Early Detection of Cancer Cervix and Management

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**CANCER CERVIX**

- Globally Cervical cancer is 4\textsuperscript{th} most common cancer in women, and the 7\textsuperscript{th} overall

- Estimated 528,000 new cases in 2012 and 266,000 related deaths annually

- Is the second most common cancer in women living in less developed regions with an estimated 445 000 new cases in 2012 (**84\% of the new cases worldwide**).

- In 2012, approximately 270 000 women died from cervical cancer; more than 85\% of these deaths occurring in low- and middle-income countries.

- Trend of increasing no. of patients with early-stage cervical cancer during child-bearing years

Ferley J. GLOBOCAN 2012

Jemal A. CA Cancer J Clin 2011
New Cases, Deaths and 5-Year Relative Survival

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<tbody>
<tr>
<td>5-Year Relative Survival</td>
<td>68.1%</td>
<td>68.0%</td>
<td>66.3%</td>
<td>72.1%</td>
<td>74.9%</td>
<td>74.4%</td>
<td>70.1%</td>
<td>70.9%</td>
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**Ca cervix: Revised FIGO Staging 2009**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)</td>
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<tr>
<td>IA</td>
<td>Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤ 5 mm and largest extension ≥ 7 mm</td>
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<tr>
<td>IA1</td>
<td>Measured stromal invasion of ≤ 3.0 mm in depth and extension of ≤ 7.0 mm</td>
</tr>
<tr>
<td>IA2</td>
<td>Measured stromal invasion of &gt; 3.0 mm and not &gt; 5.0 mm with an extension of not &gt; 7.0 mm</td>
</tr>
<tr>
<td>IB</td>
<td>Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA *</td>
</tr>
<tr>
<td>IB1</td>
<td>Clinically visible lesion ≤ 4.0 cm in greatest dimension</td>
</tr>
<tr>
<td>IB2</td>
<td>Clinically visible lesion &gt; 4.0 cm in greatest dimension</td>
</tr>
<tr>
<td>II</td>
<td>Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina</td>
</tr>
<tr>
<td>IIA</td>
<td>Without parametrial invasion</td>
</tr>
<tr>
<td>IIA1</td>
<td>Clinically visible lesion ≤ 4.0 cm in greatest dimension</td>
</tr>
<tr>
<td>IIA2</td>
<td>Clinically visible lesion &gt; 4.0 cm in greatest dimension</td>
</tr>
<tr>
<td>IIB</td>
<td>With obvious parametrial invasion</td>
</tr>
<tr>
<td>III</td>
<td>The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney **</td>
</tr>
<tr>
<td>IIIA</td>
<td>Tumor involves lower third of the vagina, with no extension to the pelvic wall</td>
</tr>
<tr>
<td>IIIB</td>
<td>Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney</td>
</tr>
<tr>
<td>IV</td>
<td>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</td>
</tr>
<tr>
<td>IVA</td>
<td>Spread of the growth to adjacent organs</td>
</tr>
<tr>
<td>IVB</td>
<td>Spread to distant organs</td>
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</tbody>
</table>
Simple Graphics of Stages of Ca Cx

**STAGE I**
- Growth limited to cervix
- Fallopian tube
- Uterus
- Uterine cavity
- Cervix
- Internal opening
- External opening
- Vagina

**STAGE II**
- Growth beyond cervix but not to pelvic wall or upper 2/3 of vagina
- IIA
- IIB

**STAGE III**
- Growth to pelvic wall or lower 1/3 vagina
- Pelvic side wall
- IIIA
- IIIB

**STAGE IV**
- Growth invading bladder, rectum or metastasis
SIGNS & SYMPTOMS

- Silent Disease in Early stages
- Abnormal vaginal bleeding: Bleeding and spotting between periods, unusually longer or heavier periods, bleeding after menopause
- Unusual or excessive vaginal discharge with foul smell
- Vaginal bleeding after having sexual intercourse
- Pain in the lower abdomen or pelvic pain
- Pain during sexual intercourse
India Statistics for Ca Cervix

Globocan 2012 data

• New cases registered: 1,23,000
• Deaths: 67,500
• Median age: 38 years (age 21–67 years).
• Rural women are at higher risk of developing cervical cancer as compared to their urban counterparts [12].
• Cervical cancer is less common in Muslim than in Hindu women
• A woman dies of cervical cancer every 8 minutes in India

Survival rate

• The relative five year survival averages to 48.7%
• Length of survival depends on the cancer stage at the time of diagnosis.
• The survival rates better with early diagnosis and treatment
Risk factors

• Infection with HPV (Human Papilloma Virus)

• Early onset of sexual intercourse
  • High parity
  • History of smoking
  • Increased number of sexual partners
  • History of sexually transmitted disease, specially HIV
  • Immuno-compromised status due to HIV, drugs etc
  • Low socioeconomic status
  • Long-term use of oral contraceptives (> 5 years)
  • Genetic factors
Pathophysiology

- Cervical cancer originates at the squamous-columnar junction (SCJ);
- It can involve the outer squamous or the inner glandular cells, or both;
- The precursor lesion is dysplasia—cervical intraepithelial neoplasia (CIN) or carcinoma in-situ—which can develop into invasive cancer;
- Squamous cell carcinoma comprises approximately 80%-90% of cervical cancers, and adenocarcinoma comprises the majority of the remaining cervical cancers;
- Sarcomas are rare.
HPV and cervical cancer

• Are group of viruses that are extremely common worldwide.
• More than 100 types exist; at least 13 are cancer-causing (also known as high risk type).
• Mainly transmitted through sexual contact, shortly after onset of sex activity.
• Can be transmitted by foreplay too.
• Cervical cancer is caused by sexually acquired infection with certain types of HPV.
• Two HPV types (16 and 18) cause 70% of cervical cancers and precancerous cervical lesions.
• Evidence links HPV with cancers of the anus, vulva, vagina and penis.
• HPV can only replicate in stratified squamous epithelium.
• Evidence exists to show that acute infection with HPV16 increases risk of developing high grade CIN by 11 fold; HPV 18 by 17 fold.
Spectrum of Changes in Cervical Squamous Epithelium Caused by HPV Infection

1. Adapted from Goodman A, Wilbur DC. N Engl J Med. 2003;349:1555–1564. Copyright © 2003 Massachusetts Medical Society. All rights reserved. Adapted with permission.

*CIN = cervical intraepithelial neoplasia
CIN – Cervical Intraepithelial Neoplasia

1. CIN most often occurs among young women, but cervical cancer rates are higher among older women.

2. Precursor lesions are graded by the amount of dysplasia present and range from CIN 1 (least dysplastic) to CIN 3 (highly dysplastic).
Treatment of Carcinoma in Situ

Treatment of pre-cancerous lesions may include the following:
Three modalities, depending on severity and need to preserve fertility:

• Cryotherapy
• Electrical loop excision
• Laser treatment
• Conisation
• Hysterectomy
Cryotherapy

Application of freezing probe application of freezing probe to destroy abnormal or diseased tissue in the cervix for about 5 minutes.
Loop electrosurgical excision procedure (LEEP) and LLETZ

An electrified wire loop that acts as a knife is used to remove abnormal and or cancerous cells in the cervix using a thin, low-voltage knife.
Conisation of Cervix
A cone of TZ from Cx is removed up to internal os
Hysterectomy
For women whose tumor cannot be completely removed by conization and who no longer want to have children

![Diagram of hysterectomy with annotations: Total hysterectomy (Removal of uterus), Total hysterectomy with salpingo-oophorectomy (Removal of uterus, fallopian tubes, and ovaries), Radical hysterectomy (Removal of uterus, fallopian tubes, ovaries, and nearby tissues). Note: Parts removed during surgery are shown in dotted line.]
Importance of screening

• Screening has reduced incidence of cervical cancer in developed countries by 70-75%
• Only 5-6% of Indian women undergo screening, lesser in rural population
• Without routine screening, the risk for cervical cancer is up to 4%
• To see reduction in incidence, population screening is essential

Bosch FX, de Sanjosé SS. J Natl Cancer Inst Monogr 2003;31:3-13
Kaarthigeyan K. Indian J Med Paediatr Oncol 2012;33:7-12
SCREENING MODALITIES

- Cytology
  
  a) Conventional – Pap Smear
  
  b) Liquid based cytology

- Visual inspection using acetic acid (VIA)
- Visual inspection using Lugol’s iodine (VILI)
- High-risk human papilloma virus (HPV) screening
- Colposcopy of suspicious findings with targeted biopsy
• Most commonly employed screening method

• Reduced mortality by cervical cancer by 70% in developed countries since 1950

Ries L. SEER Cancer Statistics Review 2004
Visual Inspection with Acetic Acid (VIA)

- Acetic acid (3-5%)
  - Reversible coagulation of nuclear protein preventing light to pass through the epithelium
  - Higher nuclear density and higher concentration of protein => white intensity increases
FIGURE 2.1:
VIA negative: No acetowhite area seen. Note the advancing edges of squamous metaplasia in the anterior and posterior lips (arrows).

FIGURE 2.16:
VIA positive: There is a well-defined, opaque acetowhite area, with regular margins, in the anterior lip, abutting the squamocolumnar junction, which is fully visible. Note the satellite lesions in the lower lip.

FIGURE 2.26:
VIA positive, invasive cancer: There is a dense acetowhite area with irregular surface contour.
VILI

Schiller / Lugol’s Iodine

- Normal squamous epithelium contains abundant glycogen - dark brown mahogany or black stain
- Abnormal epithelium contains little glycogen - remains relative unstained
- CIN & invasive cancer stain mustard yellow or saffron coloured

Sankaranarayanan R; IARC multicentre study in India. Int J Cancer 2004;110:907-13

Mustard Yellow staining
HPV DNA Testing

I. Non-amplification techniques—nucleic acid probe tests

II. Amplification techniques—
   a) Target amplification (PCR based)—Cobas 4800
   b) Signal amplification—Hybrid Capture, HCT II, Cervista HPV HR, Cervista HPV 16/18
   c) Probe amplification—ligase chain reaction

Target and signal amplification techniques are the most commonly used tests
Importance of HPV testing

• HPV is found in more than 99.7% of cervical cancers
  

• 94.6% of cervical cancers & 86.5% of HSIL’s among women in India were positive for HPV
  

• 94.7% of cancers & 84.4% of HSIL’s were positive for HPV in rural western India
  
  A meta-analysis update. FT Cutts, Int J cancer 2007;121:621-32
  Deodhar K, J Med Virol 2012;1054-60
  J Infect Dis 2007;195:1582-9
Importance of HPV testing
Time Lag to invasive cancer

* Two different cohorts (cross-sectional study) followed during the same time span to measure the rate of high-risk HPV infection in one and the rate of cervical cancer in the other.

## Screening in high-risk cases

<table>
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<tr>
<th>High Risk</th>
<th>Recommendation</th>
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<tbody>
<tr>
<td>Infected with HIV or immunosuppressed, including adolescent</td>
<td>Twice in the first year of diagnosis, annually thereafter</td>
</tr>
<tr>
<td>Treated in the past for CIN 2, CIN 3, or cancer</td>
<td>Annually for 20 years post treatment</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Routine screening to be postponed, if negative cytology within 5 years</td>
</tr>
</tbody>
</table>

European guidelines for quality assurance in cervical cancer screening Second Edition
Indications for colposcopy

• Grossly visible or palpable abnormality of the cervix

• Abnormal cervical cytology Positive screening test for cervical neoplasia such as spectroscopy, cervicography, speculoscopy

• Cervical cytology unsatisfactory due to unexplained inflammation

• Unexplained cervico-vaginal discharge

• Unexplained abnormal lower genital tract bleeding

• History of lower genital tract neoplasia (cervical, vaginal, vulvar)

• Post-treatment surveillance

DES /HPV positive
Prevention of Cancer Cervix

• Cancer Cervix is highly preventable by HPV Vaccination
• Screening and timely treatment of CIN
• Social messaging about high risk factors and seeking screening and vaccination
Screening recommendations

- The age-specific screening guidelines are as follows:
- Younger than 21 years: No screening
- 21-29 years: Cytology (Pap smear) alone every 3 years
- 30-65 years: HPV and cytology co-testing every 5 years (preferred); however, cytology alone every 3 years is also acceptable
- Older than 65 years: No screening recommended if adequate prior screening has been negative, and no high-risk factors are present
• **GSK**
  • Bivalent 16,18
  • Cross-reactive protection 45 and 31 (ONCOGENIC) - 100%
  • 98% protection against CIN 2+
  • 10 to 45 yrs
  • Dose-0, 1, 6 months
  • Pure cervical cancer vaccine

• **MSD**
  • Quadrivalent 16,18, 6, 11
  • 98% protection against CIN 2+
  • 100% against VAIN, VIN, genital warts
  • 9 to 45 years
  • Dose-0, 2, 6, months
  • Dual cervical cancer and genital warts vaccine

*Mathematical models predict that in women vaccinated with Cervarix™, HPV 16 and 18 antibody level remain detectable and above natural infection for at least 20 years.*
Indian Academy of Pediatrics (IAP) recommendations on HPV vaccination

- Only 2 doses of either of the two HPV vaccines for adolescent/pre-adolescent girls aged 9-14 years
- For girls 15 years and older, and immune-compromised individuals 3 doses are recommended
- For two-dose schedule, the minimum interval between doses should be 6 months.
- For 3 dose schedule, the doses can be administered at 0, 1-2 (depending on brands) and 6 months

- Vaccine does not guarantee complete protection against cervical cancer. Cervical screening tests are still important as:
  - Immunization with the HPV vaccine will take several years to reduce the chances of developing cervical cancer.
  - The vaccine does not protect against all HPV types.
  - Not all cases of cervical cancer are caused by the high-risk HPV16 and HPV18 strains.

- Duration of protection of vaccine:
The duration of vaccine protection is unclear. Current studies indicated that the vaccine is effective for at least 5 years. Ongoing studies are investigating the long term efficacy of the vaccine.
INDIAN SCENARIO for SCREENING

• In Indian situation 'once in a lifetime' screening at age 39 would result in reduction of 20-30% in the life-time risk of cervical cancer.
• This approach could also be one of the options for the limited resource conditions
• Train nurses and doctors to screen with VIA at PHC level
• Public health messaging on signs, symptoms and screening
• Prospects still bleak as hardly 5% get screened due to multiple constraints

Thank You Cancer
but you can leave now

Tell cancer where to go.  
Tell it to leave.