Gynecologic Oncology at Your Cervix: From Paps to Palliation

Christine Robinson, MD, FRCSC

March 2nd, 2019

Presenter Disclosure

- **Speaker: Dr. Christine Robinson**

- **Relationships with financial sponsors:**
  - **I have nothing to disclose (none)**

Mitigating Potential Bias

- Not Applicable

Objectives

- At the end of this session, participants will be able to:

1. Use the cervix check screening guidelines to determine who needs to be screened and what to do with each pap test result.

2. Describe how cervical cancer is diagnosed and staged via biopsy and physical examination.

3. Differentiate between which patients require upfront surgery and which require upfront chemotherapy and radiation for primary treatment of their disease.

4. Explain the follow up recommendations for these patients, most common recurrence presentations, and what treatments are available for the recurrent patient population.

Cervical Cancer Screening

Benefits	Harms
Decrease in cervical cancer mortality by up to 80% with pap test screening	False positives
Cervical dysplasia can be removed with procedures at colposcopy	False negatives
Detecting cancer at an earlier stage can result in simpler treatment, more options, and less need for chemotherapy	Anxiety around screening and follow-up
	Discomfort with pap or colposcopy
	Treatment with cone or LEEP could increase risk of pre-term birth, low birth wait, Cesearean section, or premature rupture of membranes

www.cancercare.mb.ca/screening/hcp

Cervical Cancer Screening Guidelines

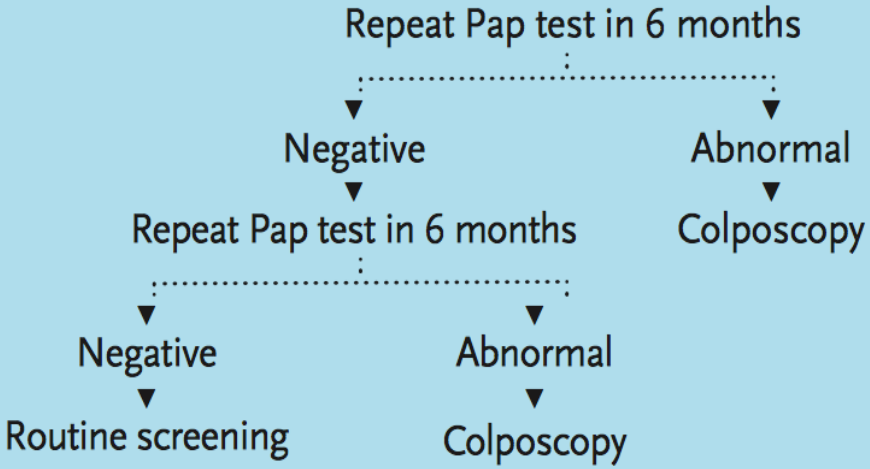
All women who have ever been sexually active	**Initiate screening with Pap tests* at age 21** **Routine screening should continue every 3 years until age 69** Health care providers should discuss the benefits and harms of screening with their patients
HPV Vaccinated	
Women having sex with women	
Transgender	
Pregnant	
Immunocompromised or HIV positive	Screen every year
Previous high-grade lesions	

www.cancercare.mb.ca/screening/hcp

Screening Guidelines

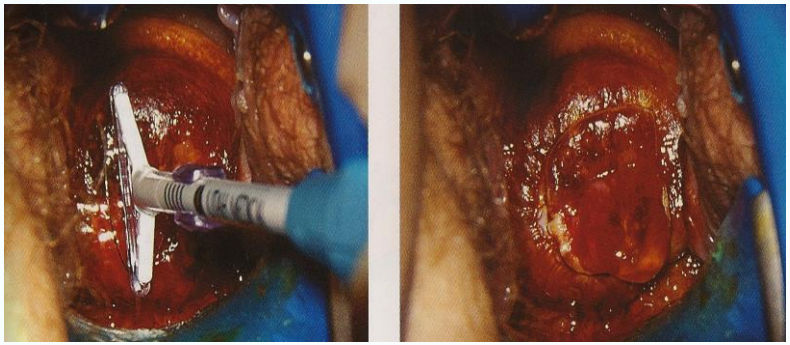
Never been sexually active Sexual activity includes intercourse, as well as digital or oral sexual activity involving the genital area with a partner of either gender	Screening **not** recommended Women who are not sexually active by age 21 should delay screening until sexually active
Hysterectomy	Screening the vaginal vault is not recommended if: • Hysterectomy was total, • Hysterectomy was performed for a benign disease (pathology negative for high-grade dysplasia), and • The woman has no previous high-grade Pap test result If Pap test results or hysterectomy pathology is unavailable, continue screening until 2 negative vaginal vault tests are obtained
70 years of age or older	**Discontinue screening if the woman has had 3 negative Pap tests in the previous 10 years**

Management of Cytology Results

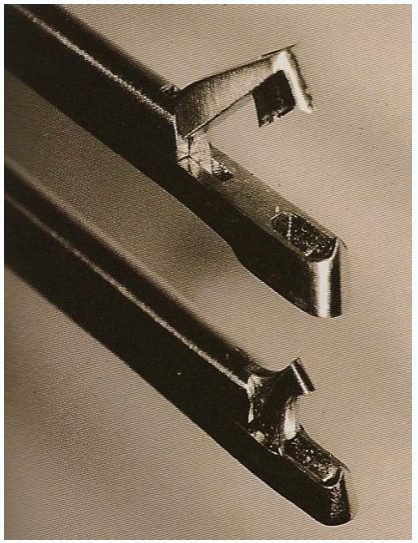
Negative	Routine screening every 3 years The absence of transformation zone is not a reason to repeat a Pap test earlier than the recommended interval
Unsatisfactory	Repeat Pap test in 3 months If persistent (2 consecutive, or 2 within 12 months) unsatisfactory due to "obscuring blood" or "obscuring inflammation," refer for colposcopy
ASC-US Atypical squamous cells of undetermined significance	
LSIL Low-grade squamous intraepithelial lesion	

Management of Cytology Results

AGC Atypical glandular cells	Refer for colposcopy and endocervical curettage If the woman is ≥ 35 years of age or has abnormal bleeding refer for endometrial biopsy
ASC-H Atypical squamous cells, cannot rule out high-grade	Refer for colposcopy
HSIL High-grade squamous intraepithelial lesion	
AIS Adenocarcinoma in situ	Refer for colposcopy and endocervical curettage
Squamous carcinoma, adenocarcinoma, other malignant neoplasms	Refer for colposcopy and oncology



Diagnosis of Cervical Cancer



- Often asymptomatic
- On biopsy at colposcopy after referral for symptoms, abnormal cervix, abnormal pap, etc.
- Can be diagnosed after cone/LEEP for high grade lesions (microscopic).
- Diagnosed on routine exam or for symptoms: postcoital bleeding, intermenstrual bleeding, postmenopausal bleeding, abnormal discharge.
- Sometimes pressure, pain, leg swelling, renal failure, fistula, GI/GU.

FIGO STAGING

Stage 1 CONFINED to Cervix

STAGE IA1 ≤3mm depth X ≤7mm extension (MICROINVASIVE)

STAGE IA2 3-5mm depth X ≤7mm extension

STAGE IB1 ≤4cm **May be Grossly visible**

STAGE IB2 >4cm

STAGE II LOCAL extension off Cervix

Stage IIA Upper vagina (IIA1 and IIA2 based on size)

Stage IIB Parametrial invasion

STAGE III FURTHER extension

Stage IIIa Lower vagina

Stage IIIb Outer parametria (pelvic wall) or hydronephrosis

Stage IV Advanced

Stage IVa Adjacent organs

Stage IVb Distant organs

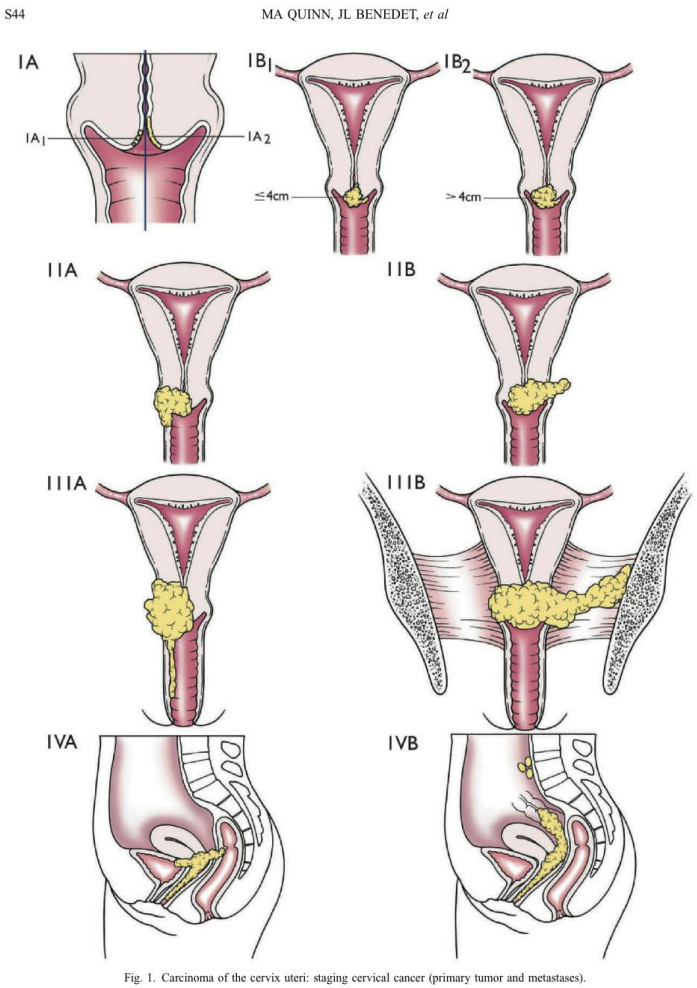


Fig. 1. Carcinoma of the cervix uteri: staging cervical cancer (primary tumor and metastases).

*Essentials of Obstetrics and Gynecology. Hacker et al. Fourth Edition 2004

TABLE 1 FIGO staging of cancer of the cervix uteri (2018).

Stage	Description
I	The carcinoma is strictly confined to the cervix (extension to the uterine 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
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
III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes[c]
IIIA	The 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 nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[c]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
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 to adjacent pelvic organs
IVB	Spread to distant organs

Pathology

- Squamous cell carcinoma
- Adenocarcinoma (mucinous, endometrioid, clear cell, papillary serous)
- Adenosquamous
- Adenoid cystic
- Glassy Cell Carcinoma
- Adenoma Malignum
- Adenoid Basal Carcinoma
- Neuroendocrine (carcinoid, small cell, large cell)
- Undifferentiated
- Melanoma
- Sarcomas (such as rhabodomyosarcomas)
- Lymphoma and metastatic carcinomas

Imaging

- IVP
- CT chest/abdomen/pelvis
- MRI pelvis
- PET

Treatment

- Stage IA1 (microinvasive)
  - Conization alone (for fertility preservation)
  - Simple hysterectomy
- Stage IA2/IB1
  - Radical trachelectomy and laparoscopic pelvic lymph node dissection
  - Radical hysterectomy and pelvic lymph node dissection

Criteria for Fertility Preservation

- Desire to preserve fertility
- Reproductive age and no clinical evidence of impaired fertility
- No high risk histologies
- Stage IA1 with LVSI, IA2 and IB
- Lesion size $\leq$2.0cm
- Limited endocervical involvement at colposcopic evaluation
- No evidence of pelvic lymph node metastasis

Roy and Plante. Pregnancies after radical vaginal trachelectomy for early stage cervical cancer. *American Journal of Obstetrics and Gynecology*. 1998; 179: 1491-1496.

Plante, M *et al*. (2011)

- 140 planned radical trachelectomies Oct 1991-Mar 2010 (125 performed).
- The highest complication rates were associated with bladder hypotonia (16%), UTI (8%), lymphocele (8%), and vulvar hematoma/edema (7%).
- Complications specific to VRT included dyspareunia(20%), dysmennorhea(24%), cervical stenosis(10%), vaginal discharge (14%), and recurrent candidiasis(14%).

Plante, M *et al*. The vaginal radical trachelectomy: An update of a series of 125 cases and 106 pregnancies. *Gynecolgic Oncolcogy*. 2011; 121: 290-297.

Oncologic Outcomes (Plante, 2011)

- Mean follow-up was 95 months.
- Fifteen patients (11%) had an abandoned procedure.
- There were 4.8% of patients who developed recurrence and 1.6% died of their disease.
- Five-year RFS 96%.
- Nine patients (7%) required adjuvant treatment.

Plante, M *et al*. The vaginal radical trachelectomy: An update of a series of 125 cases and 106 pregnancies. *Gynecolgic Oncolcogy*. 2011; 121: 290-297.

Oncologic Outcomes (Plante, 2013)

Table 1: VRT; oncologic outcome

Author	N	Fertility not Preserved	Recurrences	Deaths
Lanowska et al (2011)	225	23(6%)	8(3.8%)	4(1.9%)
Shepherd et al (2012)	208	24(11.5%)	8(3.8%)	5(2.4%)
Covens et al (2013)	180	17(9.4%)	9(2.7%)	2(1.1%)
Helpman et al (2011)				
Plante et al (2011)	140	15(10.7%)	6(4.8%)	2(1.6%)
Marchiole et al (2007)	135	17(12.6%)	7(5.7%)	5(4.2%)
Kim et al (2012)	51	9(17.6%)	2(3.9%)	1(1.9%)
Total	**924**	**95(10.2%)**	**40(4.4%)**	**19(2.1%)**

Plante, M. Evolution in fertility-preserving options for early stage cervical cancer: Radical trachelectomy, simple trachelectomy, neoadjuvant chemotherapy. *International Journal of Gynecological Cancer*. 2013; 23(6): 982-989.

Neoadjuvant Chemotherapy

- Some suggestion that neoadjuvant chemotherapy will improve outcomes in those patients that are felt to be inoperable.
- May also be an option in trying to obtain fertility preservation.
- Advantages:
  - Reducing tumor volume
  - Increasing resectability
  - Erradicate occult micrometastatic disease that can lead to distant failure.

Marchiole, P *et al*. (2011)

Table 2: Clincal and tumor recurrence data in four studies after neoadjuvant chemotherapy and different techniques of fertility sparing surgery

Author	Tumor size ≥2 cm	Fertility spared	NACT protocol	Conservative surgery	Rate of optimal pathologic reponse (CR + PR1)	Recurrences	Pregnancy
Maneo et al	8	6	TIP/TEP	Conization +PL	6/6(100%)	0/6	NR
Kobayashi et al	1	1	BOMP	Conization	1/1(100%)	0/1	1/1
Plante et al	3	3	TIP	VRT + PL	3/3(100%)	0/3	3/3
Robova et al	15	12	IP /IPD	ST + PL	9/12(75%)	3/12	7/12
Palaia et al	1	1	TIP	ST + PL	1/1(100%)	0/1	0/1
Present report	7	7	TIP/TEP	VRT + PL	4/7(57%)	0/7	1/7

Marchiole, P *et al*. Neoadjuvant chemotherapy and vaginal radical trachelectomy for fertility-sparing treatment in women affected by cervical cancer (FIGO IB - IIA1). *Gynecologic Oncology*. 2011; 122: 484-490.

Conservative Surgery

- Is radical surgery necessary?
- Does more conservative surgery affect outcomes?
- The morbidity associated with radical hysterectomy is high.
  - Voiding dysfunction (40-42%)
  - Constipation (9-18%)
  - Fistula (1-6.7%)
  - Lymphedema (3-19%)
  - Sexual dysfunction (19-36%)

Radical Hysterectomy

- Radical hysterectomy is performed to try to obtain clear margins.
- Landoni *et al*. (1997) showed that radical surgery was equal to upfront radiation therapy, but highest morbidity was in those who had surgery and RT.
- This is why many abort hysterectomy if LNs found to be positive of high risk features of tumor.
- Also has benefit of removing disease for accurate staging, sparing the ovaries in younger patients and avoiding sexual dysfunction.

Landoni, F *et al*. Randomized study of radical surgery versus radiotherapy for stage IB-IIA cervical cancer. *Lancet*. 1997;Aug 23;350(9077):535-40.

Low Risk Subgroup in stage IA1 to IB1

- Squamous cell carcinoma
- Adenosquamous carcinoma
- Adenocarcinoma
- Tumor size <2 cm
- Stromal invasion <10 mm
- No lymphovascular space invasion

Conservative Surgery in Cervical Cancer

- Currently three prospective trials examining the safety of conservative surgery in patients with early cervical cancer and favorable pathologic characteristics:
  - ConCerv Trial – K. Schmeler (MD Anderson)
  - SHAPE Trial – M. Plante (NCIC & GCIC)
  - GOG 278 – A. Covens

Adjuvant Radiation

- Try to avoid adjuvant treatment with radical surgery, but given for high risk features:
  - Intermediate-risk disease:
    - Lymph-vascular space invasion (LVSI) plus deep one third stromal invasion and any tumor size
    - LVSI plus middle one third stromal invasion and tumor size ≥2cm
    - LVSI plus superficial one third stromal invasion and tumor size ≥5cm
    - No LVSI plus middle or deep one third stromal invasion and tumor size ≥4cm
- In this case, radiation given alone (no chemotherapy)

1. Sedlis, A. *et al*. A randomized trial of pelvic radiation therapy versus no therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. *Gynecologic Oncology*. 1999; 73(2): 177.
2. Rogers, L. *et al*. Radiotherapy and chemoradiation after surgery for early cervical cancer. *Cochrane Database Systematic Review*. 2012.

Adjuvant Radiation

- High-risk disease
  - Positive margins
  - Positive lymph nodes
  - Microscopic involvement of the parametrium
- Chemotherapy with cisplatin and radiation given to these patients.
  - Cisplatin at 40mg/m2 weekly
  - 25 fractions of external beam followed by HDR brachytherapy

Peters, WA 3rd, *et al*. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiaton therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cervical cancer of the cervix. *Journal of Clinical Oncology*. 2000; 18(8):1606.

Primary Radiation Treatment

- Stage IB2-IIIB
  - Surgery not possible in these patients as margins would likely be positive.
  - Many tumors are sensitive to radiation therapy

- Radiation therapy with 25 fractions of external beam and HDR brachytherapy with an intrauterine tandem given.
- Chemotherapy with RT has been shown to reduce local recurrence, prolong PFS and improve overall survival.

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. Cochrane Database Syst. Review. 2010.

Prognosis

- Stage
- Nodal status
- Tumor volume
- Depth of cervical stromal invasion
- LVSI
- Histology

Prognosis by Stage

FIGO Stage	Five-Year Survival
IA1	98%
IA2	95%
IB1	90%
IB2	75%
IIA	73%
IIB	65%
IIIA	40%
IIIB	40%
IVA	22%
IVB	10%

Follow-up

- Patients are followed every 3 months for the first 2 years, every 4 months for the third, and every 6 months for years 4 and 5.
- Review of systems, pap, pelvic and pelvi-rectal exam.
- Concerning symptoms include N/V, weight loss, pain, bowel changes, bleeding, discharge, renal failure, DVT/PE.
- No routine imaging although some recommend PET/CT 3-4 months post-treatment.

Recurrence

- Can occur as a local recurrence in cervix/vagina.
- Also can have distant metastatic disease:
  - Retroperitoneal lymph nodes
  - Lung
  - Liver
  - Peritoneum
  - Bone
  - Skin
- Present with pain, bleeding, DVT/PE, fistula, N/V, lymphadenopathy.

Management of Recurrence

- If a central recurrence, may be a candidate for pelvic exenteration.
- If no previous radiation therapy, this can be a treatment option.
- If multiple sites of recurrence, chemotherapy is the only option for palliation.
  - Carboplatin (or cisplatin) plus paclitaxel
  - Cisplatin, ifosphamide, paclitaxel (CIT)
  - Topotecan

Kitagawa, R., *et al*. Paclitaxel Plus Carboplatin Versus Paclitaxel Plus Cisplatin in Metastatic or Recurrent Cervical Cancer: The Open-Label Randomized Phase III Trial JCOG0505. *Journal of Clinical Oncology*. 2015;33(19):2129.

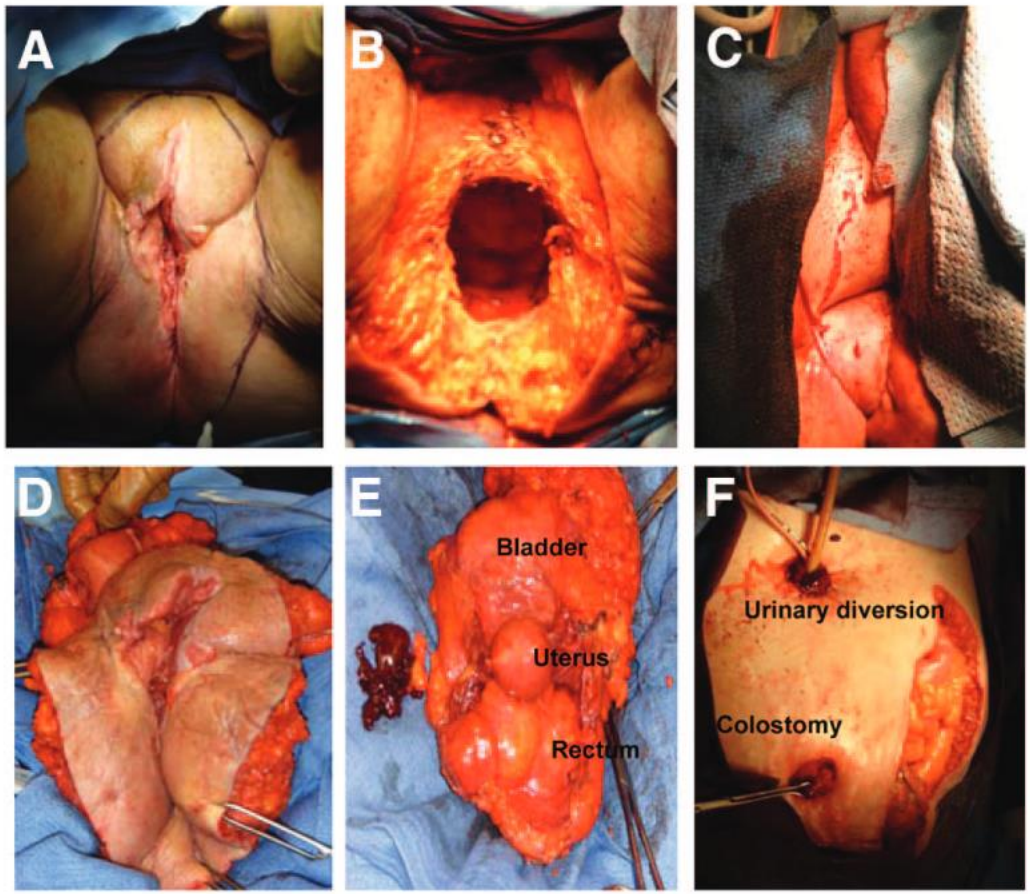


Figure 5. Palliative total pelvic exenteration. **(A):** Outline of perineal incision encompassing vulvar lesion. **(B):** Perineum after removal of pelvic structures. **(C):** Perineum after reconstruction with ventral rectus abdominus myocutaneous flap. **(D):** External view of specimen including vulva, vagina, perineal body, and anus. **(E):** Internal view of specimen including bladder, uterus, and rectum removed en masse. **(F):** Abdomen after creation of ileal conduit and diverting end colostomy.

Hope, JM & Pothuri, B. The Role of Palliative Surgery in Gynecologic Cancer Cases. *The Oncologist*. 2012; 18: 1-7.

Bevacizumab for Recurrent Cervical Cancer

- Tewari *et al*. (2014) – GOG 240.
- Patients with metastatic, persistent, or recurrent cervical cancer.
- 452 patients randomized to one of four treatment groups (q21days):
  - Cisplatin (50 mg/m^2) plus paclitaxel (135 or 175 mg/m^2) +/- bevacizumab (15 mg/kg).
  - Topotecan (0.75 mg/m^2 d1-3) plus paclitaxel (175 mg/m^2 d1) +/- bevacizumab (15 mg/kg).
- Follow-up was for 3 years.

Tewari, KS *et al*. Improved survival with bevacizumab in advanced cervical cancer. *New England Journal of Medicine*. 2014; 370(8): 734-743.

GOG 240 Results

- Significant improvement in OS (median 17 vs. 13.3 months, HR 0.71, 98%CI 0.54-0.95).
- Significant improvement in PFS (median 8 vs. 6 months, HR 0.67, 95%CI 0.54-0.82).
- Significant improvement in the ORR (48% vs. 36%).
- Side effects included grade 2 HTN, grade 3 GI or GU (3%) fistulas and thromboembolic events (8%).
- Fatal events 1.8% (equal to group without bevacizumab).

Tewari, KS *et al*. Improved survival with bevacizumab in advanced cervical cancer. *New England Journal of Medicine*. 2014; 370(8): 734-743.

Palliation of Cervical Cancer Patients

- Can be challenging to manage these patients in the palliative setting as they have unique issues:
  - Pain
  - Nausea/vomiting
  - Bowel obstruction
  - Emotional suffering
  - Renal failure
  - Fistula

Summary

- Pap smear testing starts at age 21 or when sexually active every 3 years (with some exceptions).
  - Screening guidelines found at www.cancercare.mb.ca/screening/hcp.
- Cervical cancer can be diagnosed by examination with biopsy or cone/LEEP in colposcopy after abnormal pap testing.
- Cervical cancer previously staged clinically.
- Treatment based on stage:
  - Surgical (conservative vs. radical) – fertility preservation must be considered in select patients
  - Radical chemoradiation
- Recurrence treated by radical surgery in select patients, but extensive disease treated palliatively with chemotherapy.