Diagnostic work up and staging in carcinoma cervix

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REGIONAL CANCER CENTRE

DEPTT. OF RADIO THERAPY

PGIMER CHANDIGARH

Cervical Cancer

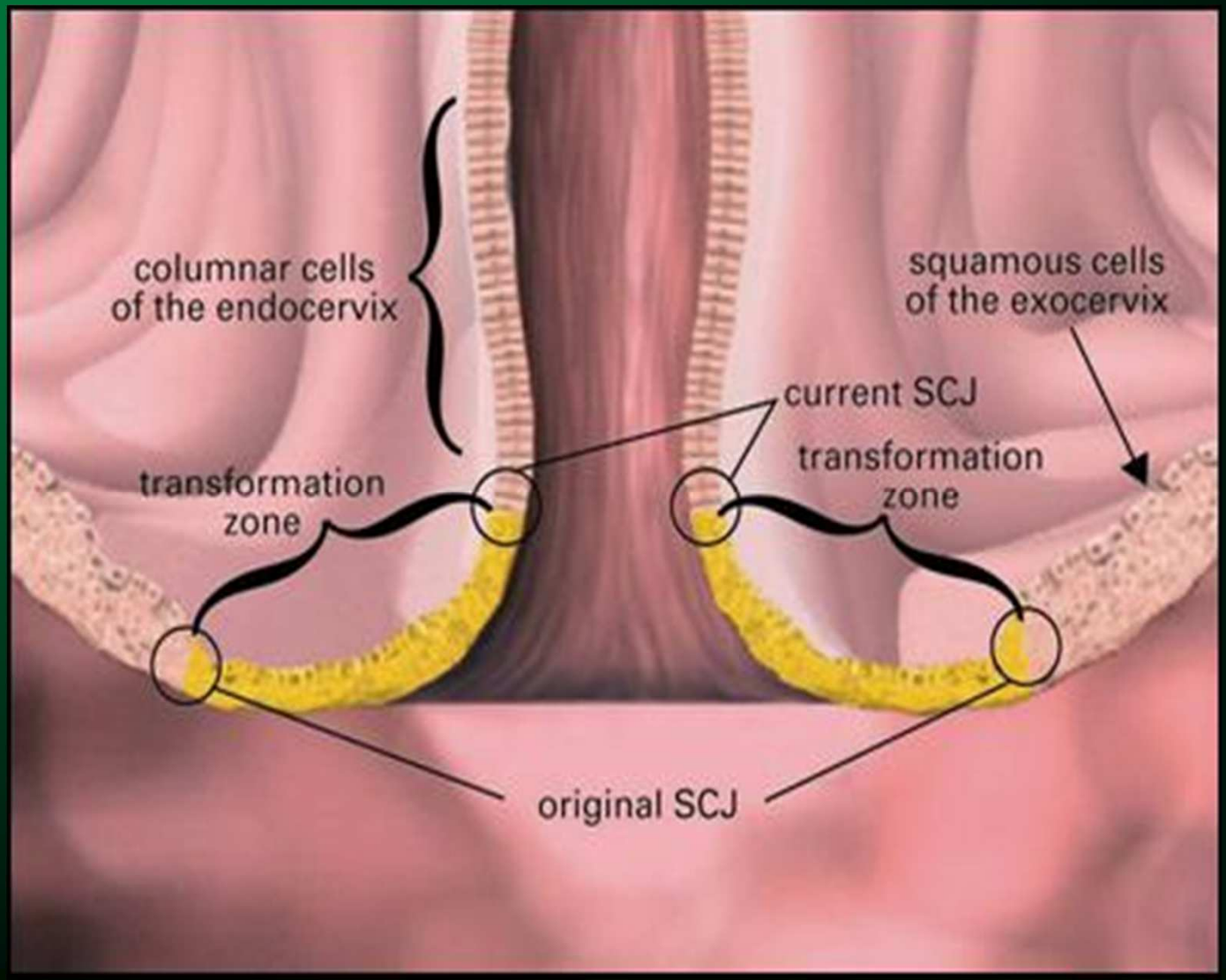
Magnitude of the Problem: -

- Cervical cancer is the SECOND most common cancer of women
- worldwide 500,000 new cases identified each year

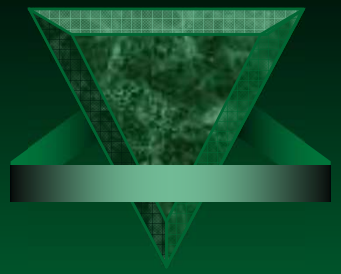
INDIA

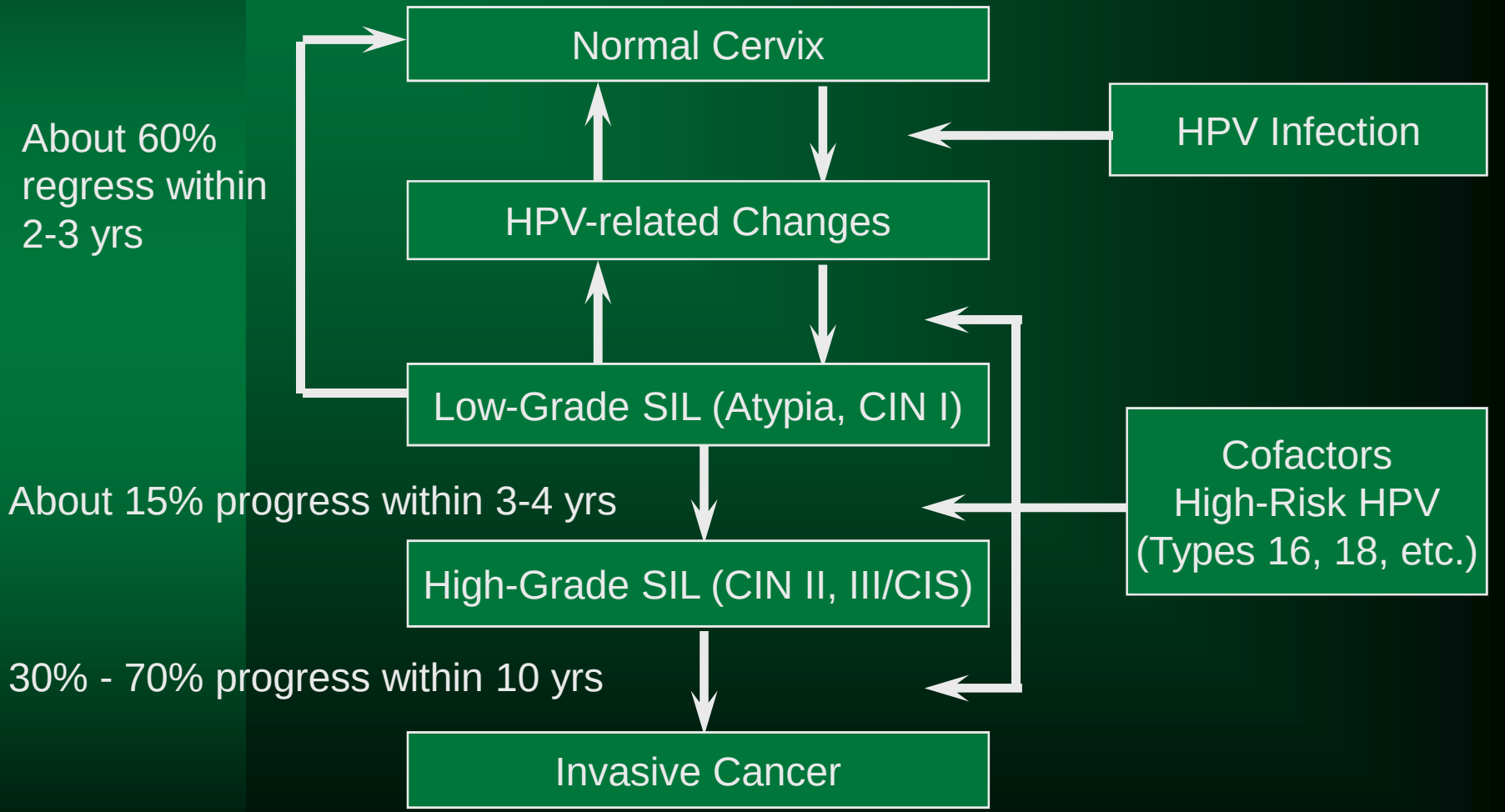
- Commonest carcinoma in females
- 1.3 lakh/year

Transformation zone



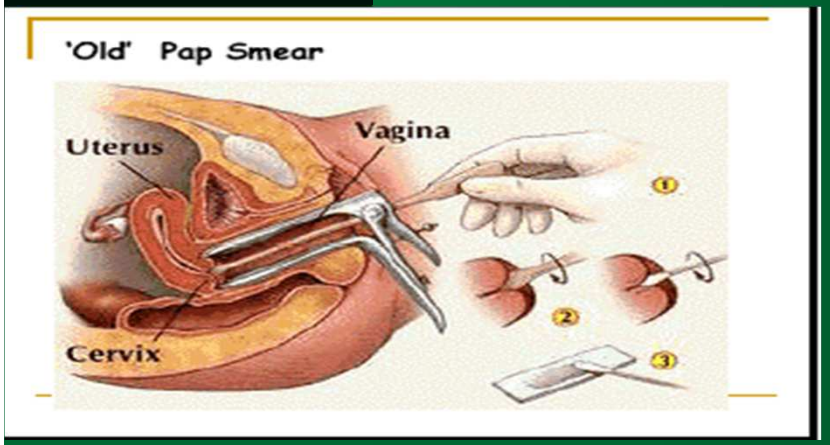
Current Understanding: -

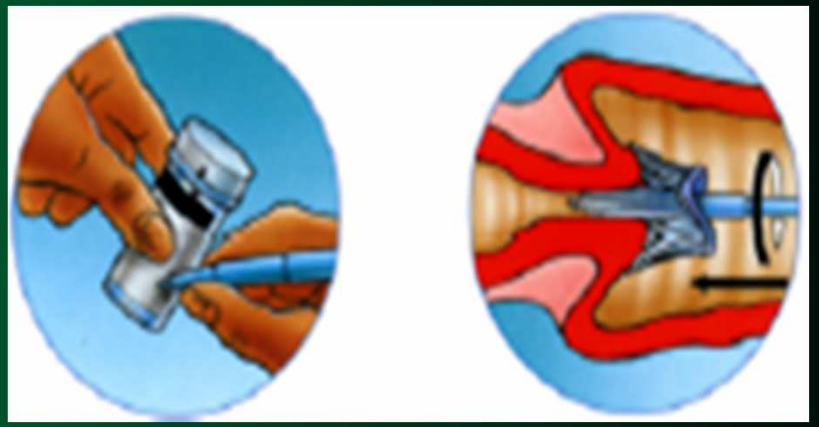




Diagnosis of preinvasive stage

- CYTOLOGIC SCREENING
- VISUAL INSPECTION
- COLPOSCOPY
- BIOPSY
- ENDOCERVICAL CURRETTAGE

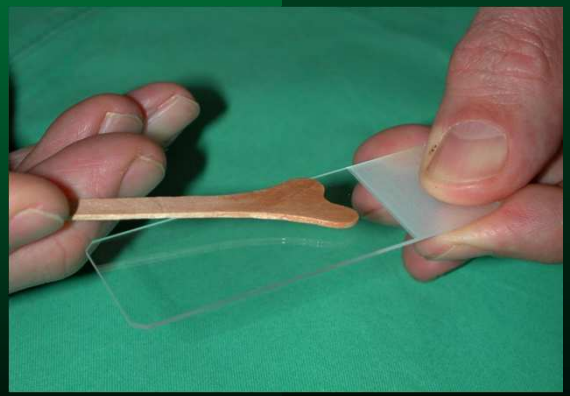


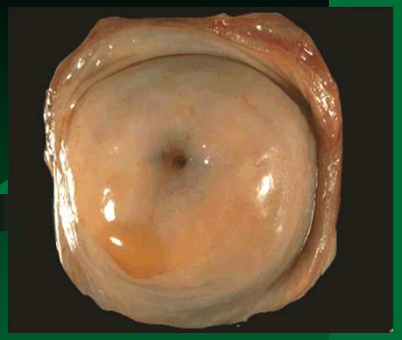


Sensitivity of PAP 51%

FALSE NEG – 5-50%

20% LAB ERRORS

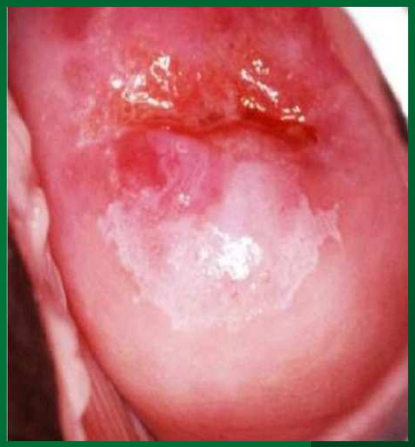




VISUAL INSPECTION METHOD

simple speculum examination

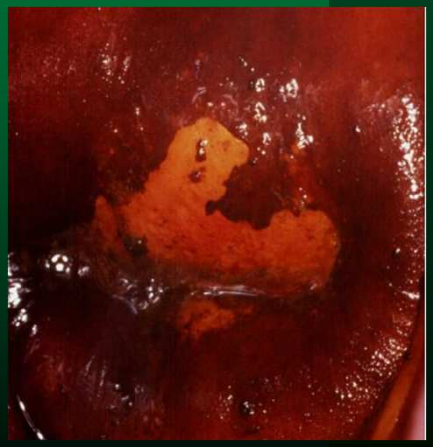
VISUAL INSPECTION WITH ACETIC ACID (VIA)



- Acetic acid – malignant cells stain white
  - Dissolves mucus
  - Induces intracellular dehydration
  - Causes coagulation of protein

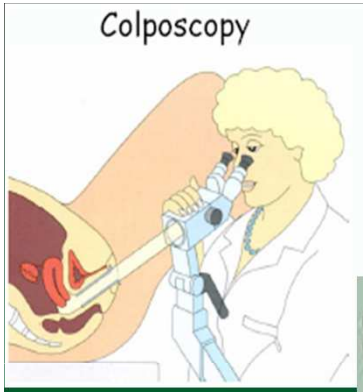
Sensitivity and specificity of VIA - 70-92%

VISUAL INSPECTION LUGOLS IODINE



Iodine being glycophilic stains only the normal squamous epithelium-mahogany brown or black

Sensitivity 91.7% specificity 85.9%



Colposcopy

Indications

Suspicious-looking cervix

Invasive carcinoma on cytology

CIN 2 or CIN 3 on cytology

Persisting (for more than 12-18 months) low-grade (CIN 1) abnormalities on cytology

CIN 1 on cytology

Persistently unsatisfactory quality on cytology

Infection with oncogenic human papillomaviruses (HPV)

Acetopositivity on visual inspection with acetic acid (VIA)

Acetopositivity on visual inspection with acetic acid using magnification (VIAM)

Positive on visual inspection with Lugol's iodine (VILI)

Colposcopy contd…

Magnification 16 times

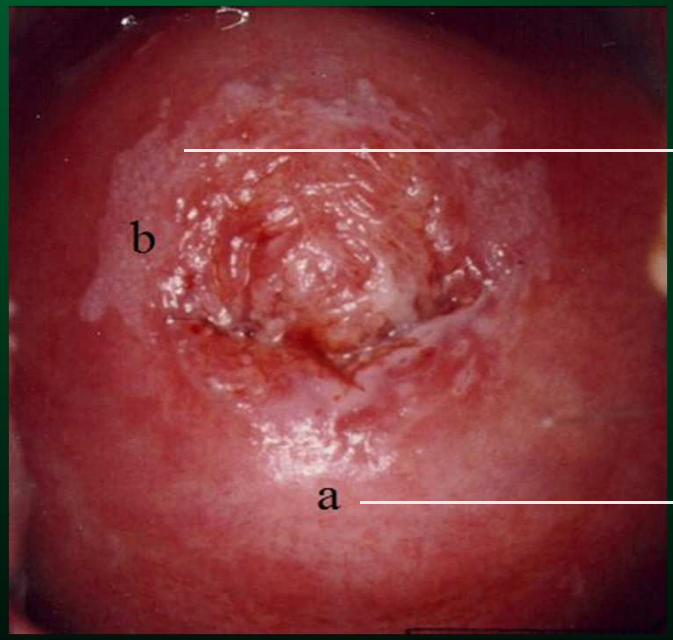
4 main features

colour changes

Intensity of acetowhitening

Marjins &contour

Vascular features



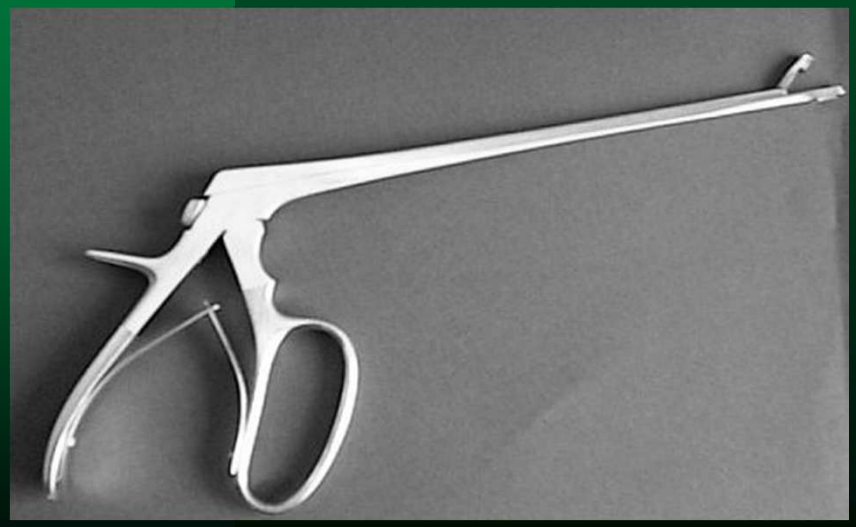
Biopsy

Colposocopy available

suscpicious area

Punch Biopsy

Or 4 quadrant biopsy



Colposcopy Not available

Employing

Schiller's or

Lugol's iodine

Ring biopsy from

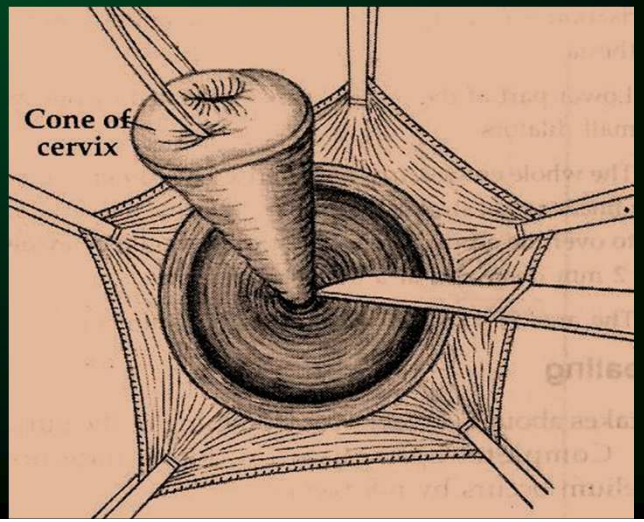
Squamocolumnar junction

Conisation (cone biopsy)

- When ?
- Unsatisfactory colposcopic findings

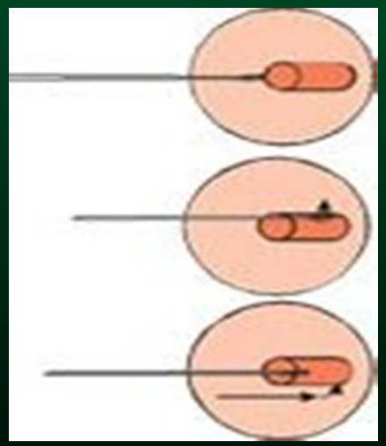
  entire margins not visualised
- Inconsistent findings– colposcopy, cytology &directed biopsy
- Positve endocervical curettage
- To exclude gross invasive ca

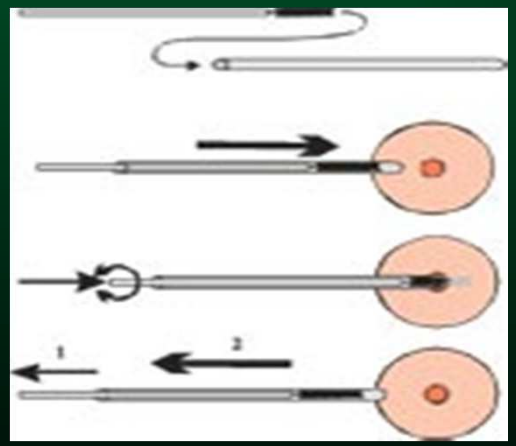
IT IS DIAGNOSTIC AS WELL AS THERAPEUTIC

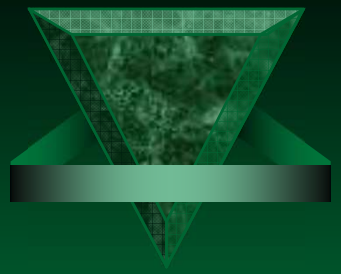


ENDOCERVICAL CURETTAGE

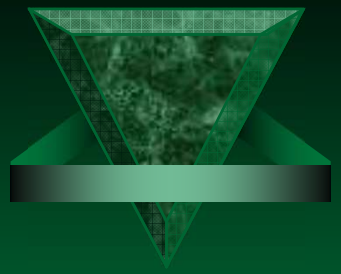
- MANDATORY after conisation
- SPECIALLY IF referral cytology indicates a glandular lesion
- If colposcopy unsatisfactory / not revealed any abnormality
- as yield of ECC is very low neg ECC should not suggest absence of neoplasia







INVASIVE CARCINOMA



- 80 % 0f lesions –ectocervix

Frank growth ---exophytic---friable, involves upper vagina

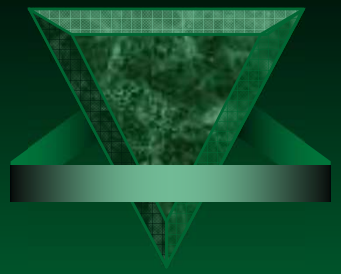
ulcerative---excavating cervix, vag fornices

infiltrative---endocervical growth

HISTOPATHOLOGY

90 % squamous cell carcinoma

10 % adenocarcinoma



Clinical Presentation

- Asymptomatic
- Bleeding P/V--- post coital / spotting
  intermenstrual
  postmenopausal
- discharge P /V ---Foul smelling
- PAIN-------pelvic/ hypogastric
  lumbosacral epigastric
  radiating to limbs
- Fatigue ,weakness
- bladder & bowel complaints
- Symptoms of metastasis
- Uraemia Sepsis cachexia

Clinical examination

GENERAL SURVEY

pallor

palpable neck nodes

pedal edema

B .P .

SYSTEMIC EXAMINATION

P/A--- tenderness, palpable lump,

palpable liver,spleen

CHEST auscultation

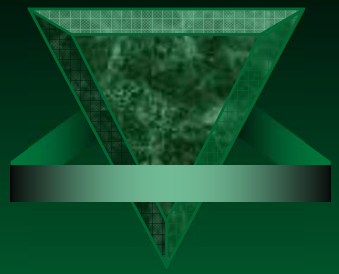
LOCAL EXAMINATION

speculum inspection---- preferably Cusco ’s bivalve speculum

digital palpation per vaginum

bimanual palpation

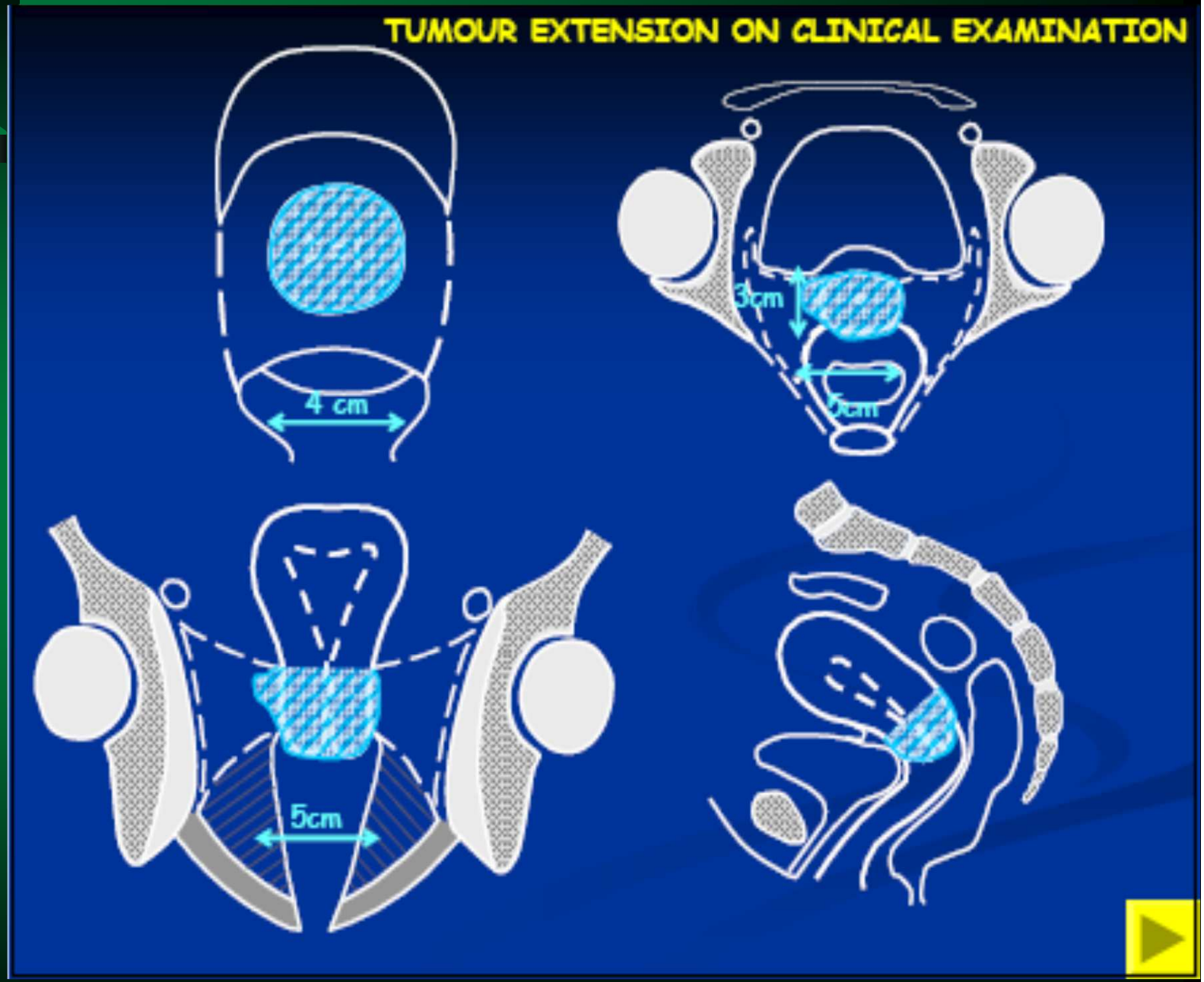
rectal examination



Local examination

- **Speculum examination**
  - red granular area on lips of cervix
  - growth– size, proliferative,necrotic,
- **Per vaginal digital palpation**
  - exact nature of growth , friable bleeds to touch,
  - infiltrative proliferative,
  - size of growth, lips of cervix involved
  - vaginal fornices, walls of vagina
- **Bimanual examination**
  - better reveals extent of growth to vagina,
  - induration of bladder base felt through ant fornix
  - in advanced cases
- **Rectal examination**
  - note involvement of parametrium--- soft or indurated
    note whether ***nodular***
  - extent to lateral pelvic wall
  - rectal mucosal involvment

TUMOUR EXTENSION ON CLINICAL EXAMINATION



Cervical Carcinoma - Outcome

Host Factors

- Anemia
- Performance status (weight loss)
- Age

INVESTIGATIONS

- I. ROUTINE / BASELINE INV
- II. DISEASE EXTENT

A.ENDOSCOPIC ASSESSMENT

B.RADIOLOGIC STUDIES

C.METASTATIC WORK UP

Routine investigations

1. HAEMOGRAM

Hb, TLC DLC, PLATELETS

Anaemia--blood loss

nutritionally deprived

depletion of fe stores in prolonged

intermittent bleeding

---level of Hb affects prognosis

↓Hb→tumour oxygenation ↓

↓

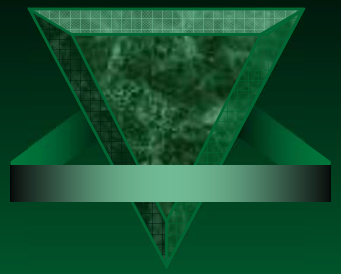
radioresistance↑

↓

Biological aggressiveness, locoregional recurrence

Optimal level-----11g/dl

Threshold for transfusion should be based on anaemia during treatment and not initial value



Renal function tests

- Urea
- Creatinine

serves as a baseline before
starting treatment by cisplatin
based chemoradiation

advanced diseases—
ureteric involovment,hydronephrosis
↑ urea, creatinine

Liver function tests baseline value
elevated enzymes----indicates metastatic disease

Urine– routine &C/S
baseline chek for absence of any UTI
symptoms of dysuria, inreased frequency--- in advanced stages

Chest X Ray assessment of cardiopulmonary status
rule out any lung mets

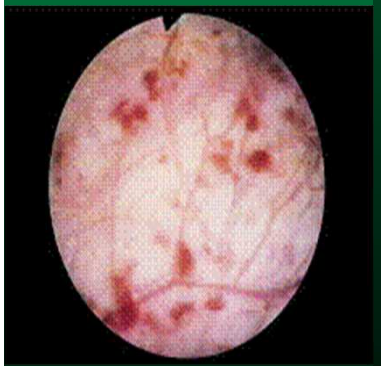
Endoscopic assessment

- 85% cases presenting to us are in advanced cases
- Endoscopic assessment for
  - bladder invasion
  - rectal invasion

CYSTOSCOPY:-

Visualisation of only mucosa---

- nodularity
- frank growth
- ridges &furrows----submucosal involvment if they remain fixed to growth during palpation (i.e. P/V or P/R during cystoscopy)



bullous edema– as such does not indicate stage IV

Urinary malignant cytology

If cystoscopy not available urinary malignant cytology to detect bladder infiltration

Overall specificity –93%

3 samples of urine specimen

Anticoagulant not necessary

Proctoscopy &sigmoidoscopy

Indications–symp– tenesmus constipation along with bleeding P/R, diarrhoea

clinical correlation– nodularity in P/R

Imaging for bladder & bowel

For urinary tract- IVP

For Bowel- barium enema &fistulography

INTRAVENOUS PYELOGRAM

Indications– in all cases of stage II&above

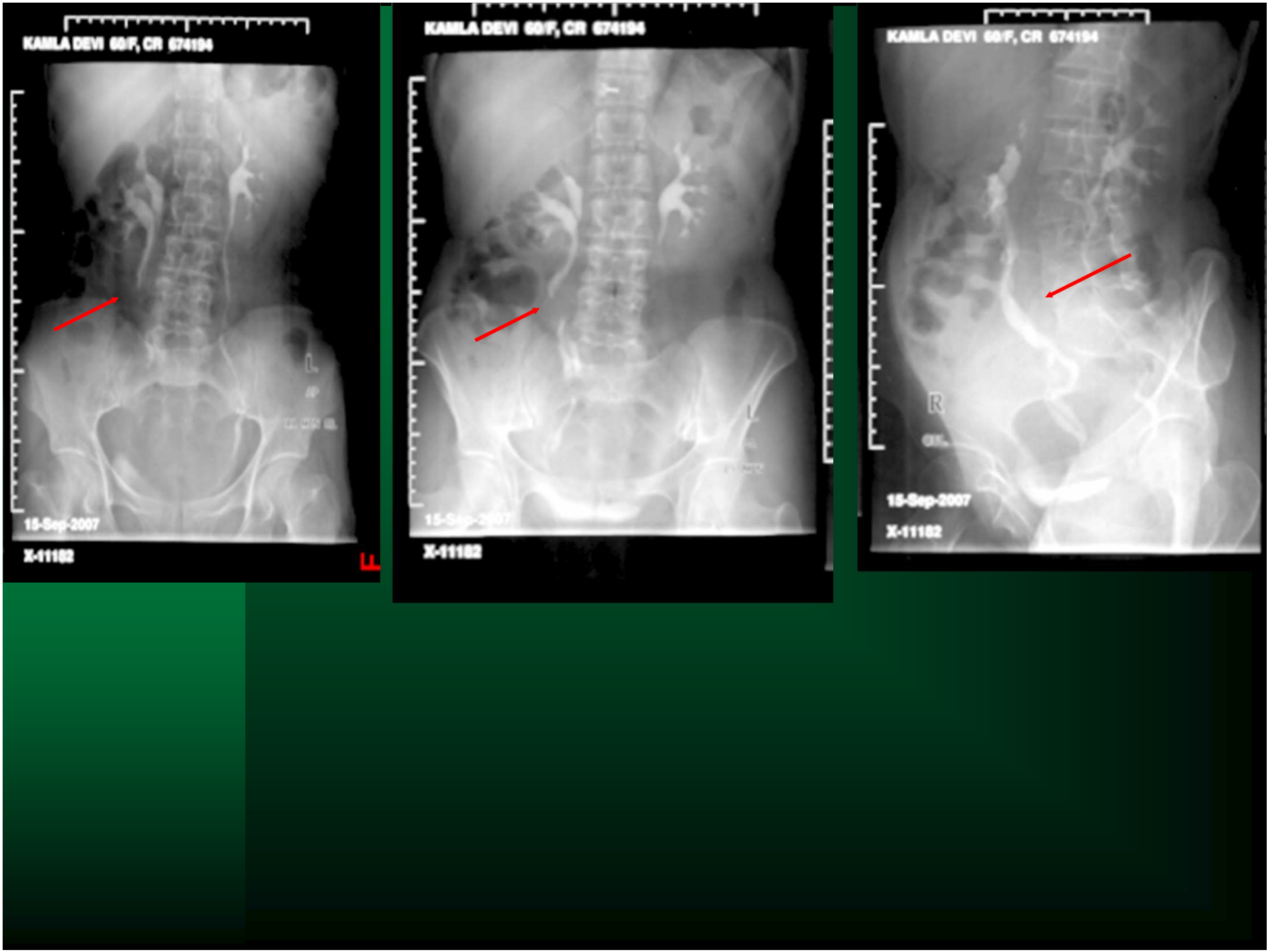
to detect ureter involvement

extaluminal compression

(? Enlarged paraaortic nodes)

Hydroureteronephrosis

Displacement of ureters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X-11182
KAMLA DEVI 60/F, CR 674194
15-Sep-2007
X-11182
KAMLA DEVI 60/F, CR 674194
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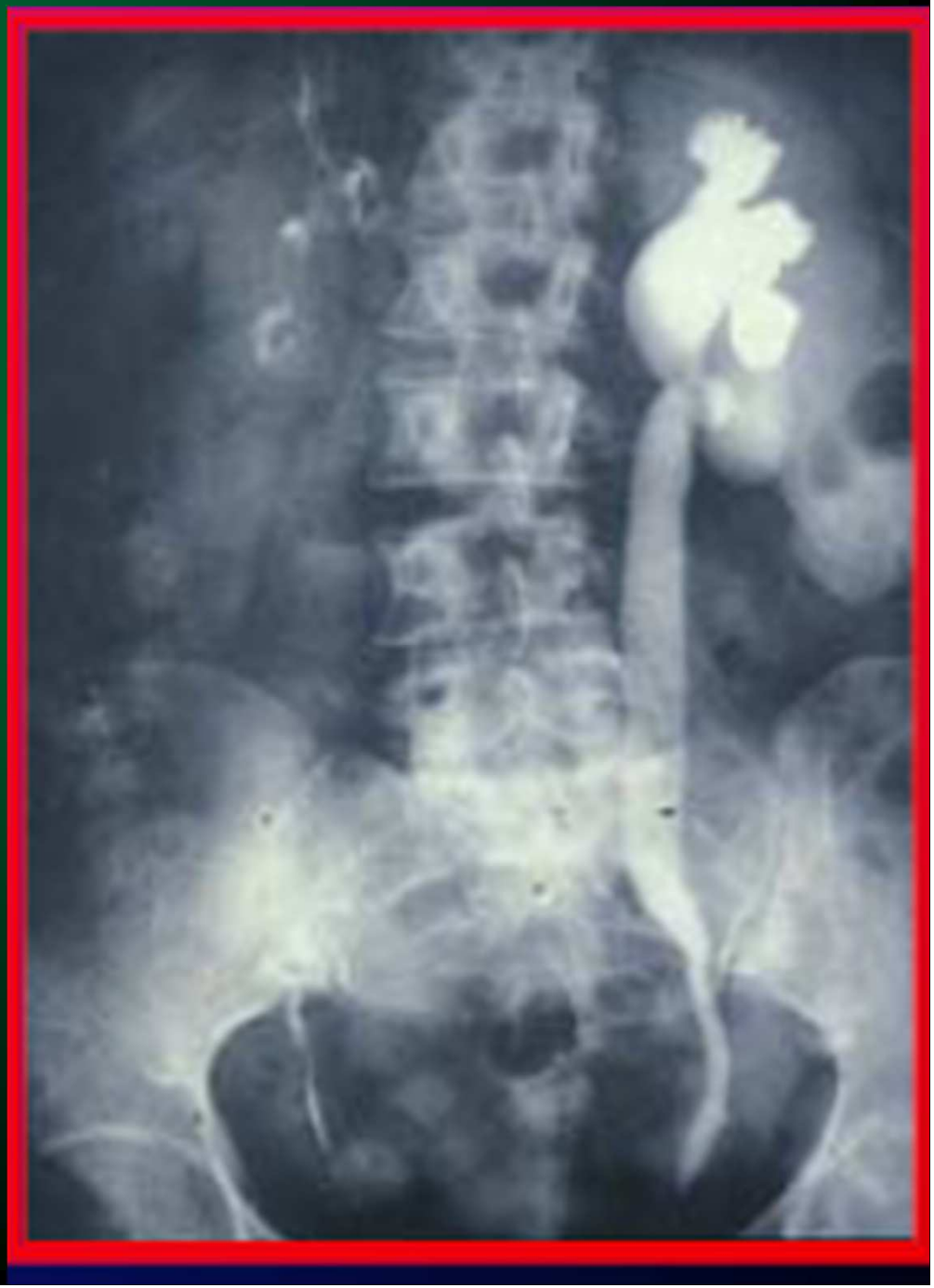
- Incidence of ureteral obstruction at diagnosis: 14 – 34.5%
- Sign of advanced sidewall disease or bulky retroperitoneal adenopathy



Low Tumor Burden

Upper vaginal disease

Parametrial disease

High Tumor Burden

Mid/distal vag disease

Hydronephrosis

Unilateral/bilateral sidewall disease

*Arthur et al IJROBP 31(4):1995

Cervical Carcinoma - Outcome

Tumor Variables

- Stage
- Tumor volume
- Parametrial/sidewall invasion
- Hydronephrosis
- Uterosacral ligament invasion

Staging of carcinoma cervix

- 1929- Radiologic subcommittee of Cancer Committee of the Health Organisation of the League of Nations began uniform staging of gynae cancers
- 1937- League of Nations classification for cervical cancer published
- 1958- staging by FIGO

FIGO staging

- **Based on clinical evaluation** (inspection, palpation, colposcopy), roentographic examination of chest, kidneys, and skeleton;

  endocervical curettage and biopsies

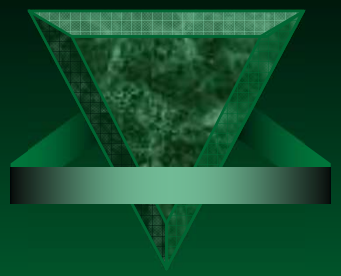
Endoscopic assessment by cystoscopy, proctoscopy,sigmoidoscopy

IVP for imaging urinary tract and to detect any hydronephrotic changes due to obstruction of ureters

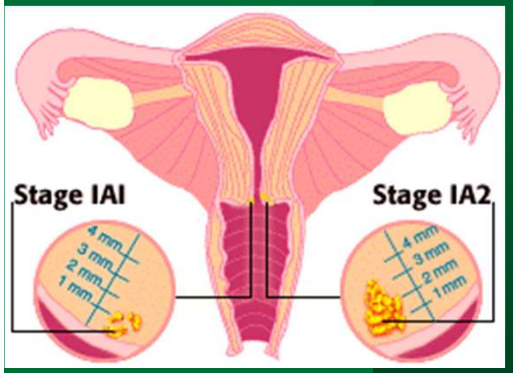
Because of the low yield of cystoscopy ,IVP, sigmoidoscopy, . and barium enema- patients with growth limited to cervix may forgo these procedures

With clinical evidence of more advanced disease ,however, cystoscopy and IVP are recommended in the pretreatment assessment.

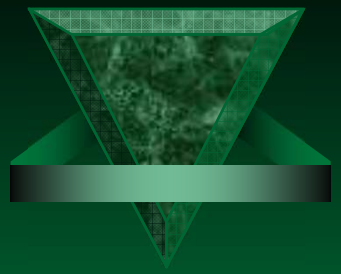
Lymphangiograms USG, CT ,MRI, are not used for clinical staging



STAGING



FIGO	
Stage	
0	Carcinoma in situ (preinvasive carcinoma)
Invasive carcinoma	
1	carcinoma confined to cervix (extension to corpus should be disregarded)
1a	Invasive carcinoma diagnosed only by microscopy.All gross lesions even with superficial invasion are stage 1B cancers. Invasion is limited to measured stromal invasion with maximum depth of 5.0 mm & no wider than 7.0 mm
$1a_1$	Stromal invasion no greater than 3.00 mm in depth and 7.00 mm or less in horizontal spread.
$1a_2$	Stromal invasion more than 3.0 mm and not more than 5.0 mm with horizontal spread 7.0mm or less



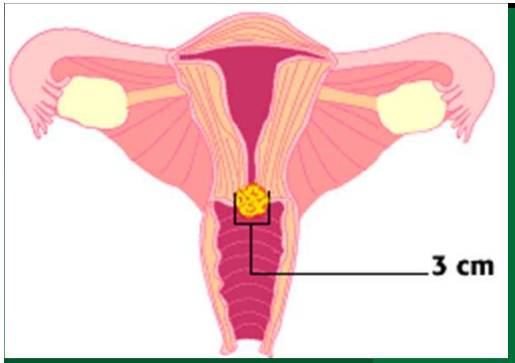
- Stage IA1 previously (1985 FIGO revision) was defined as “minimal microscopically evident stromal invasion ”
- and invasion of 5 mm or less in depth or 7 mm or less in horizontal spread as stage 1A2

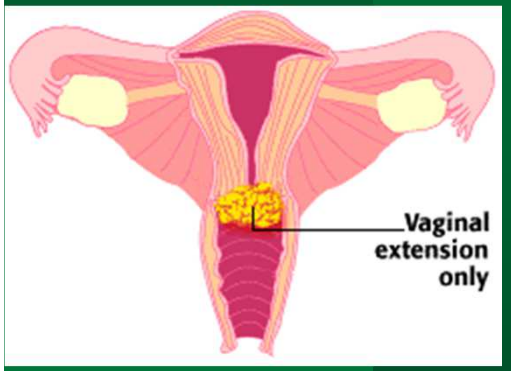
depth	Pelvic node mets
<3mm	< 1 %
3-5 mm	1-8 %
> 5 mm	5-13 %

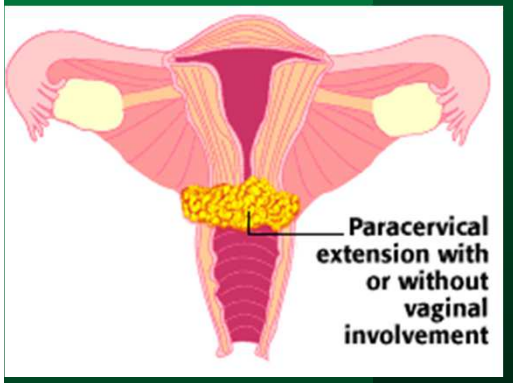
1995- FIGO revision -

1A1- invasion upto 3mm deep & 7 mm wide

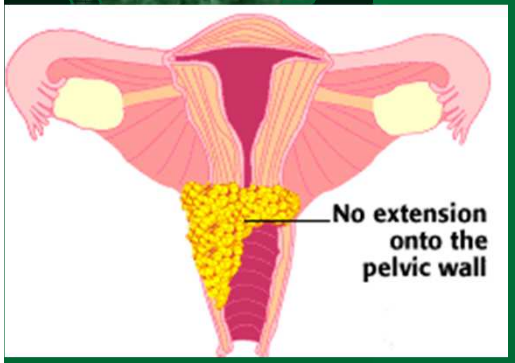
1A2- invasion between 3 and 5 mm deep & 7 mm wide

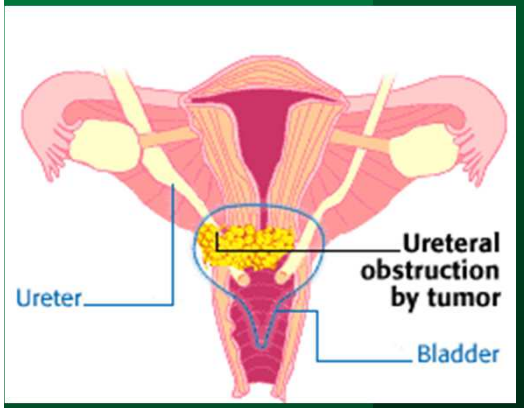




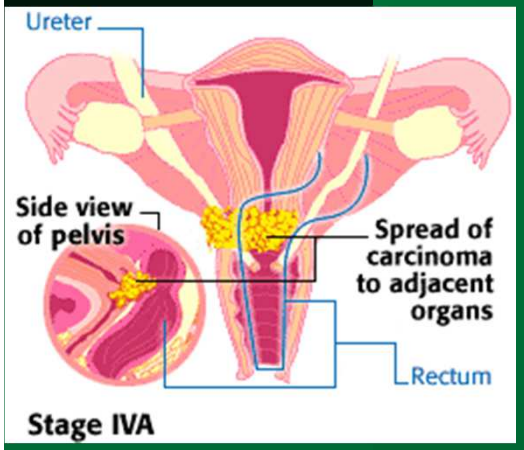


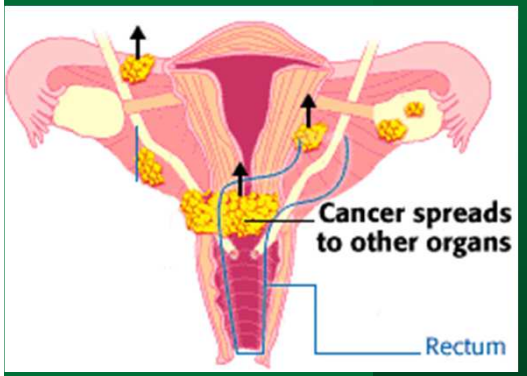
FIGO	
stages	
1B	Clinically visible lesion confined to the cervix or microscopic lesion greater than 1A2
$1B_1$	Clinically visible lesion 4.0cm or less in greatest dimension
$1B_2$	Clinically visible lesion more than 4 cm in greatest dimension
II	Tumor invades beyond cervix but not to pelvic wall or lower third of the vagina .
II a	The carcinoma involves the vagina but not as far the lower third. Without parametrial invasion
II b	Tumor invades beyond cervix with parametrial invasion but not upto pelvic wall





FIGO	
stages	
III	Tumour extends to pelvic wall . On rectal examination there is no cancer free space between the tumor and the pelvic wall . The tumour involves the lower third of vagina All cases with a hydronephrosis or nonfunctioning kidney are included **unless they are known to be due to other causes**
IIIa	Tumor involves lower third of vagina no extension pelvic wall.
IIIb	Tumor extends to pelvic wall and/or causes hydronephrosis or non functioning kidney





FIGO	
stages	
IV	Carcinoma extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum.
IV a	Tumor invades mucosa of bladder or rectum or extends beyond true pelvis
IV b	Spread to distant organs

Notes about staging

- The diagnosis of both stage 1A1 and 1A2 cases should be based on microscopic examination of removed tissues, preferably a cone ;which must include the entire lesion. The depth of lesion should not be more than 5.0 mm taken from the base of the epithelium ,either surface or glandular,from which it originates

- The second dimension , the horizontal spread , must not exceed 7 mm . Vascular space involvement , either venous or lymphatic ,should not alter staging but should be specifically recorded ,as it may affect treatment decisions in the future.

- As a rule , it is impossible to estimate clinically whether a cancer of the cervix has extended to the corpus or not . Extension to the corpus should therefore be disregarded

- A patient with a growth fixed to the pelvic wall by a short and indurated but not nodular parametrium should be alloted to stage IIB . It is impossible , at clinical examination,to decide whether a smooth and indurated parametrium is truly cancerous or only inflammatory. Therefore , the case should be placed in stage III only if the parametrium is nodular on the pelvic wall or if the growth itself extends to the pelvic wall

- **In case of doubt the lower stage is selected. After a clinical stage is assigned and treatment has been initiated the stage must not be changed because of subsequent findings by either extended clinical staging or surgical staging.**

- The presence of bullous oedema should not permit a case to be alloted to stage IV. Ridges & furrows into bladder wall – submucous invlovement of bladder if they remain fixed to growth at palpation during cystoscopy.
- Malignant cytology of bladder washings need to be correlated with further examination & biopsy from bladder

Prognosis of patients depends on…….

- Early stage

tumour size----

Depth of invasion

lymphovascular invasion

- Advanced stage

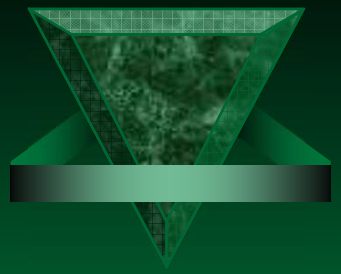
paraaortic & pelvic node

Tumour size & extent of growth

age

size	Nodal mets	5 yr survival
<3 cm	22 %	84 %
>4 cm	36 %	66 %

depth	Pelvic node mets
<3mm	< 1 %
3-5 mm	1-8 %
> 5 mm	5-13 %



stage	Pelvic node %
I	11-18
II	32-45
III	46-66

STAGE	Paraaortic node
IB- IIA	0-18%
IIB	13-33%
III	46%
IVA	57%

Additional Radiology

Tumour volume

Disease extent-

nodal spread

parametrial &

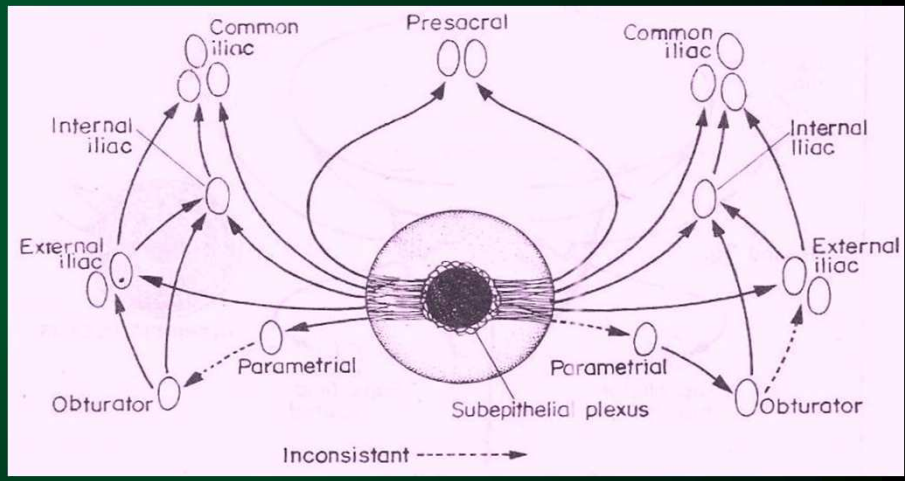
pelvic wall

involvment

- Lymphangiogram
- Ultrasound
- Computed tomograms
- Magnetic resonance imaging
- Positron emission tomogram

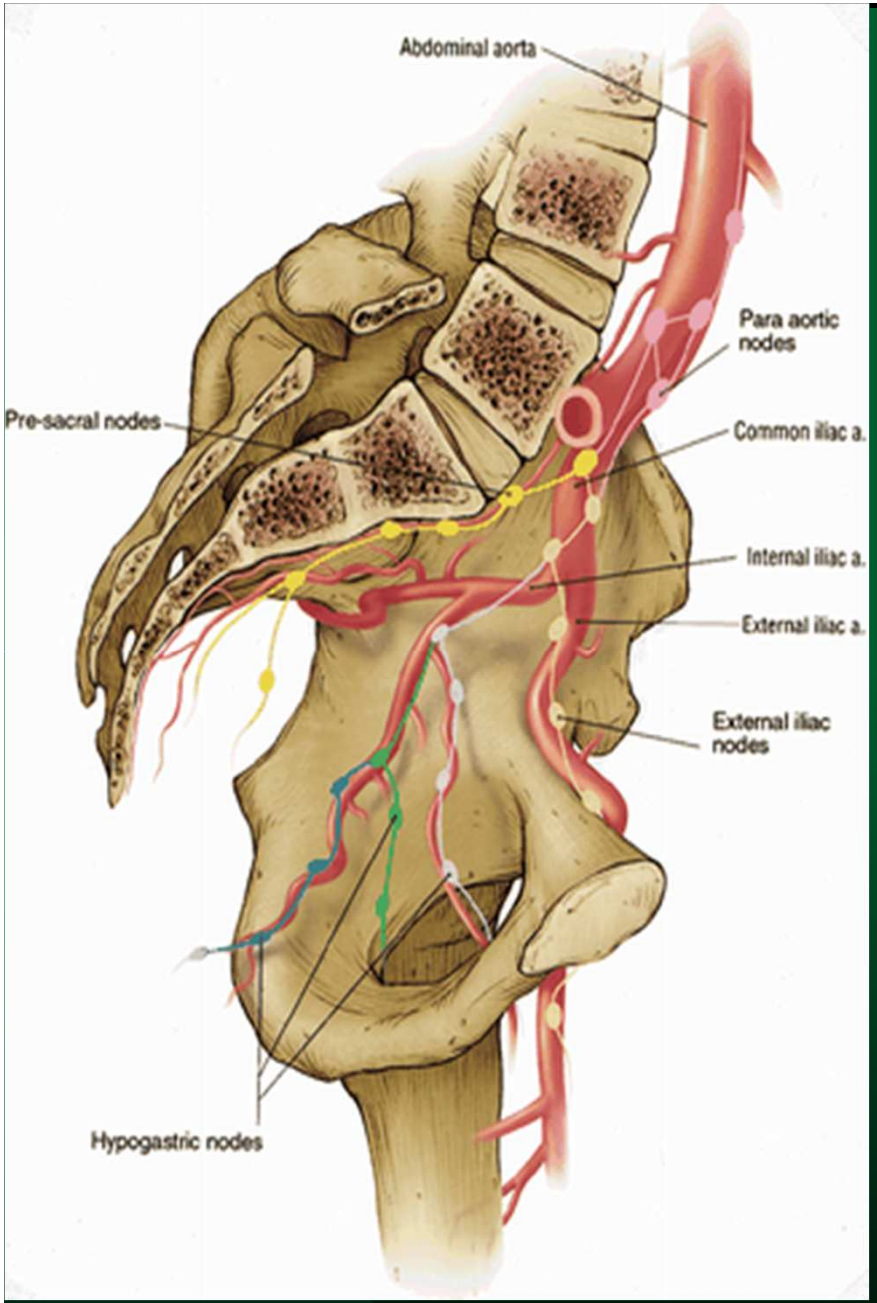
Primary goup

- Parametrial
- Paracervical
- Obturator
- hypogastric / internal iliac
- External iliac
- Sacral



Secondary group

- Common iliac
- Paraaortic
- inguinal



- **Lymphatic trunks**
  - **3 lateral trunks**

upper---terminates in high internal iliac nodes

branches to ext iliac &common iliac

interrupted by paracervical nodes

middle---originates near cardinal lig

-----obturator node

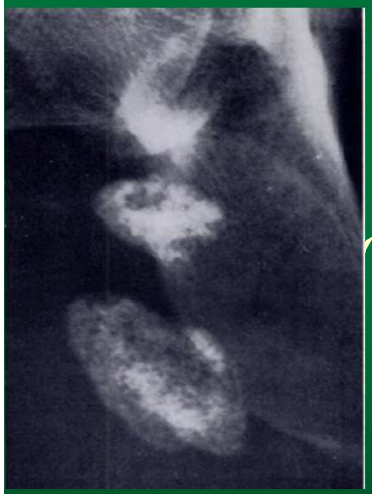
lower---presacral, inf gluteal , lower paraaortic nodes

- **Anterior---**follows bladder lymphatics to internal iliac nodes
- **Posterior----**follows uterosacral lig

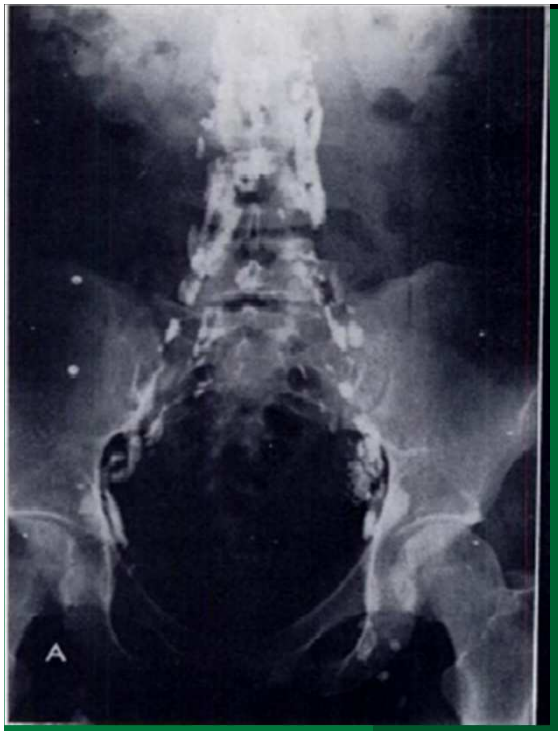
---sup rectal,presacral , common iliac

Lymphangiography

- Interpretation of lymphangiogram based on examination of both – the lymphatic phase i.e. initial roentogram taken at completion of injection and the nodal phase – 24hr roentogram



- Normal lymph node- has a granular pattern,oval or kidney shaped
- Abnormal nodes- more rounded, may have a filling defect due to tumour deposition &irregularities along periphery of node



Bipedal lymphangiography used mainly to assess pelvic &paraaortic nodes

	sensitivity	specificity
pelvic	28%	100%
paraaortic	79%	

Even if nodes are not enlarged if architectural distortion+……clue to metastasis– hence helpful in treatment planning

Disadv- peripheral goup of nodes- hypogastric, obturator,ext iliac not visualised

Small metastatic lesions may not distort architecture

Sometimes gross metastatic tumour completely obliterate lymph nodes

Long term follow up Not possible

Allergy to drug, time consuming &cumbersome

ULTRASOUND

- Ultrasound of abdomen &pelvis used to evaluate ……
  - tumour size
  - invasion of parametrium
  - pelvic side wall
  - bladder &rectal invasion
  - hydronephrotic changes
  - metastasis
  - lymph nodes (?)

TRANSABDOMINAL

TRANSVAGINAL

TRANSRECTAL

CT SCAN

- **Value of CT scan in invasive Ca cervix** --*assessment of advanced disease (stage>IIB)*

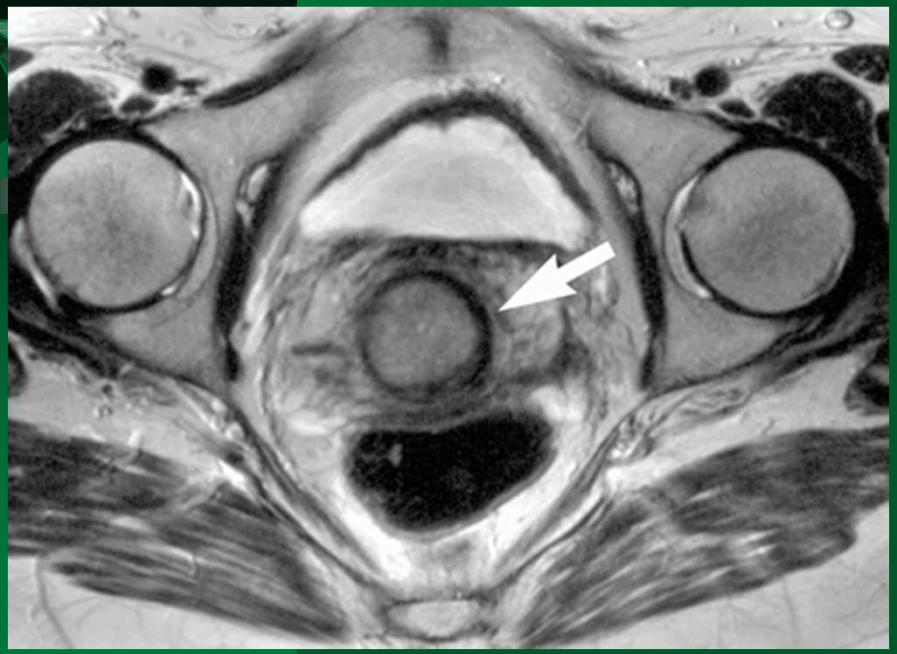
  -- *detection &biopsy of suspected lymph node metastasis*

  --*radiation treatment planning--- contouring GTV,CTV,PTV,TV,IV*

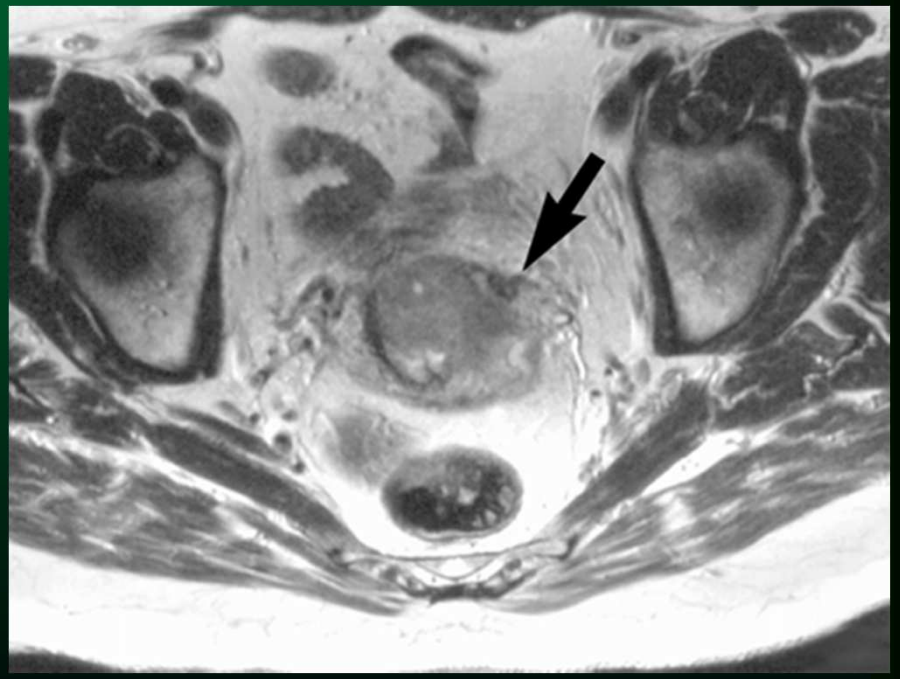
Magnetic Resonance Imaging

- Pelvic imaging like USG &CT scan – limited capability for tissue characterisation
- MRI superior soft tissue resolution-
- Most effective in evaluating
  - tumour volume
  - endocervical lesions
  - local extension
  - lymph node status
  - monitoring therapeutic response
  - recurrent disease

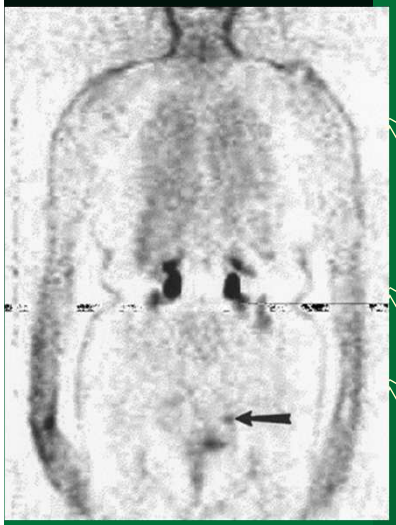
MRI contd…….



Preservation of stromal ring – noninvasive cervical ca



Disruption of stromal ring– reliable sign of parametrial invasion



PET SCAN

- PET --- functional test of glycolytic activity of tumour &relative deficiency of glucose 6 P in tumour cells
- MRI --- cannot image occult distant metastasis
- Whole body PET can detect these occult mets---

	sensitvity	specificity	accuracy
Paraaortic	67 %	95%	88 %
pelvic	91 %	94 %	92 %

	sensitivity	Specificity
PET	88 %	92 %
CT	72 %	93 %
MRI	50 %	95 %
PET.CT	72 %	92 %

TNM staging

Developed by Pierre Denoix 1943- 1952 and 1st published in 1953

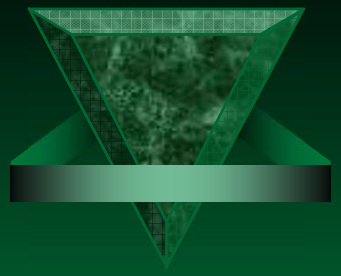
Endorsed by American Joint Committee on Cancer (AJCC)

- **Tumour size (T)** – primary tumour that has not been previously treated
- **Nodal involvement-** regional lymph nodes include paracervical,parametrial,hypogastric(obturator);

  common , internal and external iliac; presacral and sacral nodes. Metastasis to lymph nodes outside the regional nodal group is classified as distant metastasis

Metastatic involvement – excludes peritoneal metastasis

STAGE GROUPING



Stage 0	Tis	No	M0
Stage IA	T1a	No	M0
Stage IA_1	$T1a_1$	No	M0
StageIA_2	$T1a_2$	No	M0
Stage 1B	T1b	No	M0
Stage $1B_1$	$T1B_1$	No	M0
Stage $1B_2$	$T1b_1$	No	M0
Stage IIA	T2a	No	M0
Stage IIB	T2b	No	M0
Stage IIIA	T3a	No	M0
Stage IIIB	**T1,T2,T3a,T3b**	**N1**	M0
Stage IVA	T4	Any N	M0
Stage IV B	Any T	Any N	**M1**

- Hence TNM staging helps in estimation of prognosis and also planning therapy

- Moreover TNM staging is a dual system
  - clinical
  - pathological (pT, pN ,pM)
    (postoperative histopathological)

This also allows quality assurance of clinical staging

FIGO staging– should CT /MRI be incorporated ….?

- Management of cervical cancer is based on assessment of parametrial extension & nodal involvement
- Radical hysterectomy – for medically fit Stage I patients or with minimal extension to proximal vagina (Stage IIA)

  Radiation therapy for Stage IIB or greater
- FIGO staging takes into account tumour size but still does not include lymph node metastasis
- Errors of FIGO staging

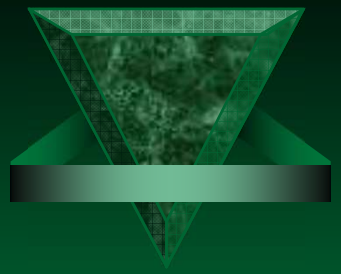
  stage IB---17-32%

  stage II- IV--- 67%

- 24.3% patients of stage IIIB present with hydronephrosis

  Excretory urography unnecessary when CT & MRI are used because of comparable accuracies of IVP,CT.MRI in detecting urinary obstruction

- CT evaluation not only imp for detecting locoregional extent but also for radiation treatment planning



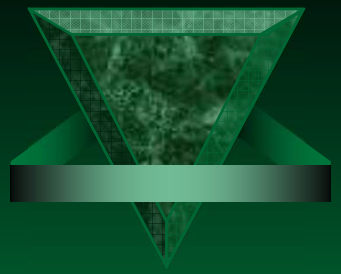
- HENCE…..CT /MRI may be preffered as primary diagnostic modality in ca cx
- However…….sometimes overestimation of tumour size by MRI –19%

CT & MRI may prove to be beneficial in clinically staged early disease by early detection of nodal metastasis & parametrial invasion ----treatment plan may change

But in late/advanced staged disease

no change of treatment option

no benefit in overall survival



Moreover

- MRI costly, not universally available
- higher false positive rates of CT to detect parametrial invasion
- low diagnostic accuracy of CT 58% compared to clinical accuracy92% in detecting parametrial invasion
- Lack of uniform quality in performing , interpreting CT & MRI

FIGO staging is still clinical

CT /MRI adds to diagnostic accuracy

Other investigations

HIV SCREENING –HIV1,HIV 2, HIV RNA,
CD 4 counts

- TUMOUR ANTIGEN----SCC Ag
  ↑**60 % cases,**

Persistent levels 3 – 12 mo after T/T---failure

TUMOUR MARKERS

CA125----- 21.5 % Adenoca
CA19-9----32 %
CEA

PROG RECEPTORS + ----- ↑DFS
↓COX 2 LEVELS ----- better 5 yr survival
c erb 2 ---- 49 % adenoca
38 % SCC

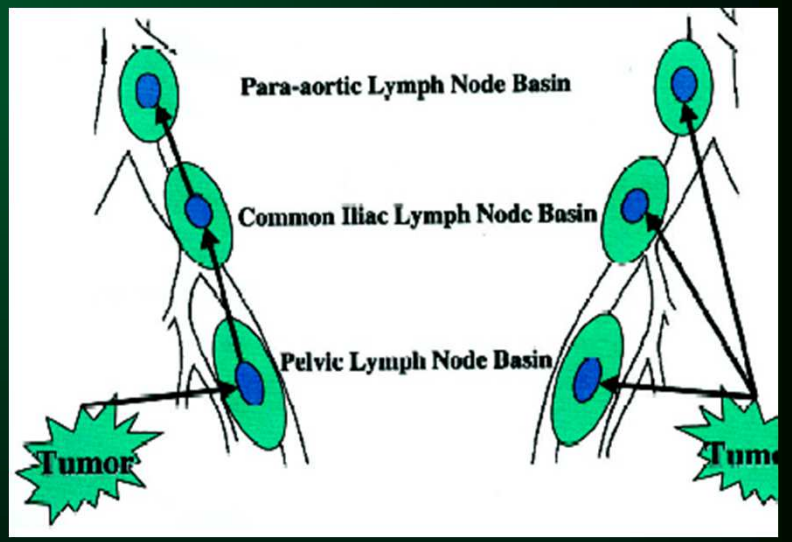
Role of sentinel node scintigraphy

Sentinel node--- specific node that is 1st to receive drainage from malignancy & primary site for metastasis

- Presence or absence of metastatic disease in sentinel node reflects status of nodal basin as a whole
- Lymphatic mapping of cervix--- 2 possible drainage sites
- Sensitivity

65%-- 87%

- Presently purely inv

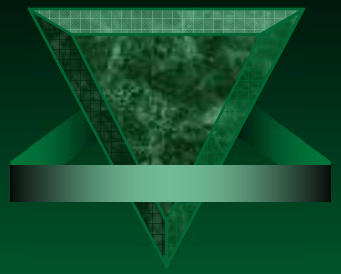


- Phase III trials with survival end points necessary to establish its definite diagnostic role in ca cervix

CONCLUSIONS

Carcinoma of cervix is the leading cause of gynaecological cancers in INDIA

For invasive disease recommendations for diagnostic evaluation and treatment planning have evolved into 2 distinct processes--- clinical staging & extended clinical staging



Nodal metastasis & parametrial invasion are of paramount importance in treatment planning & prognosis

For stage I & IIA disease MRI &CT owing to satisfactory accuracy in evaluation of main prognostic factors ensures correct treatment planning

However >85% of cases presenting to us are > stage III hence still today diagnostic work up in carcinoma cervix is primarily clinical based on FIGO guidelines


Thank You