Screening for Cervical Cancer

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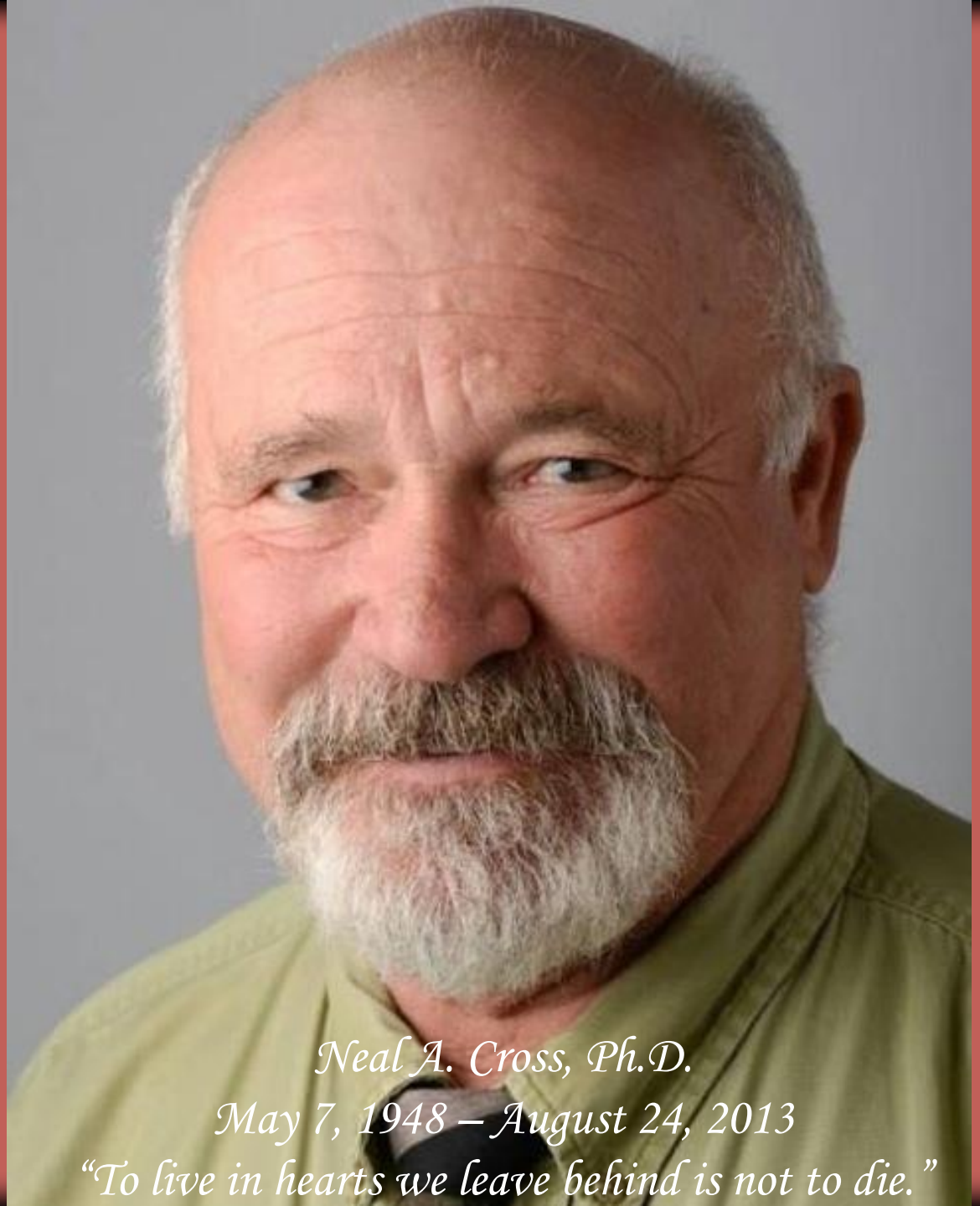

Neal A. Cross, Ph.D.

May 7, 1948 – August 24, 2013

"To live in hearts we leave behind is not to die."

Disclosures

- The content of this presentation does not relate to any product of a commercial interest
- I have nothing to disclose with regard to commercial relationships
- No commercial investments, endorsements nor bias’

Objectives

- Provide the clinician with the latest clinical management guidelines regarding Screening for Cervical Cancer as dictated by the U.S. Preventative Services Task Force and The American College of Obstetricians and Gynecologists
- Equip the physician with the natural history of Cervical Neoplasia and Cervical Cytology
- Review clinical considerations, recommendations and management of screening results

Screening for Cervical Cancer Overview

- Cervical Cancer in the U.S.
  - Incidence:
    - ↓ more than 50% in past 30yrs because of screening with cervical cytology
    - 1975 rate was 14.8 per 100,000 ♀
    - 2008 rate was 6.6 per 100,000 ♀
  - Mortality:
    - 1975 rate was 5.55 per 100,000 ♀
    - 2008 rate was 2.38 per 100,000 ♀

Screening for Cervical Cancer Overview 2

- American Cancer Society estimated 12,170 new cases of cervical cancer in U.S. in 2012, with 4,220 deaths.
- Cervical cancer is much more common worldwide, particularly in countries without screening programs
  - 530,000 new cases and 275,000 deaths/yr
  - Cervical cancer screening programs show marked reductions in cervical cancer incidence

Background

- Most cervical cancer occurs in ♀ who were either never screened or were inadequately screened
- 50% ♀ in whom cervical cancer is diagnosed never had cervical cytology testing
- 10% had not been screened within the 5yrs before diagnosis
- ~60% of diagnoses of cervical cancer are a result of inadequate screening
- Immigrants to the U.S., lacking regular source of health care and the uninsured are especially at high risk

Natural History of Cervical Neoplasia

- Human papillomavirus (HPV) is divided into 2 classes:
  - 1. Oncogenic (high-risk)
  - 2. Nononcogenic
- Infection with oncogenic HPV usually is a necessary but not sufficient factor for the development of squamous cervical neoplasia
  - Therefore, only a small fraction of ♀ infected with HPV will develop significant cervical abnormalities and cancer

Natural History of Cervical Neoplasia 2

- Current model of cervical carcinogenesis posits that HPV infection results in either *transient* or *persistent* infection
- Most HPV infection is *transient* and poses little risk of progression
- Only a small fraction of infections are persistent but persistent infection at 1yr and 2yrs strongly predicts subsequent risk of cervical intraepithelial neoplasia (CIN) or cancer regardless of age

Natural History of Cervical Neoplasia 3

- HPV genotype appears to the most important determinant of persistence and progression
  - HPV-16 has **highest** carcinogenic potential
    - 55-60% of all cervical cancer worldwide
  - HPV-18 is second most common
    - 10-15% of cases of cervical cancer
  - ~10 other genotypes are associated with the remainder of cases of cervical cancer

Natural History of Cervical Neoplasia 4

- Known cofactors that ↑ likelihood of persistence include:
  - Cigarette smoking
  - Compromised immune system
  - HIV infection
- HPV is most common in teenagers and ♀ in early 20s, with a ↓ in prevalence as women age

Natural History of Cervical Neoplasia 5

- Women <21yo have an effective immune response that clears the infection in an average of 8 months or reduces the viral load 85-90% of ♀ to undetectable levels in an average of 8-24 months
- Most CIN will also spontaneously resolve in this population
- HPV infection detected in ♀ older than 30yrs is more likely to reflect persistent infection
  - This correlates with ↑ rates of occurrence of high-grade squamous intraepithelial lesions (HGSILs) with ↑ age

Natural History of Cervical Neoplasia 6

- Low-grade neoplasia, or CIN 1, is a manifestation of acute HPV
  - A high rate of regression to normal histology is present; therefore, expectant management is prudent
- CIN 2 is controversial because of challenge in accurate diagnosis and uncertainty regarding ideal management
  - A high degree of interobserver variability applies to diagnosis of CIN 2
  - Prognosis of CIN 2 lesions seems to represent a mix of low-grade and high-grade lesions that cannot be easily differentiated by histology

Natural History of Cervical Neoplasia 7

- Limitations of CIN 2 categorization led the College of American Pathologists to adopt a revised two-tiered histologic classification LGSILs and HGSILs to eliminate CIN 2 as a separate category
- CIN 3 cumulative incidence of invasive cancer was reported to be 30.1% at 30yrs
  - CIN 3 poses a significant risk for progression to cervical cancer

Natural History of Cervical Neoplasia 8

- Time required for disease progression:
  - Most HPV-related types of cervical neoplasia are very slow to progress
  - A severe dysplasia may take 3-7yrs to progress to invasive cervical cancer
  - Well suited to less frequent testing

Cervical Cytology Screening Techniques

- Both liquid-based (processed in lab) and conventional (transferred directly to slide and fixed) methods of cervical cytology specimen collection are acceptable for screening
- Exfoliated cells are collected from the transformation zone of cervix
- Contaminating blood, discharge, and lubricant may interfere with specimen interpretation
  - If H_20-based lubricant is used, minimize amount that comes into contact with cervix

Cervical Cytology Screening Techniques 2

- A small amount of water-soluble lubricant on the speculum does not reduce the quality of cervical cytology test results
- The liquid-based method of cervical cytology specimen collection has advantage of allowing a single specimen to be used to perform cytology, HPV testing, evaluate **A**typical **S**quamous **C**ells of **U**ndetermined **S**ignificance (ASC-US) cytology and test for gonorrhea and chlamydia

Cytologic Test Result Reporting

- The Bethesda System of cervical cytologic test result reporting:
  - *Specimen Type*
  - *Specimen Adequacy*
  - *General Categorization (Optional)*
  - *Interpretation/Result*
  - *Ancillary Testing*
  - *Educational Notes and Suggestions (Optional)*

HPV Testing

- Several tests are approved by FDA for detection of cervical HPV DNA
- Assess exfoliated cervical cells for the presence of subsets of the 15-18 potentially cancer causing “high-risk” HPV genotypes
- Most test for 13-14 of the most common high-risk genotypes

HPV Testing 2

- HPV testing indications:
  - Determination of the need for colposcopy in ♀ with an ASC-US cytology result (“reflex testing”)
  - Use as an adjunct to cytology for cervical cancer screening in ♀ aged 30-65yrs and older (“co-testing”)

HPV Testing 3

- Testing should be performed only to detect the presence of high-risk HPV
- **No role** for testing for low-risk genotypes and tests for low-risk HPV should **not** be performed
- HPV genotyping
  - Two FDA-approved HPV DNA genotyping tests are commercially available
    - HPV-16, HPV-18 or both
    - Guidelines support use of HPV genotyping for ♀ ages 30-65yrs who are undergoing co-testing and have **negative Pap** test results but **+ high-risk HPV** test results, and either test can be used

HPV Vaccination

- Vaccine targets HPV-16 and HPV-18 in primary prevention of cervical cancer
- Limited cross-protection against approximately 30% of cases of cervical cancer caused by HPV genotypes other than HPV-16 and HPV-18
- Advisory Committee on Immunization Practices (ACIP) and ACOG recommend vaccine to ♀ aged 9-26yrs
- ACIP advocates vaccine to girls before they reach an age when they may get exposed to HPV
- Many will receive the vaccine when older and after viral exposure

HPV Vaccination 2

- Cervical cancer screening remains the best approach to protect ♀ from cervical cancer
- Screening recommendations apply **regardless** of HPV vaccine status

Risks / Benefits in Cervical Cancer Prevention

- Primary goal of screening: Protection from cervical cancer
- Effects of invasive diagnostic workups (ie: colposcopy and biopsy) and overtreatment of lesions likely to regress have adverse consequences related to costs and potentially to reproductive outcomes
- Anxiety and stigmatization associated with HPV infection are significant concerns

“The Meat…Just the *Meat!!!*”

~Dr. Laverne R. VanDeWall

Clinical Considerations and Recommendations

- This recommendation statement applies to ♀ who **have a cervix, regardless of sexual history**
- Does **not** apply to ♀ who:
  - Have received a diagnosis of high-grade precancerous cervical lesion or cervical cancer
  - ♀ with in utero exposure to diethylstilbesterol or who are immunocompromised (HIV)

Summary of Recommendations and Evidence

- USPSTF recommends screening for cervical cancer in ♀ aged 21-65yrs with cytology (Papanicolaou [Pap] smear) q3yrs
- ♀ aged 30-65yrs who wish to lengthen the screening interval, screening with a combination of cytology and HPV testing q5yrs

Summary of Recommendations and Evidence 2

- USPSTF recommends **AGAINST** screening for cervical cancer in ♀ who:
  - <21yrs regardless of sexual history
  - >65yrs who have had adequate prior screening and are not otherwise a high risk for cervical cancer
  - Hysterectomy with removal of the cervix and who do not have a history of a high-grade precancerous lesion (CIN 2 or 3) or cervical cancer
  - With HPV testing alone or in combination with cytology, in ♀ <30yo
  - **All are Grade D recommendations*

USPSTF Grade Definitions

- Grade A: The USPSTF recommends the service
  - There is a **high** certainty that the net benefit is substantial
  - Offer or provide the service
- Grade B: The USPSTF recommends the service
  - There is a high certainty that the net benefit is **moderate** or there is **moderate** certainty that the net benefit is **moderate** to substantial
  - Offer or provide this service

USPSTF Grade Definitions 2

- Grade C: The USPSTF recommends **selectively** offering or providing this service to individual patients based on professional judgment and patient preferences
  - There is at least **moderate** certainty that the net benefit is **small**
  - Offer or provide this service for selected patients depending on individual circumstances

USPSTF Grade Definitions 3

- Grade D: The USPSTF recommends **against** the service
  - There is **moderate** or **high** certainty that the service has **no net** benefit or that the harms outweigh the benefits
  - Discourage the use of this service

Timing of Screening

- Cervical cancer is rare <21yrs
- USPSTF found **little** evidence to determine whether and how sexual history should affect the age at which to begin screening
- Although exposure of cervical cells to sexually transmitted HPV during vaginal intercourse may lead to cervical carcinogenesis, the process has multiple steps, involves regression, and is generally **not** rapid

Timing of Screening 2

- There is evidence that screening earlier than 21yrs, regardless of sexual history, would lead to more harm than benefit
- Harms are greater in this younger age group because abnormal test results are likely to be transient and to resolve on their own
- Treatment may have an adverse effect on childbearing

Timing of Screening 3

- Women >65yrs
  - Does the patient meet criteria for adequate prior testing and appropriate follow-up per guidelines?
    - Adequate prior screening is 3 consecutive **negative** cytology results or 2 consecutive **negative** HPV results within 10yrs before cessation of screening, with the most recent test occurring within 5yrs
    - Routine screening should continue for at least 20yrs after spontaneous regression or appropriate management of high-grade precancerous lesion, **even if** this extends screening past age 65yrs
    - Screening should not resume in ♀ >65yrs even if she reports having a new sexual partner

Timing of Screening 4

- Women >65yrs who have never been screened:
  - May be clinically indicated in older ♀ for whom the adequacy of prior screening cannot be accurately accessed or documented
    - Limited access to care
    - Minority ♀
    - Countries where screening is not available
    - H/O HGSIL, cervical cancer, DES exposure in utero, or immunocompromised

Assessment of Risk

- HPV infection is associated with nearly all cases of cervical cancer
- Other risk factors:
  - HIV
  - Compromised immune system
  - In utero exposure to DES
  - Previous treatment of high-grade precancerous lesion
  - Cervical cancer

Assessment of Risk 2

- ♀ who had a hysterectomy with removal of cervix and no history of high-grade precancerous lesion or cervical cancer are not at risk for cervical cancer and should **not** be screened
- ♀ who had their cervix removed during surgery for ovarian or endometrial cancer are **not** at high-risk for cervical cancer and would not benefit from screening

Treatment

- Screening aims to ID high-grade precancerous cervical lesions to prevent development of cervical cancer and early-stage asymptomatic invasive cervical cancer
- High-grade lesions may be treated with ablative and excisional therapies
  - Cryotherapy
  - Laser ablation
  - Loop excision
  - Cold-knife conization

Treatment 2

- Early-stage cervical cancer may be treated with surgery (hysterectomy) or chemoradiation
- Overall effect of HPV vaccination on high-grade precancerous cervical lesions and cervical cancer is not yet known
  - Current trials do not provide data on long-term efficacy
  - ♀ who have been vaccinated should continue to be screened

Management of Abnormal Results

- ♀ with ASC-US cytology and **negative** HPV = very **low risk** of CIN 3 → continue with routine screening
- H/O CIN 2, CIN 3, or adenocarcinoma in situ → routine age-based screening for 20yrs after the initial post-treatment surveillance period, even if it requires that screening continue past age 65yrs
- Continue to be screened if total hysterectomy and have history of CIN 2 or higher in the past 20yrs or cervical cancer

Management of Abnormal Results 2

- Continued screening for 20yrs is recommended in ♀ who still have a cervix and history of CIN 2 or higher
  - Screening with cytology alone q3yrs for 20yrs after initial post-treatment surveillance periods seems reasonable for ♀ after a hysterectomy

Management of Abnormal Results 3

- **Negative** cytology and **positive** HPV co-testing results who are aged 30yrs and older should be managed in one of two ways:
  - 1. Repeat co-testing in 12 months
    - If repeat cervical cytology test result is LGSIL or higher, or HPV test result is still **positive** → colposcopy
    - Otherwise → return to routine screening

Management of Abnormal Results 4

- 2. Immediate HPV genotype-specific testing **for** HPV-16 alone or HPV-16/18 should be performed
  - If **positive** results for HPV-16 alone or HPV-16/18 → referred directly for colposcopy
  - If **negative** results from HPV-16 or HPV-16/18 → retested in 12 months with management of results as described
  - *Reminder Vaccine
    - ♀ who have received the HPV vaccine should be screened according to the same guidelines as ♀ who have not been vaccinated

Carcinoma of the cervix uteri.

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
IA1	Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm
IA2	Measured 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
IVB	Spread to distant organs

*All macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not >7.00 mm. Depth of invasion should not be >5.00 mm taken from the base of the epithelium of the original tissue—superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with "early (minimal) stromal invasion" (~1 mm).
The involvement of vascular/lymphatic spaces should not change the stage allotment.

**On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

Cervical Cancer Treatment by Stage

- **Stage 0** (carcinoma in situ)
  - Cancer cells in CIS are only in the surface layer of the cervix
    - Cryosurgery
    - Laser surgery
    - **L**oop **E**lectrosurgical **E**xcision **P**rocedure (LEEP/LLETZ)
    - Cold-knife conization

Cervical Cancer Treatment by Stage 2

- Stage 1A: 1A1 and Stage 1A2
  - 1A1: 3 options
    - 1. If you still want to be able to have children → cone biopsy → watchful waiting
    - 2. If cone biopsy doesn't remove all cancer (or if done childbearing) → uterus removed (hysterectomy)
    - 3. If cancer has invaded blood vessels of lymph vessels → radical hysterectomy along with removal of pelvic lymph nodes
      - If ♀ desires children → radical trachelectomy (removal of the uterine cervix)

Cervical Cancer Treatment by Stage 3

- 1A2: 3 options
  - 1. Radical hysterectomy along with removal of lymph nodes in the pelvis
  - 2. Brachytherapy with or without external beam radiation therapy to the pelvis
  - 3. Radical trachelectomy with removal of the pelvic lymph nodes (if desire children)
  - *If cancer is found in any pelvic lymph nodes during surgery, some of the lymph nodes that lie along the aorta may be removed
    - +parametria + → radiation therapy +/- chemotherapy'
    - Positive margins → pelvic radiation with cisplatin chemotherapy

Cervical Cancer Treatment by Stage 4

- Stage 1B: 1B1 and Stage 1B2
  - 1B1: 3 options
    - 1. Standard treatment is radical hysterectomy with removal of lymph nodes in pelvis with para-aortic lymph node removal
    - If positive margins → radiation therapy + chemotherapy after surgery
    - 2. Radiation with both brachytherapy and external beam radiation therapy
    - 3. Radical tracelectomy with removal of pelvic (and some para-aortic) lymph nodes (if desires children)

Cervical Cancer Treatment by Stage 5

- Stage 1B2: 3 options
  - 1. Standard treatment is combination of chemotherapy with cisplatin and radiation therapy to the pelvis plus brachytherapy
  - 2. Radical hysterectomy with removal of pelvic (and some para-aortic) lymph nodes
    - If cancer found in lymph nodes removed, or in margins → radiation therapy given with chemotherapy after surgery
  - 3. Neoadjuvant chemotherapy (followed by hysterectomy)

Cervical Cancer Treatment by Stage 6

- Stage II: IIA and Stage IIB
  - Stage IIA: Treatment for this stage depends on the size of the tumor
    - 1. Brachytherapy and external radiation therapy
      - Most often recommended if the tumor is >4.0cm (about 1.5inches)
      - Chemotherapy (cisplatin) + radiation
      - Recommend removing the uterus after radiation therapy is complete
    - If cancer <4.0cm → radical hysterectomy and removal of lymph nodes in pelvis (some para-aortic)
      - If positive margins or +LNs → radiation treatments to pelvis + chemotherapy +/- brachytherapy

Cervical Cancer Treatment by Stage 7

- Stage IIB:
  - Combined internal and external radiation therapy
  - Radiation + cisplatin

Cervical Cancer Treatment by Stage 8

- Stage III and IVA
  - Combined internal and external radiation therapy given + cisplatin
  - If cancer + LNs (especially LN in upper abdomen) → metastasis
  - CT/MRI to evaluate size of LNs
    - May biopsy suspicious LNs
    - If para-aortic LN + → further testing to evaluate metastasis

Cervical Cancer Treatment by Stage 9

- Stage IVB
  - Cancer spread beyond pelvis to distant organs
  - Not considered curable
  - Treatment options:
    - Palliative radiation therapy +/- chemotherapy
      - Platinum-based compound (cisplatin or carboplatin) + paclitaxel (Taxol), gemcitabine (Gemzar) or topotecan

Recurrent Cervical Cancer

- Locally (pelvic organs near cervix) or distant areas (lymph/blood → lung/bone)
  - If recurrence in pelvis only → extensive surgery (pelvic exenteration) (40-50% success rate)
    - +/- radiation/chemotherapy for palliative treatment

Recurrent Cervical Cancer 2

- If distance recurrence → chemotherapy or radiation therapy
  - If chemotherapy → weight risks/benefits and quality of life, performance status
  - 15-25% of patients *may* respond, at least temporarily, to chemotherapy

Cervical Cancer in Pregnancy

- Small number of cervical cancers are found in pregnant ♀
- If Stage IA → safe to continue pregnancy to term
- Several weeks post-delivery → hysterectomy or cone biopsy recommended
  - Cone biopsy suggested for substage IA1

Cervical Cancer in Pregnancy 2

- If Stage IB or higher → decide whether or not to continue pregnancy
  - If no → radical hysterectomy and/or radiation
  - If yes → baby delivered by cesarean section as soon as it is able to survive outside of womb
    - More advanced cancers should be treated immediately

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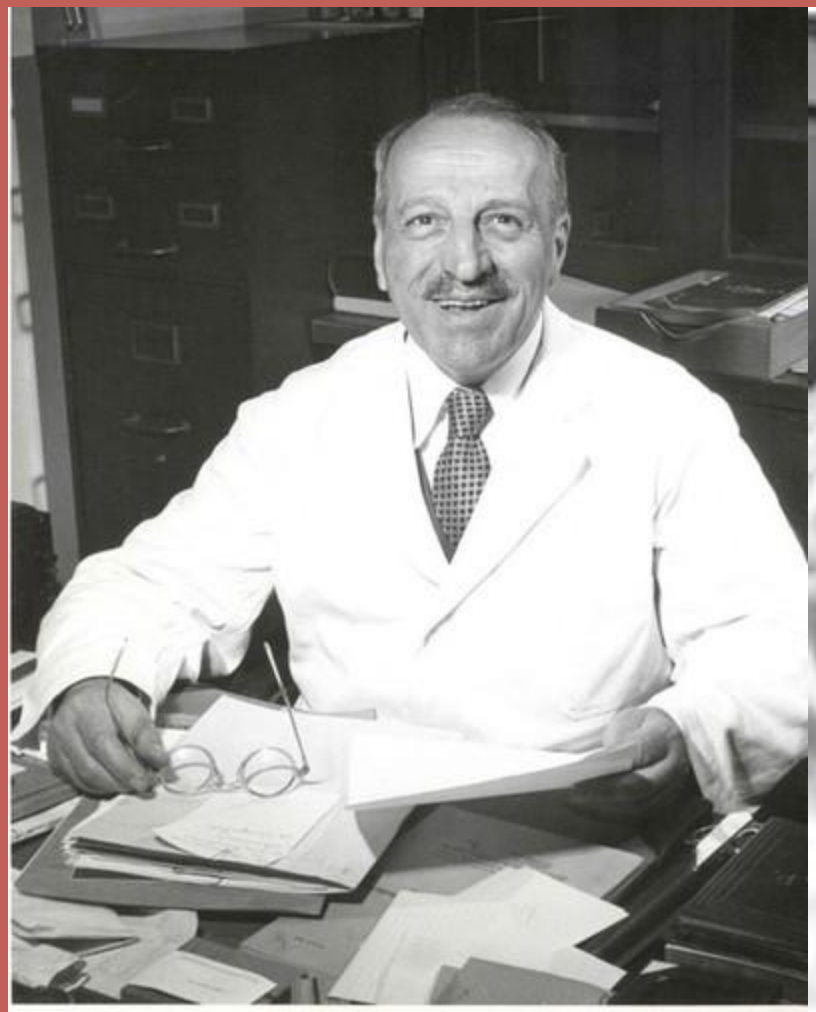

Ευχαριστώ!

(pronounced “Efxaristo”)