

LOYOLA UNIVERSITY HEALTH SYSTEM

- What is it?

“Old” Staging - Clinical

LOYOLA UNIVERSITY HEALTH SYSTEM

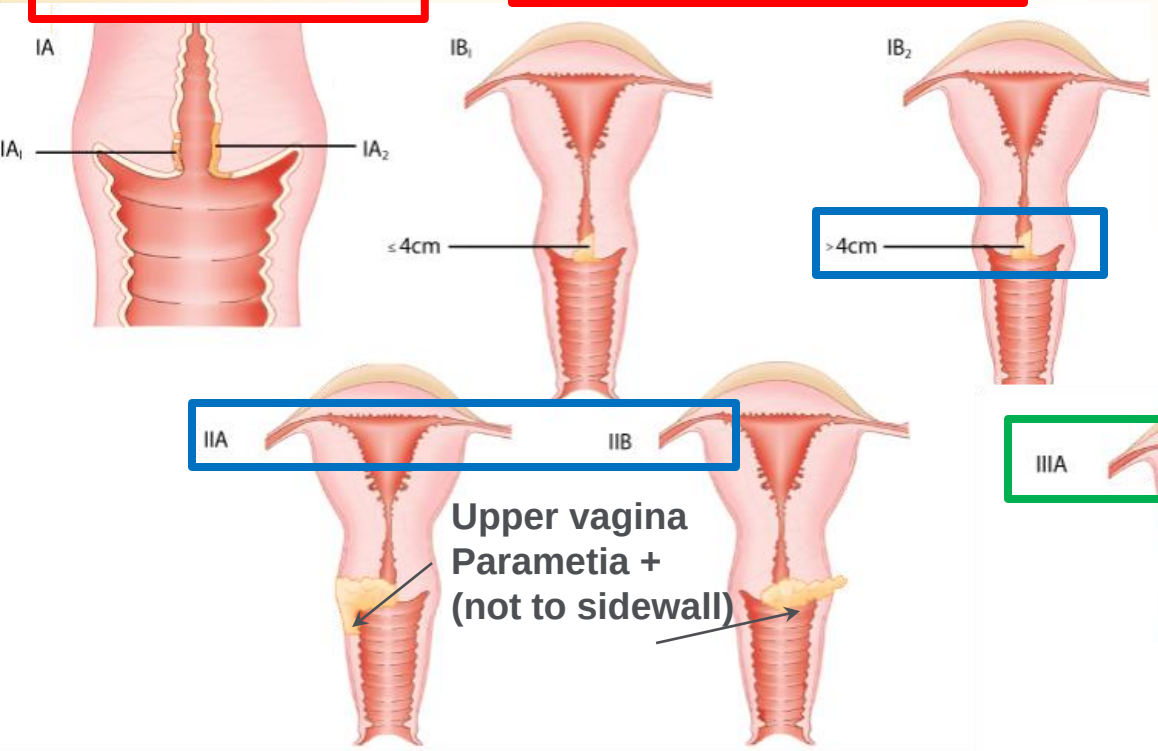
- **FIGO**
  - H&P
    - vaginal and rectal exam
    - nodal exam (neck/supraclavicular and inguinal)
  - EUA, cystoscopy, hysteroscopy, proctoscopy,
  - CXR
  - IV pyelogram
- **USA** – Nodal status very important!
  - PET/CT skull to midthigh
  - Pelvic MRI
- **3 Categories**
  - Cervix Confined, tumor <4cm = Surgery
  - Locally advanced = Radiation
  - Distant mets (lung, liver, supracalvicular node) = Chemotherapy

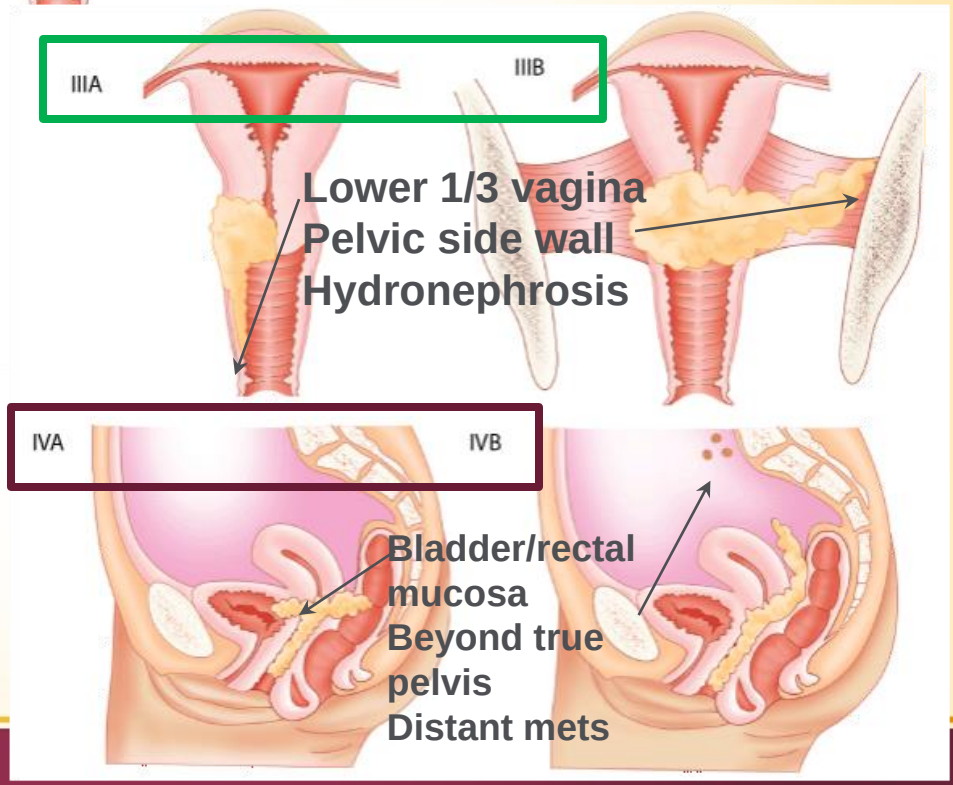
Cervical Cancer Staging

LOYOLA UNIVERSITY HEALTH SYSTEM

microscopic

visible lesion





Source: Schorge JO, Schaffer JI, Halvorson LM, Hoffman BL, Bradshaw KD, Cunningham FG, Williams gynecology: http://www.accessmedicine.com

Carcinoma of Cervix: Staging

LOYOLA UNIVERSITY HEALTH SYSTEM

Stage I The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)

- **IA** Invasive carcinoma which can be diagnosed only by **microscopy**, with deepest invasion ≤ 5 mm and largest extension ≥7 mm, dx on LEEP/CKC or Hysterectomy Specimen
  - **IA1** stromal invasion of **≤3.0 mm** in depth and extension of **≤ 7.0 mm**
  - **IA2** stromal invasion of **>3.0 mm** and **not >5.0 mm** with an extension of **not >7.0 mm**
- **IB** Clinically **visible** lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA*
  - **IB1** Clinically visible lesion **≤ 4.0 cm** in greatest dimension
  - **IB2** Clinically visible lesion **>4.0 cm** in greatest dimension

Stage II Cervical carcinoma invades **beyond the uterus**, but not to the pelvic wall or to the lower third of the vagina

- **IIA** Without parametrial invasion
  - **IIA1** Clinically visible lesion **≤ 4.0 cm** in greatest dimension
  - **IIA2** Clinically visible lesion **>4 cm** in greatest dimension
- **IIB** With obvious **parametrial invasion**

Stage III The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney**

- **IIIA** Tumor involves **lower third of the vagina**, with no extension to the pelvic wall
- **IIIB** Extension to the **pelvic wall and/or hydronephrosis** or non-functioning kidney

Stage IV The carcinoma has **extended beyond the true pelvis** or has involved (biopsy proven) the **mucosa of the bladder or rectum**. A bullous edema, as such, does not permit a case to be allotted to Stage IV

- **IVA** Spread of the growth to **adjacent organs, mucosa of the bladder or rectum**
- **IVB** Spread to **distant organs**

New Staging! 2018

LOYOLA UNIVERSITY HEALTH SYSTEM

Box 1 FIGO staging of carcinoma of the cervix uteri (2018).

Stage I:

The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded)

- IA Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm[a]
  - IA1 Measured stromal invasion <3 mm in depth
  - IA2 Measured stromal invasion ≥3 mm and <5 mm in depth
- IB Invasive carcinoma with measured deepest invasion ≥5 mm (greater than stage IA), lesion limited to the cervix uteri[b]
  - IB1 Invasive carcinoma ≥5 mm depth of stromal invasion and <2 cm in greatest dimension
  - IB2 Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
  - IB3 Invasive carcinoma ≥4 cm in greatest dimension

Stage II:

The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall

- IIA Involvement limited to the upper two-thirds of the vagina without parametrial involvement
  - IIA1 Invasive carcinoma <4 cm in greatest dimension
  - IIA2 Invasive carcinoma ≥4 cm in greatest dimension
- IIB With parametrial involvement but not up to the pelvic wall

Stage III:

The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic lymph nodes[c]

- IIIA Carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
- IIIB Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
- IIIC Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[c]
  - IIIC1 Pelvic lymph node metastasis only
  - IIIC2 Paraaortic lymph node metastasis

Stage IV:

The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to stage IV

- IVA Spread of the growth to adjacent organs
- IVB Spread to distant organs

[a]Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumor size and extent, in all stages.

[b]The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.

[c]Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be stage IIIC1r and, if confirmed by pathological findings, it would be Stage IIIc1p. The type of imaging modality or pathology technique used should always be documented. When in doubt, the lower staging should be assigned.

- Big Changes
  - lateral spread removed
  - IB (1,2,3)
  - IIIC (1,2, r, p)

Treatment

LOYOLA UNIVERSITY HEALTH SYSTEM

Stage	Treatment
IA1 (neg LVSI):	CKC, simple hysterectomy
IA2:	Modified Radical hysterectomy + PLND ± PALND
IB1, IB2:	Radical hysterectomy + PLND ± PALND
IB3 – IVA:	Chemo/XRT
IVB: cisplatin/paclitaxel +/- bevacizumab, +/- palliative XRT	

“old IB1” Surgery = XRT

LOYOLA UNIVERSITY HEALTH SYSTEM

	Surgery	Radiation
Survival	**91%**	**89%**
Serious complications	Urologic Fistula (1-2%)	Intestinal and Urinary strictures and fistulae (1.4 -5.3%)
Vaginal function	Initially shortened	Fibrosis and stenosis
Ovarian function	**Conserved**	**Destroyed**
Chronic effects	**Atonic bladder (3%)**	**Radiation enteritis (6-8%)**

NB: ovarian transposition is not generally supported → oocyte/embryo freezing and HRT, there are grants to help with fertility preservation costs for cancer patients, NW has a program

XRT if IB1 but
-not surgical candidate, often VTE, AMI (on plavix)

Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer

Fabio Landoni, Andrea Maneo, Alessandro Colombo, Franco Placa, Rodolfo Milani, Patrizia Perego, Giorgio Favini, Luigi Ferri, Costantino Mangioni

LOYOLA UNIVERSITY HEALTH SYSTEM

- IB, IIA (old) can be cured with XRT (***EBRT and brachytherapy***) or surgery, toxicity and morbidy differ
- Prospective RCT
- Adjuvant tx in 62/114 (<4cm tumor), 46>55 (>4cm tumor)

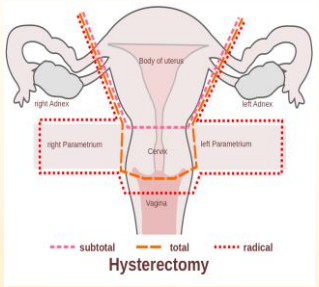
	Surgery	XRT
N	170	167
5yr OS	83%	74%
Recurrence	42 (25%)	44 (26%)
Severe Morbidity	48 (28%)	19 (12%)

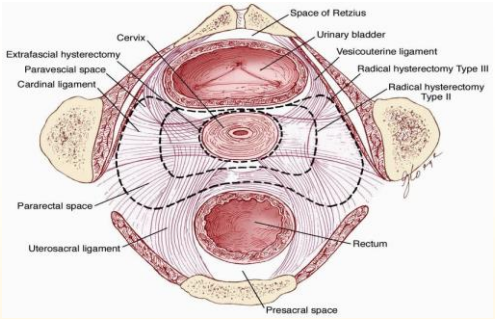
Lancet 1997; **350:** 535–40

Types of Hysterectomy

LOYOLA UNIVERSITY HEALTH SYSTEM

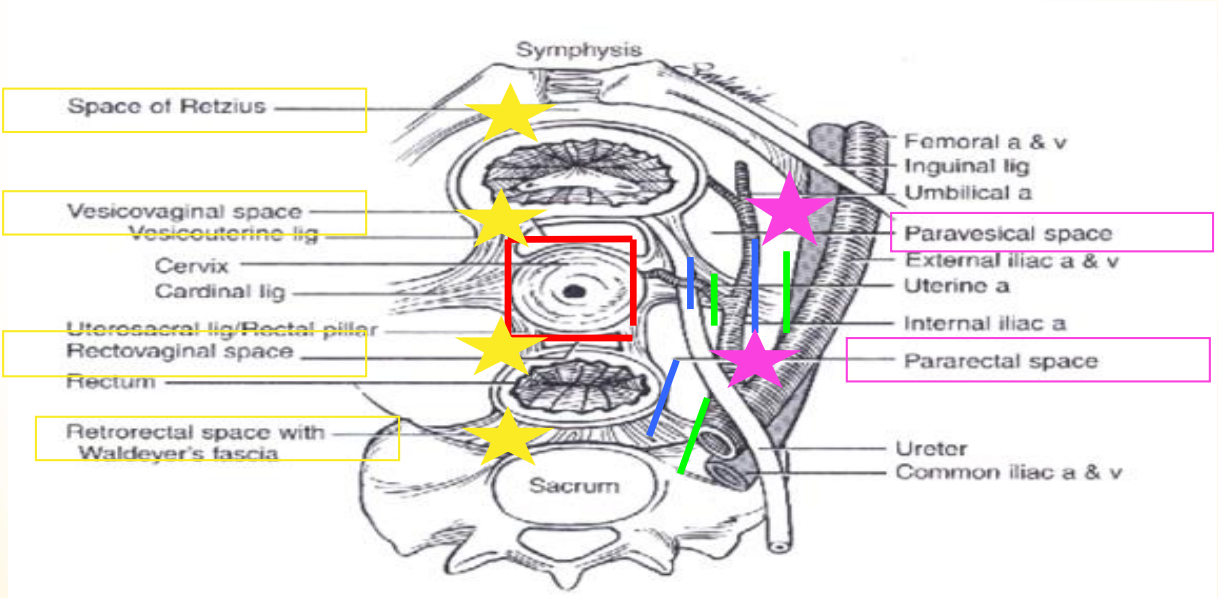
Type	Name	Vagina	Bladder	Ureter	Uterine Artery	Parametria	Uterosacral Ligament
I	Extrafascial (Simple)	Minimal	Partially Mobilized	Not Mobilized	At the uterus	Minimal	At the uterus
II	Modified Radical	Upper 1-2 cm removed	Partially Mobilized	Unroofed in parametrial tunnel	Medial to ureter	Medial to ureter	At midpoint
III	Radical	Upper 1/3 – 1/2 removed	Completely mobilized	Dissected until entry into bladder	At the origin (internal iliac/superior vesical)	At Pelvic Side Wall	At distal attachment
IV	Extended Radical	Upper 3/4	Completely mobilized	All peri-ureteral tissue removed	At origin (and ligation of sup. Vesical)	As Class III	As Class III
V	Partial Exenteration	As Class IV	Portion of bladder resected	Distal Ureter removed	As Class IV	As Class III	As Class III





Radical Hysterectomy

- 1895!



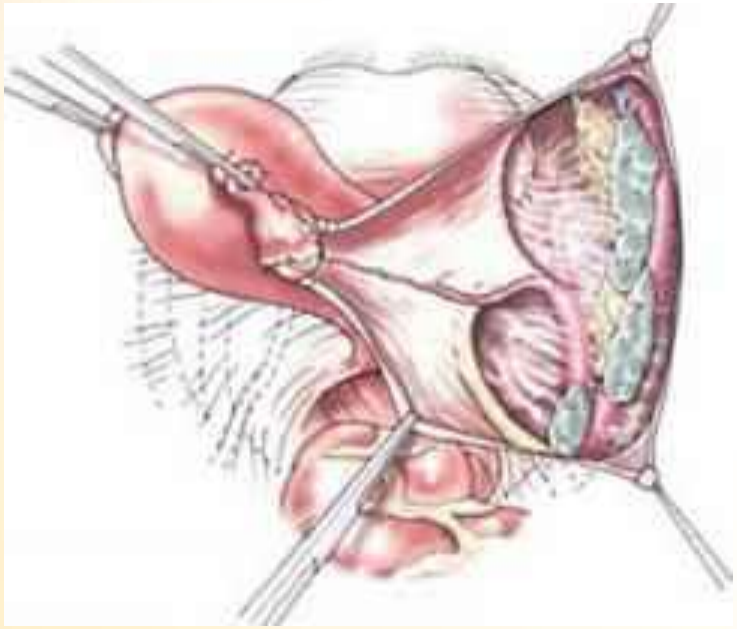
Class I
Class II
Class III

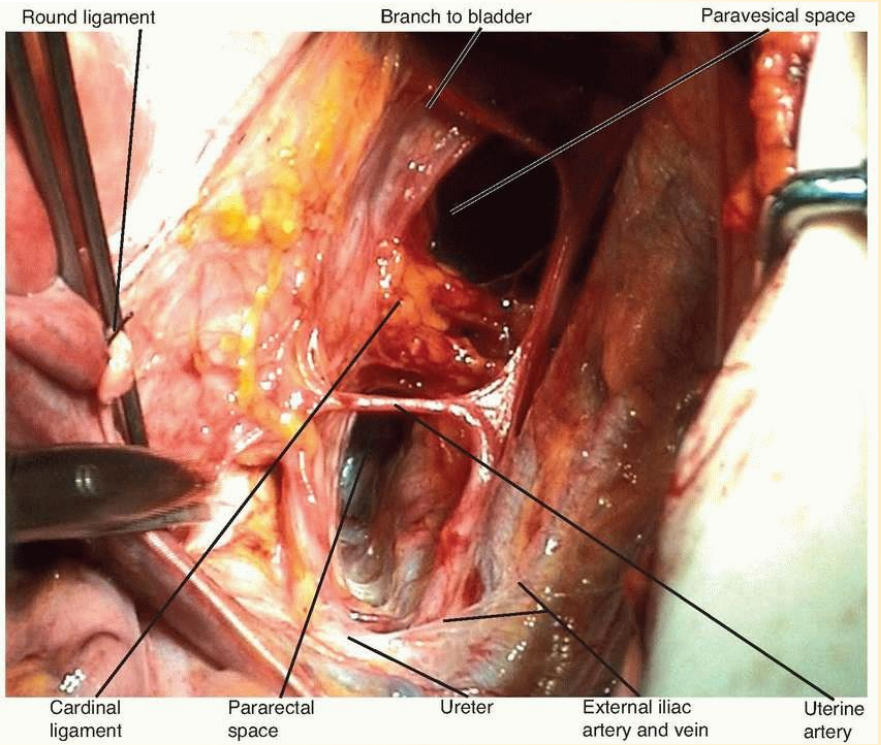
[1] Piver et al. Obstet Gynecol 1974;44:265.

Spaces

LOYOLA UNIVERSITY HEALTH SYSTEM

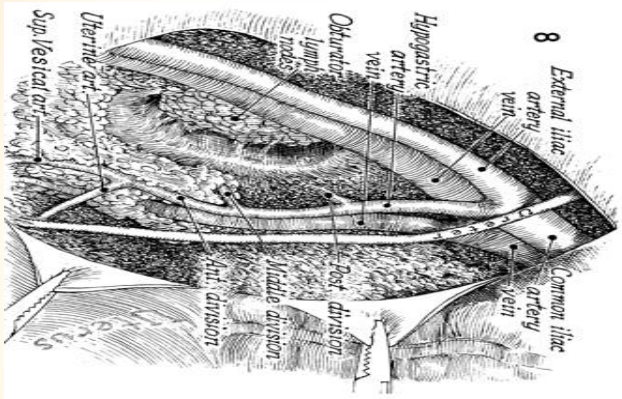
- Parametria = cardinal and uterosacral ligaments, free the ureter and transect uterine artery

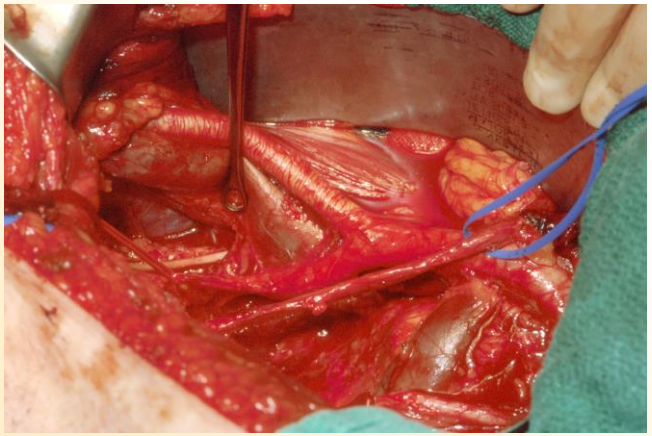


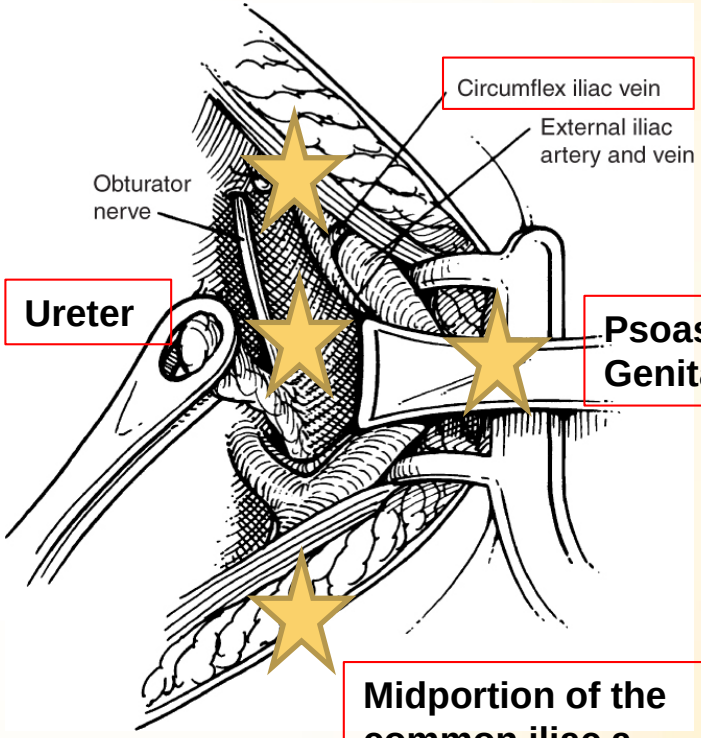


Pelvic LAD

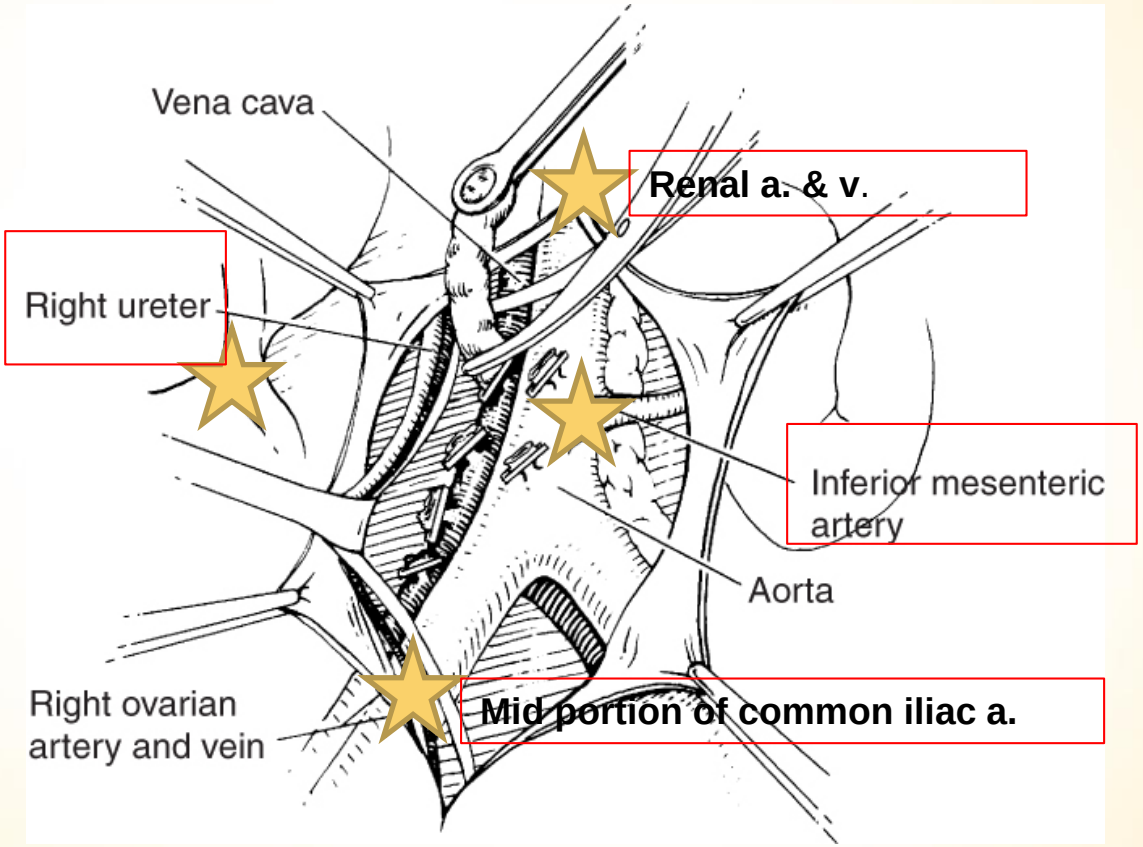
- Important prognostic information!



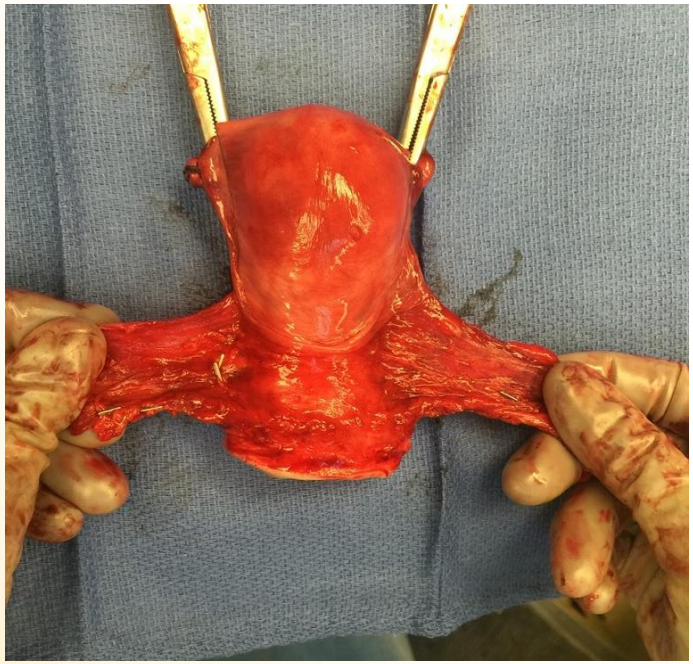


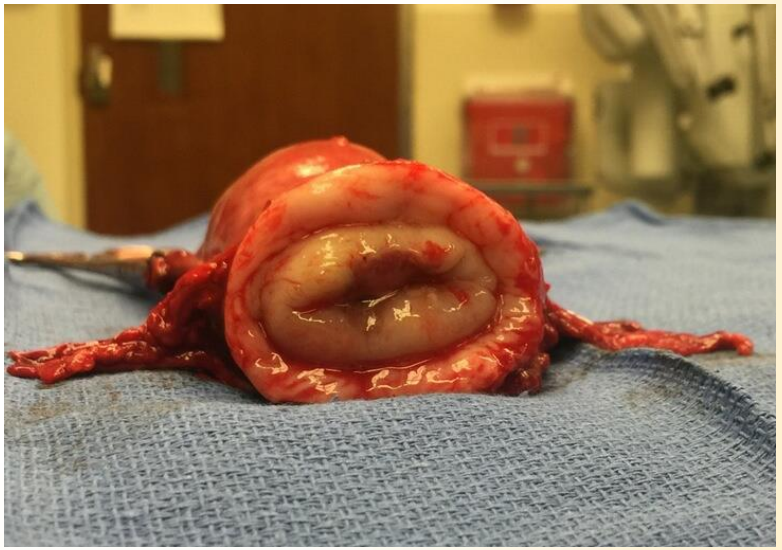


Para-aortic LAD



3 hours later…





Complications of radical surgery

LOYOLA UNIVERSITY HEALTH SYSTEM

- GU
  - Voiding dysfunction
  - 2.1% fistula
  - urine retention
    - Foley or Suprapubic catheter
- Anal dysfunction

Surgical Approach

LOYOLA UNIVERSITY HEALTH SYSTEM

- MIS = Open

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 15, 2018 VOL. 379 NO. 20

Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer

Pedro T. Ramirez, M.D., Michael Frumovitz, M.D., Rene Pareja, M.D., Aldo Lopez, M.D., Marcelo Vieira, M.D., Reitan Ribeiro, M.D., Alessandro Buda, M.D., Xiaojian Yan, M.D., Yao Shuzhong, M.D., Naven Chetty, M.D., David Isla, M.D., Mariano Tamura, M.D., Tao Zhu, M.D., Kristy P. Robledo, Ph.D., Val Gebski, M.Stat., Rebecca Asher, M.Sc., Vanessa Behan, B.S.N., James L. Nicklin, M.D., Robert L. Coleman, M.D., and Andreas Obermair, M.D.

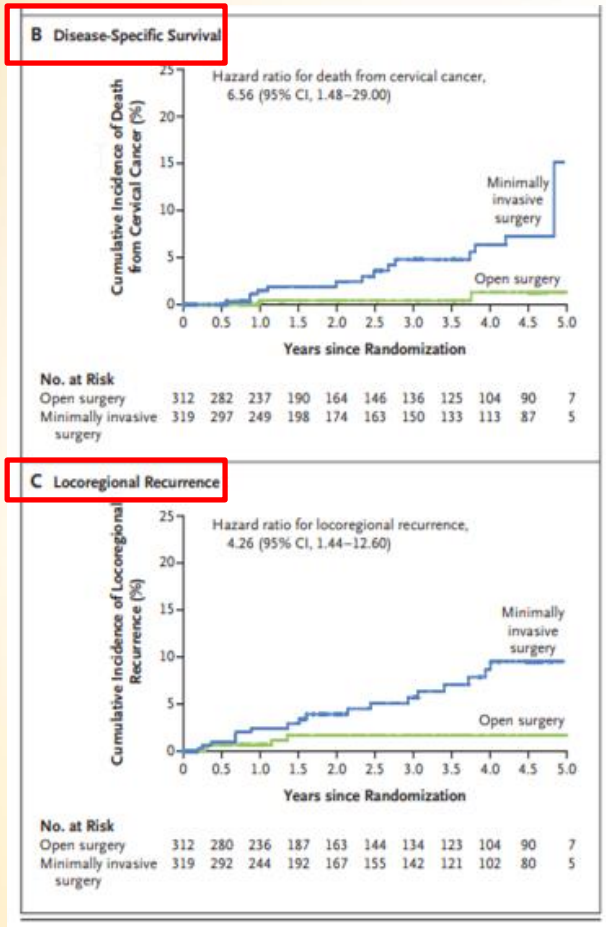
LOYOLA UNIVERSITY HEALTH SYSTEM

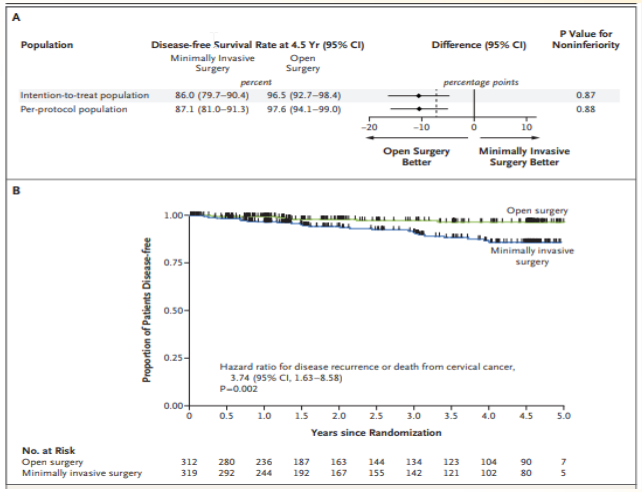
LACC: laparoscopic approach to cervical cancer

- Phase III prospective international, multicenter non-inferiority RCT of laparoscopic or robotic vs abdominal radical hysterectomy in patients with early stage cervical cancer
- Well designed with good surgical technical validity
- ?Is DFS with MIS not inferior to open? In early stage SCC, adeno, or adenosquamous (IA1 LVSI → IB1)
  - 90% power to declare non-inferiority at 4.5yrs with 7.2% margin
- Mean age 46yo, **91% IB1**

LACC

LOYOLA UNIVERSITY HEALTH SYSTEM





	MIS (84.4% lpsc, 15.6% robotic)	Open
N	319	312
4.5yr DFS	**86%**	**96.5%**
3yr DFS	91.2%	97.1%
3yr OS	93.8%	99%
HR death from any cause 6 (1.77-20.3)		

ORIGINAL ARTICLE

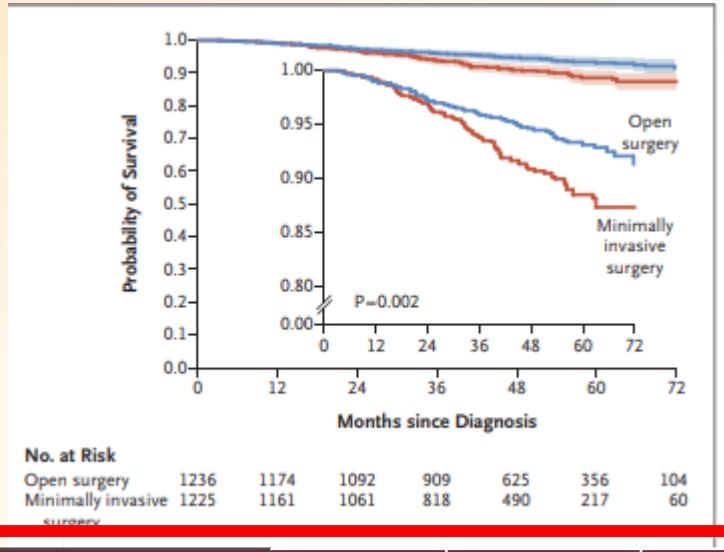
Nov 2018

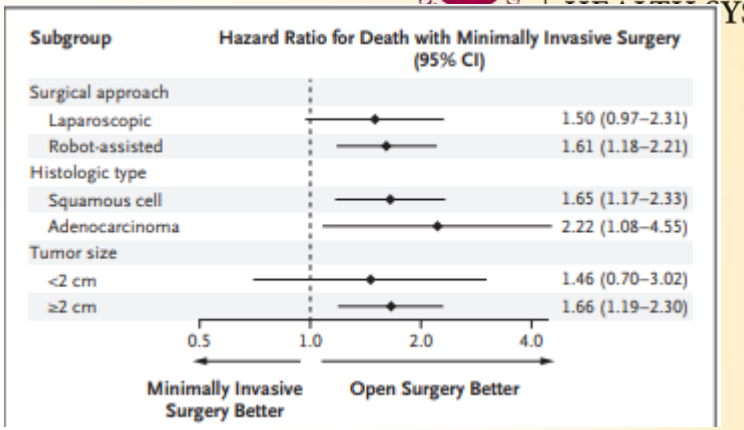
Survival after Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer

Alexander Melamed, M.D., M.P.H., Daniel J. Margul, M.D., Ph.D., Ling Chen, M.D, M.P.H., Nancy L. Keating, M.D., M.P.H., Marcela G. del Carmen, M.D., M.P.H., Junhua Yang, M.S., Brandon-Luke L. Seagle, M.D., Amy Alexander, M.D., Emma L. Barber, M.D., Laurel W. Rice, M.D., Jason D. Wright, M.D., Masha Kocherginsky, Ph.D., Shohreh Shahabi, M.D., E.M.H.A., and J. Alejandro Rauh-Hain, M.D., M.P.H.

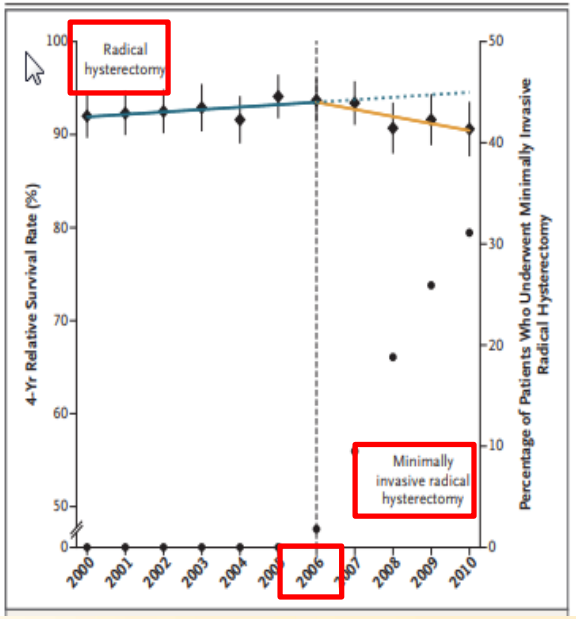
- A cohort study of Stage IA2 or IB1 cervical cancer from 2010-2013
- To determine effect of MIS on all cause mortality of women undergoing radical hysterectomy
- Median f/u 45 months
- 1225/2461 (49.8%) had MIS

SEER





	MIS	Open	HR
4 year mortality	9.1%	5.3%	1.65



4yr relative survival rate of early stage cervical cancer tx with radical hyst: Annual % change		
	Open	MIS
2000-2006	0.3%	
2006-2010		Decline 0.8% per year after 2006

ASCO 2018, Abstract #5502: outcomes and costs of open, robotic, and laparoscopic radical hysterectomy for stage IB1 cervical cancer

LOYOLA UNIVERSITY HEALTH SYSTEM

- SEER 2010-2013 IB1 SCC or adenocarcinoma of the cervix s/p radical hysterectomy: open = 982, MIS = 910,
- **Tumor ≥ 2cm 5yrOS**: MIS 81.3% (75.6-87.3%) vs open 90.8% (87.7-93.9%),
- **HR: 2.14** (95%CI) (1.36-3.38), p <0.001
- Cost: Open ($12,080) > Robotic ($11,562) > Lpsc ($9,649)

- Radical hysterectomy with bilateral pelvic lymph node dissection (with or without SLN mapping) is the preferred treatment for FIGO stage IA2, IB1, IB2 and select IB3-IIA1 lesions when fertility preservation is not desired. Radical hysterectomy results in resection of much wider margins compared with a simple hysterectomy, including removal of parts of the cardinal and uterosacral ligaments and the upper 1–2 cm of the vagina; in addition, pelvic and sometimes para-aortic nodes are removed. The Querleu and Morrow classification system[1] is a modern surgical classification that describes degree of resection and nerve preservation in three-dimensional (3D) planes of resection.[2] Procedural details for the most commonly used types of hysterectomy are described in Table 1 (see CERV-C 5 of 7).
- The standard and historical approach for radical hysterectomy is with an open abdominal approach. Previous iterations of the guidelines indicated that radical hysterectomy could be performed via open laparotomy or minimally invasive surgery (MIS) laparoscopic approaches, using either conventional or robotic techniques. However, several key contemporary reports have questioned the presumed therapeutic equivalency of open vs. MIS approaches. A prospective randomized trial[3] demonstrated that minimally invasive radical hysterectomy was associated with lower rates of DFS and OS than open abdominal radical hysterectomy. Moreover, two recent epidemiologic studies also demonstrated that minimally invasive radical hysterectomy was associated with shorter OS than open surgery among women with stage IA2-IB1 cervical cancer.[4,5] See Discussion for additional details.
- Given recently presented findings of significantly poorer survival outcomes with the minimally invasive approach compared to the open approach in a randomized controlled trial of women with early-stage cervical cancer, women should be carefully counseled about the short-term versus long-term outcomes and oncologic risks of the different surgical approaches.[3-5]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Cervical Cancer

NCCN Evidence Blocks™

Version 4.2019 — March 29, 2019

2019 ASCO ANNUAL MEETING

Abstract #5504

Recurrence rates in cervical cancer patients treated with abdominal versus minimally invasive radical hysterectomy: A multi-institutional analysis of 700 cases.

LOYOLA UNIVERSITY HEALTH SYSTEM

- Retrospective multi-institutional review
- Stage IA1, IA2, IB1 from 2010-2017
- N=704
- Multivariate analysis:
  - MIS OR recurrence 2.37 (p=0.031)
    - (race, comorbidities, preop tumor size, histology, grade, smoking, LVSI, vaginal margin status, adjuvant tx)

	Open	MIS – 90% robotic	p
N	185 (26.3%)	519 (73.7%)	
recurrence	13/185 (7%)	42/519 (8.1%)	NS
death	10/185 (5.4%)	26/519 (5%)	NS
Recurrence rate tumor </= 2cm	5/121 (4.1%)	25/415 (6%)	0.34

Abstract #5504

LOYOLA UNIVERSITY HEALTH SYSTEM

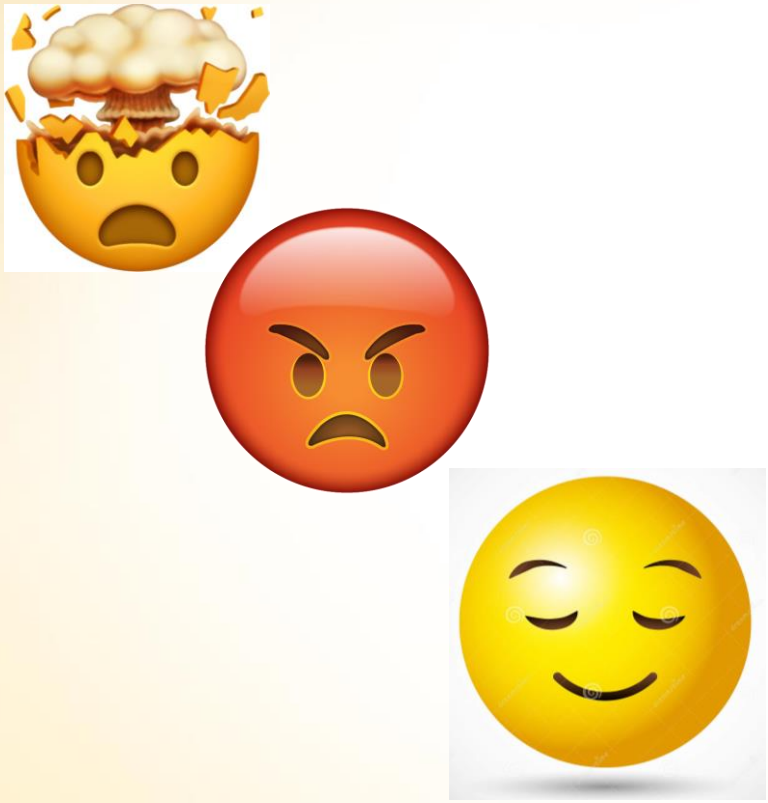
- <2cm MIS may be ok but data not consistent, and surgeon correct about lesion size <2cm only 75%
- Uterine manipulator?...likely not the culprit

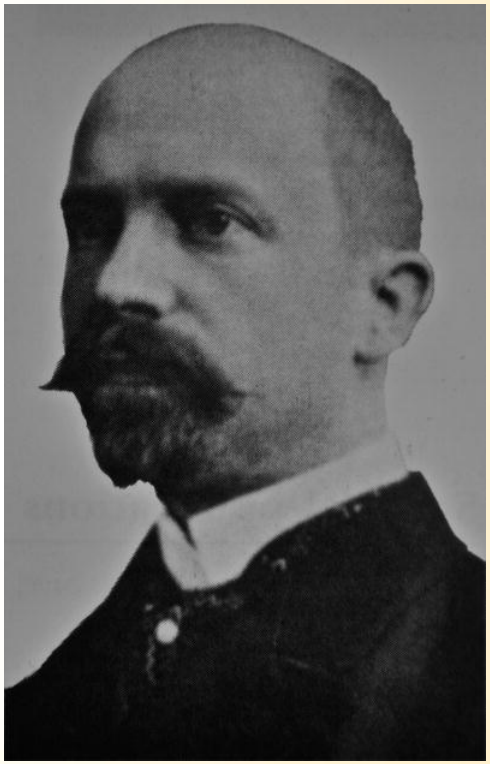
	Recurrence
No vaginal manipulator	0/26
Intra-uterine: (Vcare, Zumi, Rumi)	19/270 (7%)
Vaginal manipulator: (EEA, colpo probe)	22/210 (11%)

- # rad hysts on decline, resource effort: is open rad hyst that bad vs put effort into vaccination and prevention

Today: Data vs emotion

LOYOLA UNIVERSITY HEALTH SYSTEM





Fertility Preservation

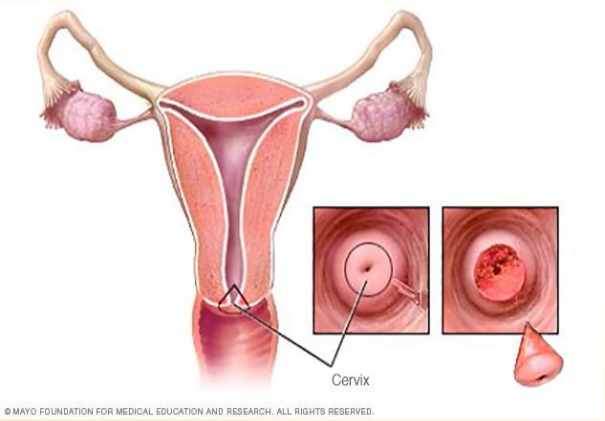
LOYOLA UNIVERSITY HEALTH SYSTEM

- 40% early stage cervical cancer <40yo
- HB 2617 – active now
  - IL is the 5th state to do this
  - mandates IL insurance cover oncofertility and fertility preservation
  - Oocyte, sperm, embryo preservation
- Patient resources
  - Kristin Smith: Chicago
    - ksmith@nm.org
  - Jennifer Elvikis: West suburbs,
    - jelvikis@nm.org
      - Oak Brook office

Fertility Sparing Surgery

LOYOLA UNIVERSITY HEALTH SYSTEM

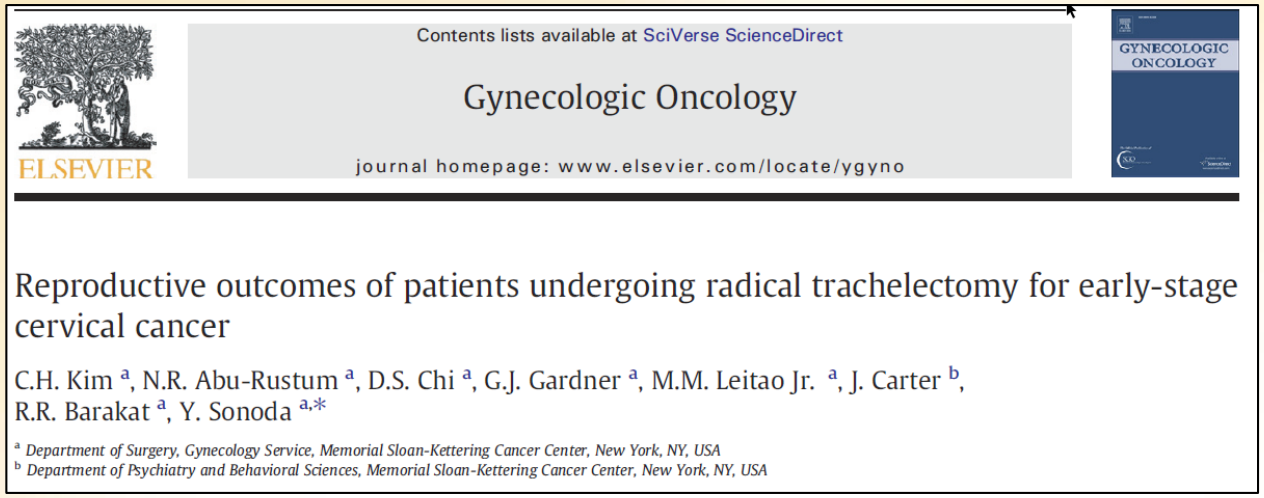
- Stage IA1 without LVSI
  - Conization
    - SEER database study (n = 1409)
      - Age ≤40 years with stage IA1 cervical cancer
      - No significant difference in 5 yr survival between those who underwent conization versus hysterectomy (98 vs 99%)



Fertility Sparing Surgery: Radical trachelectomy (Plante)

LOYOLA UNIVERSITY HEALTH SYSTEM

- <40yo, no impaired fertility, lesion <2cm, stage IA-IB1(old), negative upper endocervical margin (at least 5mm), negative nodes
- 2-4% recur
- 2-6% mortality
- 70% of attempts at pregnancy are successful with 50% term delivery rate
- 16% 1st trimester miscarriage, 4% 2nd trimester loss



Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Reproductive outcomes of patients undergoing radical trachelectomy for early-stage cervical cancer

C.H. Kim [a], N.R. Abu-Rustum [a], D.S. Chi [a], G.J. Gardner [a], M.M. Leitao Jr. [a], J. Carter [b], R.R. Barakat [a], Y. Sonoda [a,*]

[a] Department of Surgery, Gynecology Service, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
[b] Department of Psychiatry and Behavioral Sciences, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

- N=105, 2001-2010 with IB1 (75%) tx with radical trachelectomy, PLND, cerclage
- Median age 32
- 1st trimester miscarriage: 4% (N=1)
- 2nd trimester miscarriage: 11% (N=3)
- 74% conceptions → live 3rd trimester births
  - 32-36weeks: 35%
  - 37weeks: 65%

OB outcomes (Kim, et al)

LOYOLA UNIVERSITY HEALTH SYSTEM

- 35/105 attempted conception 6 months after surgery
- 23/35 (66%) were successful in conceiving
- 4 patient had 2 pregnancy
  - 2nd all delivered 32-36 weeks
- 20 live births → all deliveries C-section
- ART use (N=18): 10 cervical stenosis
- Route of trachelectomy did not matter
- Preterm and 2nd trimester loss due to cerclage disruption

Obstetrical outcomes of 23 women after radical trachelectomy.

Total no. of conceptions	27	RAT	RVT	RRT
Total live births				
C/S at 32–36 6/7 weeks	7 (35%)	1	6	0
C/S at ≥37 weeks[a]	13 (65%)	4	9	0
Spontaneous abortions				
1st trimester	1 (4%)	0	1	0
2nd trimester	3 (12%)	3	0	0
Elective terminations				
1st trimester	2 (8%)	0	2	0
2nd trimester	1 (4%)	0	1	0

C/S: Cesarean section, RAT: radical abdominal trachelectomy, RVT: radical vaginal trachelectomy, RRT: radical robotic trachelectomy.

[a] The 2 patients who were pregnant during the study time period have since delivered full term via C/S.

Fertility Sparing: Unique IB1 or less Big CKC and Pelvic lymphadenectomy

LOYOLA UNIVERSITY HEALTH SYSTEM

- **Stage IA1 with LVSI, IA2, or IB1**
  - Squamous carcinoma or adenocarcinoma histology
  - **Lesion size ≤2 cm** with limited endocervical extension as assessed by colposcopy and MRI
  - No evidence of lymph node metastasis

- Less is More?
  - recurrence (4.4 %)
  - mortality (2.1 %)

Evolution in fertility-preserving options for early-stage cervical cancer: radical trachelectomy, simple trachelectomy, neoadjuvant chemotherapy. Plante MInt J Gynecol Cancer. **2013** Jul;23(6):982-9.

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

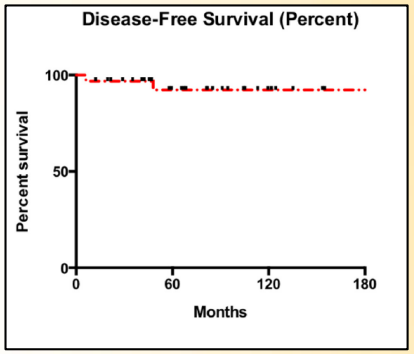
Long-term results of fertility-sparing treatment for early-stage cervical cancer

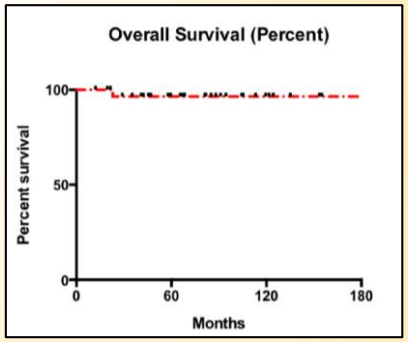
Giorgio Bogani [a], Valentina Chiappa [a], Daniele Vinti [a,b,c], Edgardo Somigliana [a,b,c], Francesca Filippi [a,b], Giulia Murru [a,*], Ferdinando Murgia [a], Fabio Martinelli [a], Antonino Ditto [a], Francesco Raspagliesi [a]

[a] Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Italy
[b] Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milan, Italy
[c] Department of Obstetrics-Gynecology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Italy

LOYOLA UNIVERSITY HEALTH SYSTEM

- Prospective study of 32 women <40 with Stage IA2 (9,28%), IB1(21, 66%), IB2 (2, 6%) tx with CKC and pelvic LAD (30) or SLN (2)
- Median f/u 75 months
- DFS 94%, OS 97%
- Safe, but 1/5 needed more treatment





April 2019

Pregnancy outcome, Bogani et al

LOYOLA UNIVERSITY HEALTH SYSTEM

- 11/16 (69%) who attempted to conceive became pregnant
- Important because trachelectomy associated with more OB complications than CKC

Table 4
Reproductive outcomes of patients willing to preserve their childbearing potential.

Reproductive-related parameters	Characteristics ($n = 25$)
No wishing pregnancy at the moment	9 (36%)
Wishing pregnancy	16 (64%)
Achieving pregnancy	11 (44%) considering all patients preserving fertility potential 11 (69%) considering patients wishing pregnancy
I trimester miscarriage	0
II trimester miscarriage	1 (4%)
Ongoing pregnancy	1 (4%)
Live children[a]	9 (36%)
Uneventful term pregnancies	8 (32%)
Preterm delivery	1 (4%)

Data are expressed in number (%).
[a] Two patients were submitted to prophylactic cervical cerclage.

OB outcomes:
Term = 8
Preterm (32 week) = 1
2nd trimester miscarriage = 1
Early pregnancy = 1

Ovaries

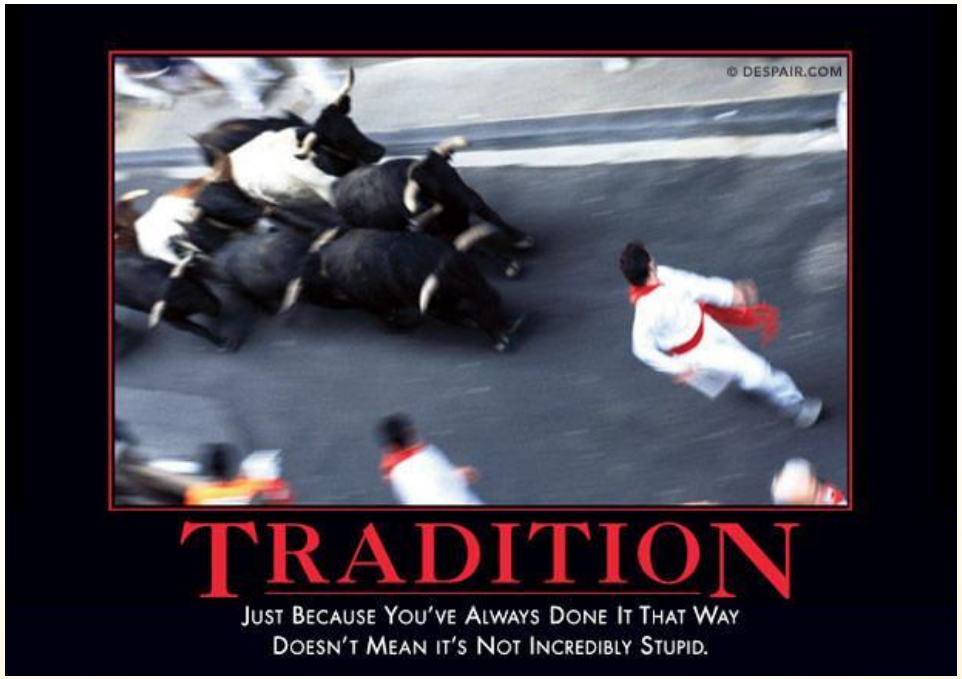
LOYOLA UNIVERSITY HEALTH SYSTEM

- SCC, <1% ovary mets
- Stage IB adenocarcinoma 1.3-7.7% ovary mets, higher for higher stages
- transposed ovaries fail 20% if unirradiated, 42% with irradiation
- benign adnexal mass after RT up to 4%

SLN (Sentinel Lymph Nodes)

LOYOLA UNIVERSITY HEALTH SYSTEM

- Lymph node most important prognostic factor
- PLND → 20% lymphedema



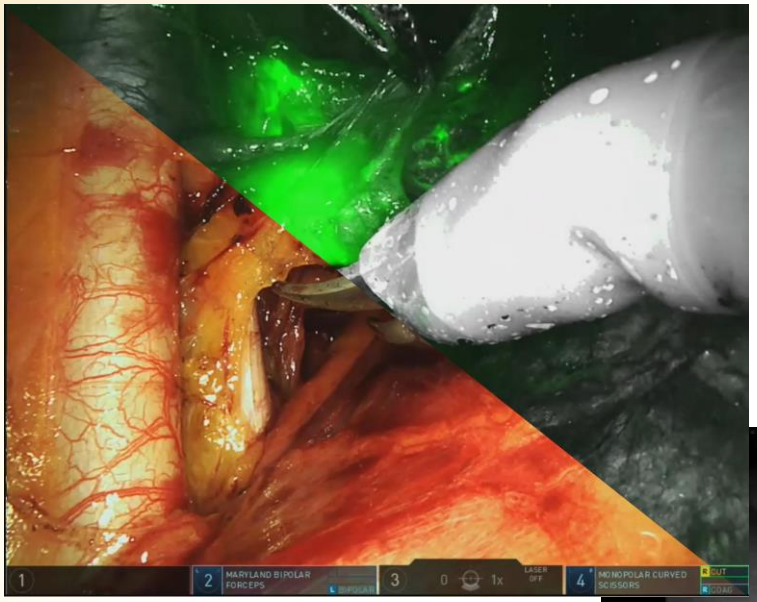
Sentinel lymph nodes

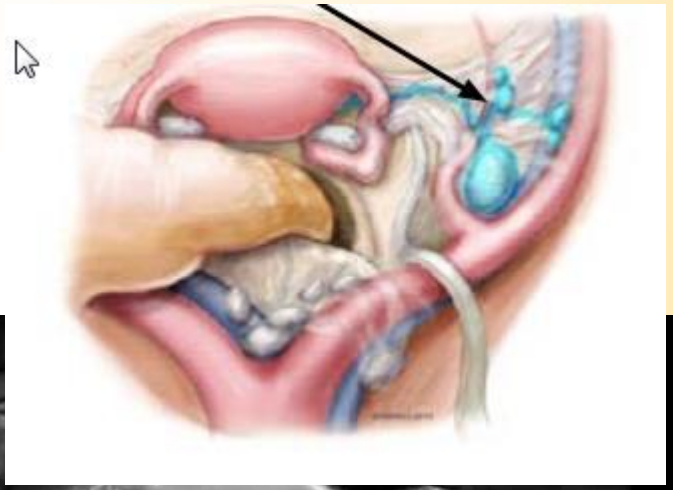
LOYOLA UNIVERSITY HEALTH SYSTEM

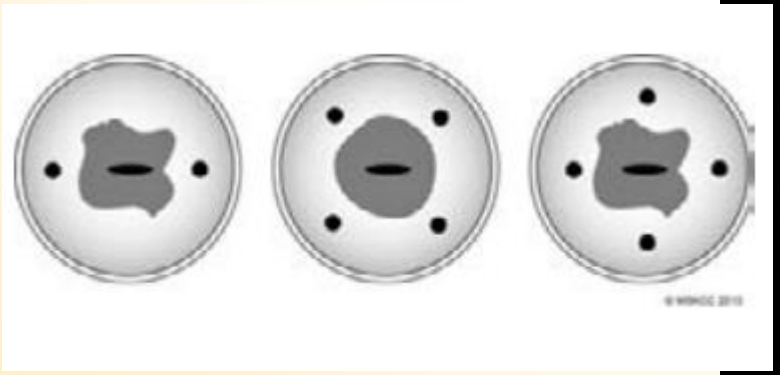
- Blue dye (**isofulfan blue**) CI: sulfa allergy
- Technetium 99 (Tc99)
- Near infared (**ICG**: indocyanine green) water soluble CI: iodine/shellfish allergy (requires FIREFLY technology)
- Ultrastaging: IHC for pancytokeratin AE1 and AE3, cytokeratin
- Macro met: >2mm foci or mets, micro mets: 0.2-2.mm tumor, isolated tumor cells: <2mm or individual cells

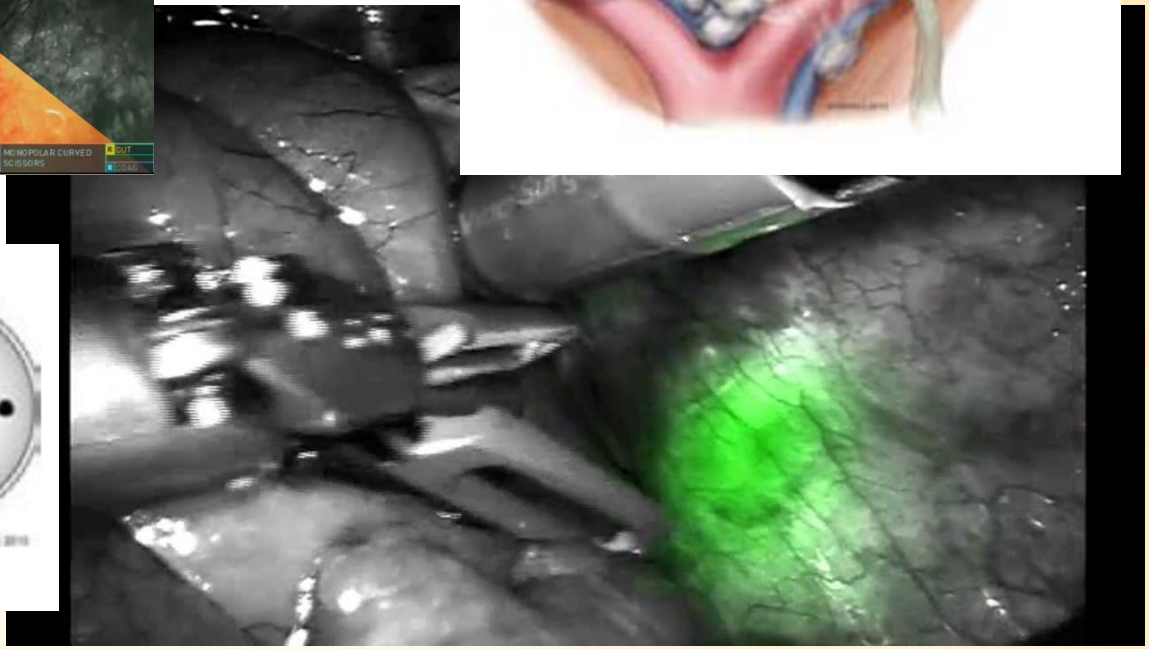
Photos firefly, blue dye

LOYOLA UNIVERSITY HEALTH SYSTEM









SLN - Cervix

LOYOLA UNIVERSITY HEALTH SYSTEM

- Still investigational, but included in NCCN guidelines
- Sensitivity 92%, NPV 98%
- Tumor </= 2cm
  - Detection 95.4%, Sensitivity 100%
- Tumor >2cm
  - Detection 80.1%, Sensitivity 89.3%

	Sensitivity	Specificity
SLN	91%	100%
PET	75%	98%
MRI	56%	93%
CT	58%	92%

Adjuvant XRT after surgery

LOYOLA UNIVERSITY HEALTH SYSTEM

- Sedlis and Peters criteria

LVSI	Stromal Invasion	Tumor Size (cm) (determined by clinical palpation)
+	Deep 1/3	Any
+	Middle 1/3	≥2
+	Superficial 1/3	≥5
-	Middle or deep 1/3	≥4

LVSI: Lymphovascular space invasion

Locally advanced Cervix

LOYOLA UNIVERSITY HEALTH SYSTEM

- Med Onc, Rad Onc, GYN Onc
- Cisplatin
- If toxicity, carbo AUC 2 weekly

- Main treatment XRT based

CONCURRENT CISPLATIN-BASED RADIOTHERAPY AND CHEMOTHERAPY FOR LOCALLY ADVANCED CERVICAL CANCER

PETER G. ROSE, M.D., BRIAN N. BUNDY, PH.D., EDWIN B. WATKINS, M.D., J. TATE THIGPEN, M.D., GUNTHER DEPPE, M.D., MITCHELL A. MAIMAN, M.D., DANIEL L. CLARKE-PEARSON, M.D., AND SAM INSALACO, M.D.

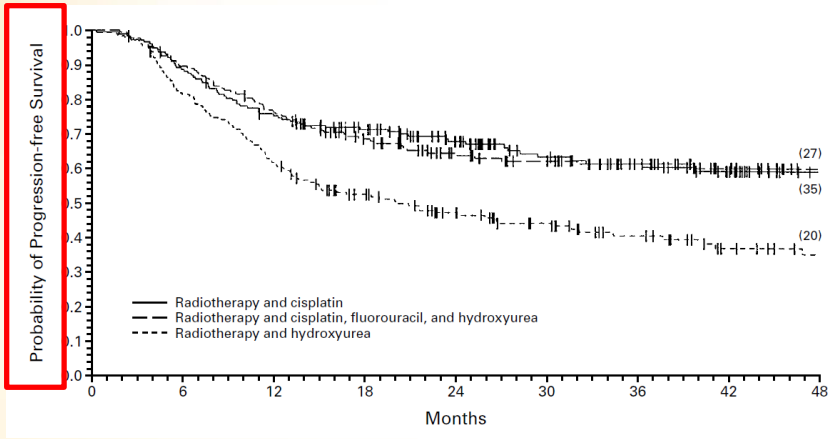
LOYOLA UNIVERSITY HEALTH SYSTEM

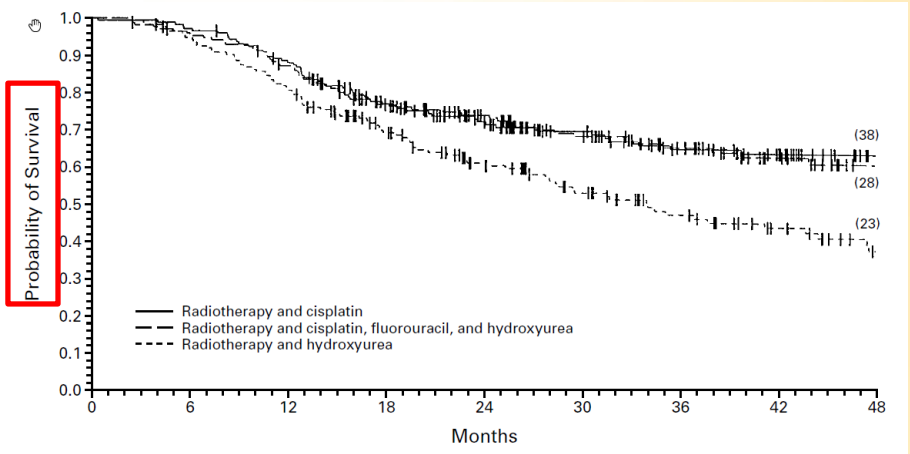
- Stage IIB, III, IVA (locally advanced)
- XRT vs XRT cis vs XRT cis/5FU/hydroxyurea vs XRT hydroxyruea

	CISPLATIN	FLUOROURACIL	HYDROXYUREA
Regimen			
Cisplatin	40 mg/m² of body-surface area IV 4 hr before radiotherapy at weeks 1–6		
Cisplatin, fluorouracil, and hydroxyurea	50 mg/m² IV on days 1 and 29	4 g/m², as a 96-hour infusion, on days 1 and 29	2 g/m² orally twice weekly 2 hr before radiotherapy at weeks 1–6
Hydroxyurea			3 g/m² orally twice weekly 2 hr before radiotherapy at weeks 1–6

The New England Journal of Medicine April 15, 1999

- Chemo improved all outcomes and cisplatin based chemo regimens best
- Less toxicity in cisplatin alone





	Cis	Cis/5FU/hydroxy	Hydroxy
RR progression	0.57 (0.42-0.78)	0.55 (0.4-0.71)	Baseline
RR death	0.61 (0.44-0.85)	0.58 (0.41-0.81)	baseline

NCCN alert

LOYOLA UNIVERSITY HEALTH SYSTEM

- Feb 1999
- Concomitant chemo therapy and radiation should be considered in all cervix cancer patients

Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis

John A Green, John M Kirwan, Jayne F Tierney, Paul Symonds, Lydia Fresco, Mandy Collingwood, Christopher J Williams

LOYOLA UNIVERSITY HEALTH SYSTEM

- 10% survival benefit with addition of chemo to XRT
- Meta-analysis (N=4580)
- chemoXRT improves OS , HR 0.71

THE LANCET • Vol 358 • September 8, 2001

Outback Chemo

LOYOLA UNIVERSITY HEALTH SYSTEM

- Outback Trial, GOG 274: awaiting results, carbo/taxol after cis/XRT
- RTOG 0724: enrolling, carbo/taxol after adjuvant chemo/XRT for high risk patients

Other Highlights

LOYOLA UNIVERSITY HEALTH SYSTEM

- No indication for completion hysterectomy in locally advanced cervix
- NACT → rad hyst → postop XRT vs XRT worse DFS, toxicity and no change in OS
- Cis/gem concurrent with XRT followed by outback cis/gem significantly more toxicity

Metastatic (Tewari et al)

LOYOLA UNIVERSITY HEALTH SYSTEM

Final Overall Survival of the Phase III Randomised Trial of Chemotherapy with and without Bevacizumab for Advanced Cervical Cancer: An NRG Oncology/Gynecologic Oncology Group Study

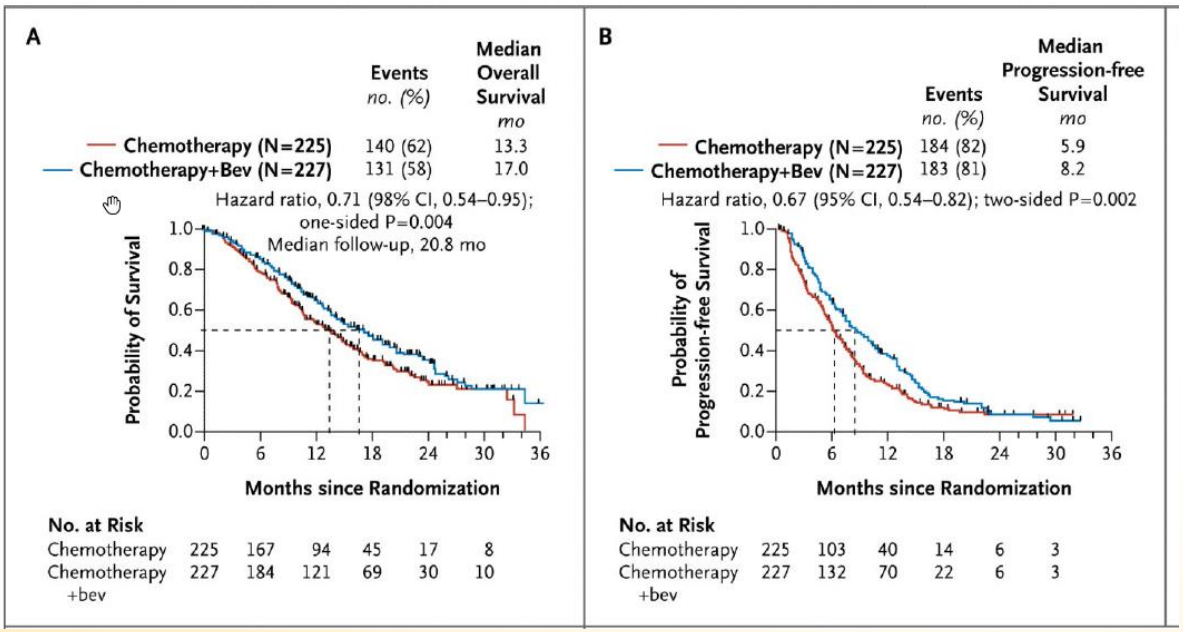
- Phase III RCT with 90% power to detect 30% reduction in risk of death
- Cisplatin 50mg/m2 + paclitaxel 135 or 175mg/m2 IV +/- bevacizumab 15mg/kg q21 days
- Topotecan 0.75mg.m2 IV D1-3 + paclitaxel 175mg/m2 +/- bevacizumab 15mg/kg q21days
- Until toxicity, progression, complete response

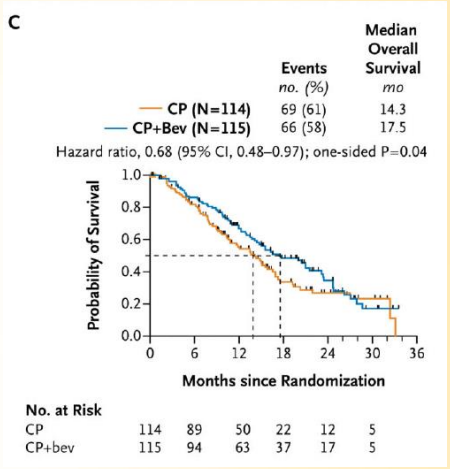
Lancet. 2017 October 07; 390(10103):

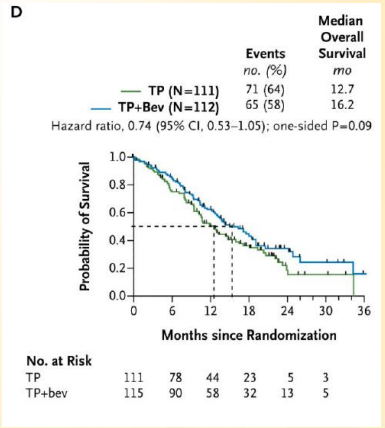
Improved Survival with Bevacizumab in Advanced Cervical Cancer

LOYOLA UNIVERSITY HEALTH SYSTEM

- Topo/taxol not superior to cis/taxol (HR 1.2)
- Addition of bev to chemo increased OS from 13 to 17 months (4month increase OS), HR death 0.71, higher response rates
- Bev side effects : HTN, VTE, GI fistula





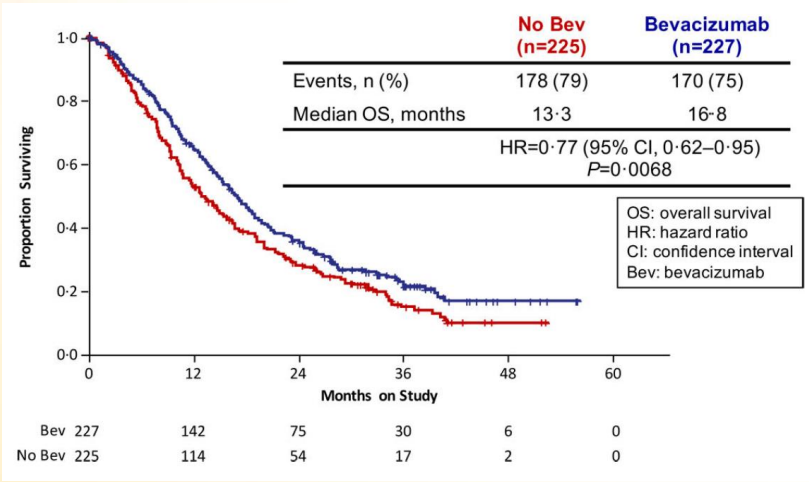


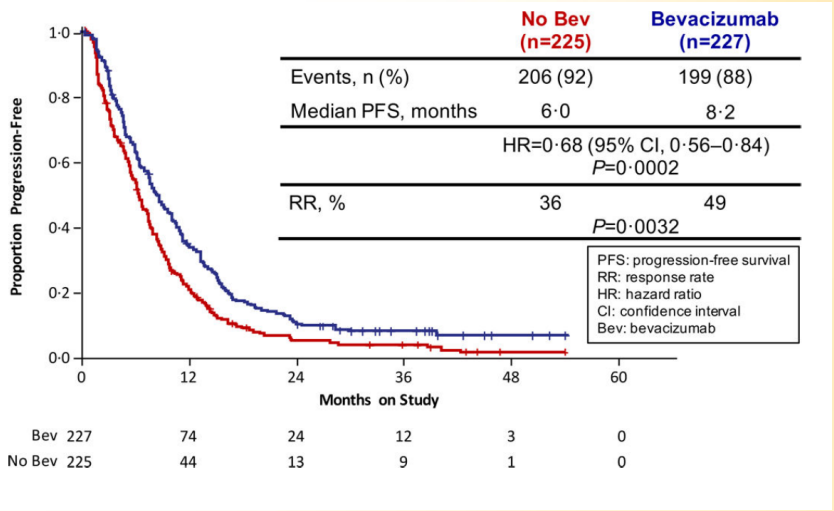
N Engl J Med. 2014 February 20; 370(8): 734–743.

Tewari Final Update

LOYOLA UNIVERSITY HEALTH SYSTEM

- Improved OS and PFS with bev
- Bev improved OS and PFS with either chemo regimen





Recurrent (Chemo vs Surgery)

LOYOLA UNIVERSITY HEALTH SYSTEM

Surgery = anterior or posterior of total pelvic exetenteration.
-isolated central pelvic recurrence with negative surgical margins.

Chemo: based on toxicity
-platinum/taxane +/- bev preferred initial tx
    -cisplatin preferred if platinum naïve
-taxol/avastin
-Pembrolizumab becoming more prime time
-gem, topotecan, single agent avastin

NCCN

LOYOLA UNIVERSITY HEALTH SYSTEM

SYSTEMIC THERAPY REGIMENS FOR CERVICAL CANCER[a]

Chemoradiation		
Preferred Regimens • Cisplatin • Carboplatin if patient is cisplatin intolerant See Evidence Blocks on CERV-F (EB-1) and CERV-F (EB-2)		
Recurrent or Metastatic Disease		
First-line combination therapy[b,c]	**Possible first-line single-agent therapy[c]**	**Second-line therapy[e]**
Preferred Regimens • Cisplatin/paclitaxel/bevacizumab[d,1] (category 1) • Carboplatin/paclitaxel/bevacizumab[d] **Other Recommended Regimens** • Cisplatin/paclitaxel (category 1)[2,3] • Carboplatin/paclitaxel[4,5] (category 1 for patients who have received prior cisplatin therapy) • Topotecan/paclitaxel/bevacizumab[d,1] (category 1) • Topotecan/paclitaxel[1] • Cisplatin/topotecan[6]	**Preferred Regimens** • Cisplatin[3] **Other Recommended Regimens** • Carboplatin[7] • Paclitaxel[8,9]	**Preferred Regimens** • Pembrolizumab for PD-L1–positive[f] or MSI-H/dMMR tumors[g] **Other Recommended Regimens** (All agents listed here are category 2B unless otherwise noted) • Bevacizumab[d] • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Ifosfamide • Irinotecan • Mitomycin • Pemetrexed • Topotecan • Vinorelbine **Useful in Certain Circumstances** • Larotrectinib or entrectinib for *NTRK* gene fusion-positive tumors (category 2B)

Clinical trials

LOYOLA UNIVERSITY HEALTH SYSTEM

- Listeria injections

Thanks!

LOYOLA UNIVERSITY HEALTH SYSTEM

Questions