Radiotherapy in the Management of Uterine Cancers

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Uterine cancers

- Cervical cancers are the commonest cancers in females in the developing world
- In India, the incidence & prevalence of breast cancers has now gone past that of cervical cancers in the urban areas
- In rural areas of India, the commonest cancer in females, as well as the commonest gynaecological cancer, is still cervical cancer
- Endometrial cancers are much more common in the developed world, but their incidence, in urban India, is on the rise

Aetiological factors-Cervical Cancers

- Human Papilloma Virus (HPV) type 16,18
- Early marriage/ early age of 1st intercourse
- Multiparity

Aetiological cancers- Endometrial Cancer

- Early menarche
- Late menopause
- Obesity
- Hypertension
- Diabetes Mellitus
- Estrogen-only OCPs

Symptoms

- Dyspareunia

- Perimenopausal/postmenopausal bleeding PV
- Vaginal discharge

- Low back pain
- Tenesmus
- Dysuria

Investigations

- History & physical examination
- Routine bloods-CBC, urea & creatinine, LFT

- Cervical Pap Smear
- Colposcopy & biopsy
- Cervical punch biopsy

- Hysteroscopy & endometrial biopsy
- D & C biopsy

Imaging Investigations-FIGO

- Chest X ray (PA)
- Intravenous urogram
- Barium enema
- Cystoscopy

Other imaging investigations

- MRI pelvis > USG/CECT
- CECT upper abdomen> USG
- PET-CT is NOT yet a standard of care

Biopsy-proven Cervical Cancer

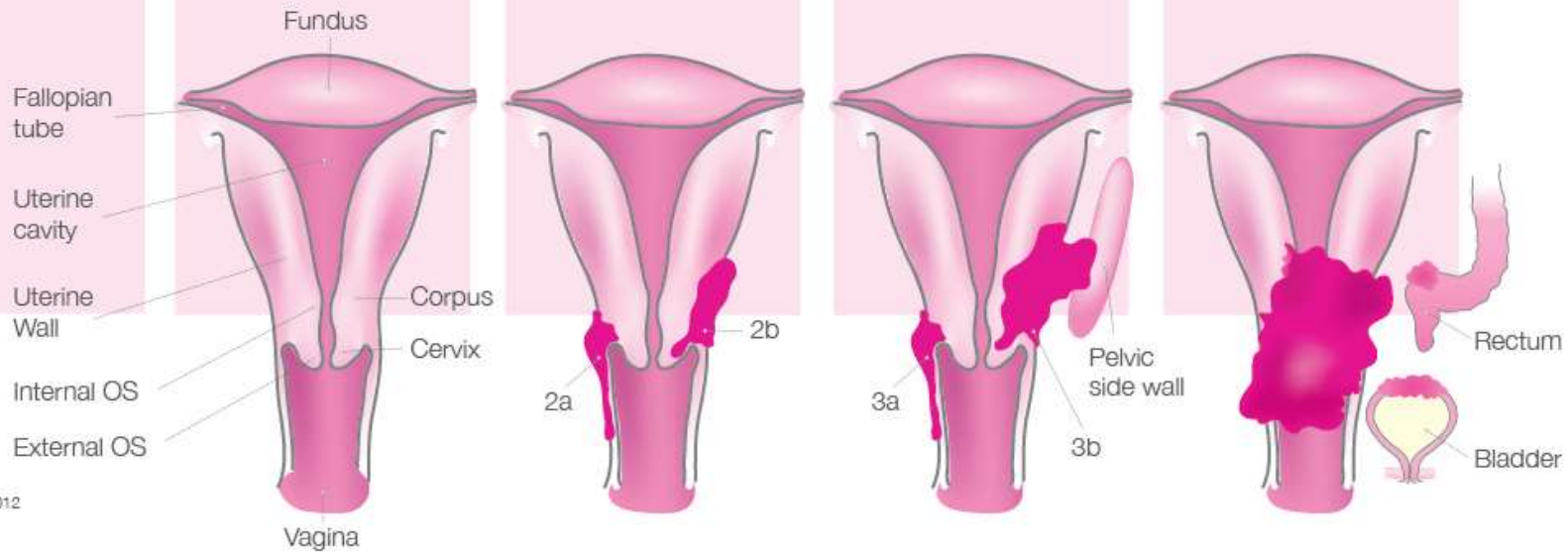
- Management protocol is the same for squamous cell carcinoma & adenocarcinomas
- Adenocarcinomas tend to be bulkier & present in more advanced stage, as they are endocervical
- However, stage for stage, there is no definite evidence that adenocarcinomas do any worse than SCC

Staging –Cervical Cancer

- IA1: microscopic lesion , depth of invasion <3mm, lateral extent <7mm
- IA2: microscopic lesion ,depth of invasion 3-5mm, lateral extent <7mm
- IB1: microscopiclesion ,depth of invasion >5mm/ lateral extent >7mm/ clinically visible lesion =<4cm confined to cervix
- IB2:clinically obvious lesion >4cm confined to cervix
- IIA1: extends outside uterus but not to parametria/lower vagina, <4cm
- IIA2: extends outside cervix but not to parametria/lower vagina, >4cm
- IIB: extends to parametria but not upto lateral pelvic wall
- IIIA: extends to lower third of vagina
- IIIB: extends to parametria upto lateral pelvic wall/hydronephrosis/non-functioning kidney from any cause
- IVA: extends to mucosa of urinary bladder/rectum
- IVB: distant metastases

Staging of Cervical Cancer

	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
Extent of tumor	Carcinoma in-situ	Confined to Cervix	Disease beyond cervix but not to pelvic wall or lower 1/3 of vagina	Disease to pelvic wall or lower 1/3 of vagina	Invades bladder, rectum or metastasis
5-year survival	100%	85%	65%	35%	7%
Stage at presentation		47%	28%	21%	4%



Stage	Treatment	Survival
0	Local / Cone /LLETZ	
I A1	Local / Cone /LLETZ	100%
I A2	Simple hysterectomy (local for fertility sparing)	
I B1	Radical hysterectomy / trachelectomy plus nodes	65%
I B2	Chemoradiotherapy (CRT)	
~~IIA1~~	~~Radical Hysterectomy / CRT plus nodes~~	~~Similar~~
IIA2	CRT	to IB
IIB	CRT	61%
IIIA	CRT	
IIIB	CRT	44%
IVA	CRT	20%
IVB	Individual	5%

Stage IA/IB1

- IA1=LLETZ/conisation
- IA2=simple hysterectomy
- IB1=Surgery [radical hysterectomy (type III extrafascial/Wertheim)] & RT are equally good options
- Concurrent chemoradiation is superior to radiotherapy alone
- Radical trachelectomy is a fertility-preserving option for small lesions <2cm, low grade, LVSI -

Stage IB2-IVA

- Radical chemoradiation is the treatment of choice

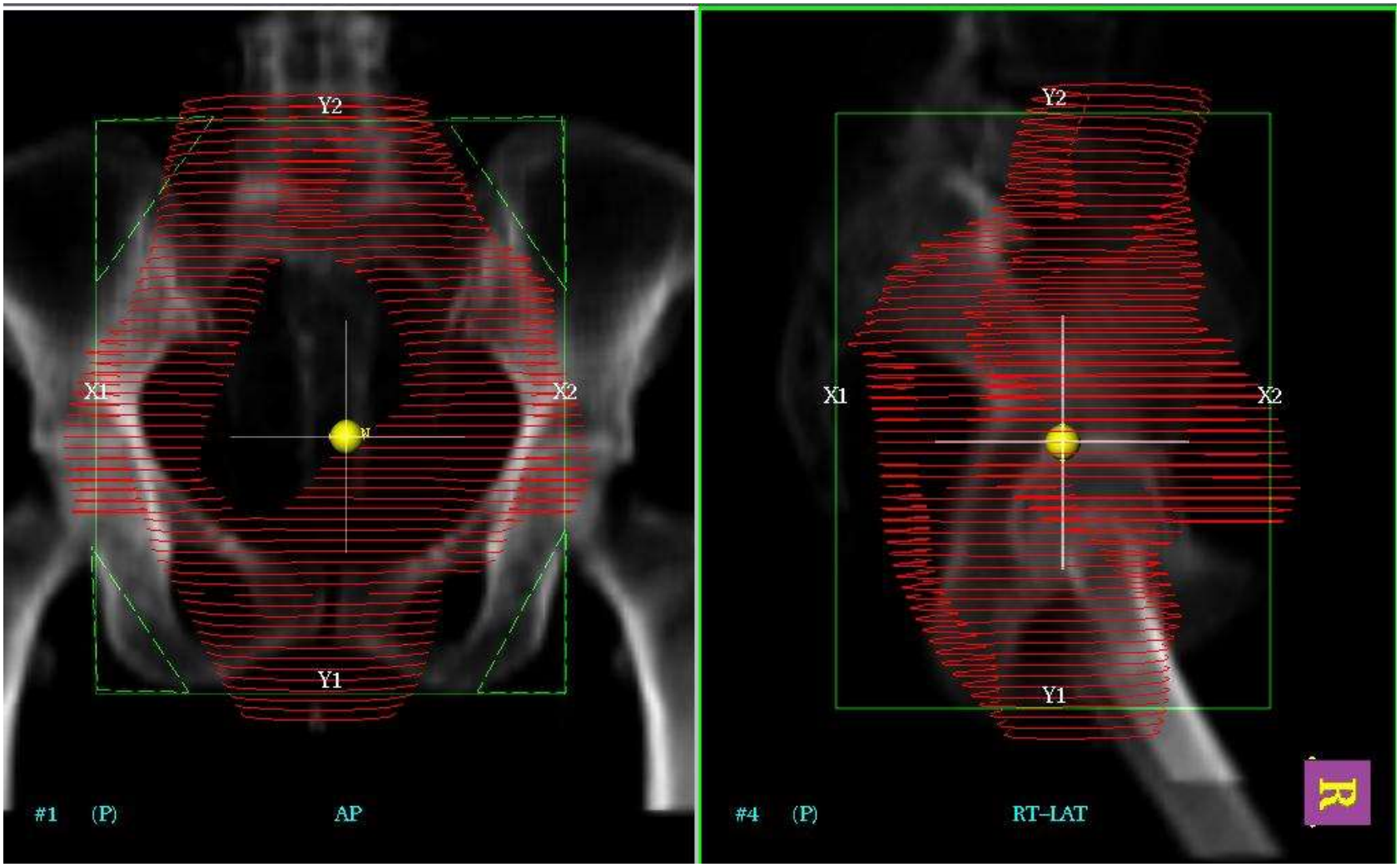
- Although stage IB2 & IIA are operable stage, they will usually require adjuvant radiotherapy/chemoradiotherapy. This adds to the burden of morbidity, hence single-modality treatment is preferred in these cases.

- For bulky stage IVA, neoadjuvant chemotherapy is sometimes used, both to increase chance of cure & to select out good responders, who have better prognosis

EBRT

- Delivered by Telecobalt/Linear Accelerator
- Dose= 45-50Gy/25#/5 weeks
- Target volume is whole pelvis.
- Usually a 4-field box arrangement is used

- Upper border=L4-L5 junction
- Lower border= lower border of obturator foramen/ 2cm beyond lower extent of disease in vagina
- Lateral border=1-2 cm beyond pelvic brim
- Anterior border=anterior cortex of pubic symphysis
- Posterior border=S2-S3 junction


Y2
X1
X2
Y1
#1 (P) AP
Y2
X1
X2
Y1
#4 (P) RT-LAT
R

Conformal RT

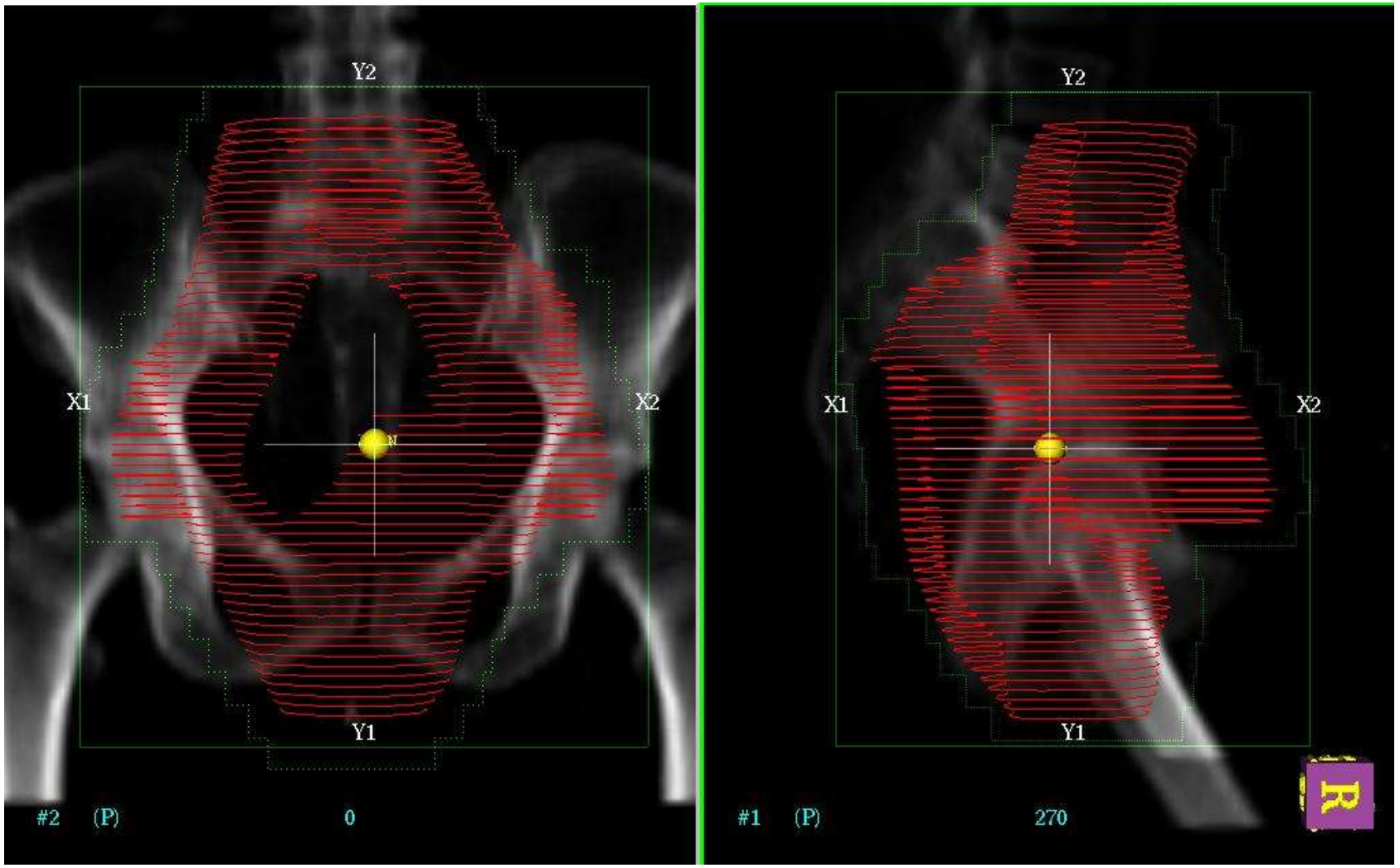
Clinical target volume :

- Gross disease in cervix +/- vagina +/- parametria
- Uterine corpus & adnexae
- Parametria upto lateral pelvic wall
- Vagina (2cm below lower extent/ upto introitus)

- Bilateral external & internal iliac LN
- Para-aortic LN (where grossly involved)

Organs at risk:

- Urinary bladder
- Rectum
- Sigmoid colon
- Small intestines


Y2
X1
X2
Y1
#2 (P) 0
Y2
X1
X2
Y1
#1 (P) 270
R

Common toxicities

- Dermatitis
- Diarrhoea
- Dysuria
- Anorexia

Do’s and Don’t’s

- No soap/oil over skin of pelvis from umbilicus to mid-thigh
- Drink plenty of water 3L/day
- Eat low-residue diet; small frequent meals
- ORS for mild-moderate diarrhoea
- Anti-diarrhoeals for severe diarrhoea only (>5-6 episodes/day). Antibiotics are not routinely used unless infection is strongly suspected.

Concurrent chemotherapy

- Additional 5-year OS benefit of 6%.
- Weekly Inj Cisplatin 40 mg/m2 OR 3-weekly Cisplatin 100 mg/m2
- Usually given on day-care basis
- Requires hydration before & after
- Renal function needs monitoring & corresponding dose adjustments
- Carboplatin can be substituted for mild renal impairment
- No chemotherapy for creatinine clearance <30 ml/min
- Emesis & anorexia common
- Some patients may experience peripheral neuropathy & hearing problems

Brachytherapy

- Radiation source placed within the patient's body
- Commonly hollow applicators are placed,1 in uterus & 2 in vaginal fornices [intracavitary brachytherapy]
- For bulky parametrial disease, percutaneously titanium needles are placed through a template [interstitial brachytherapy]
- Usually done on day-care basis
- Patients are admitted after bowel clearance on overnight fasting.
- Insertions are done in the Operation Theatre after spinal anaesthesia.
- Post-insertion, imaging & treatment planning done, following which applicators are removed & patient is discharged.

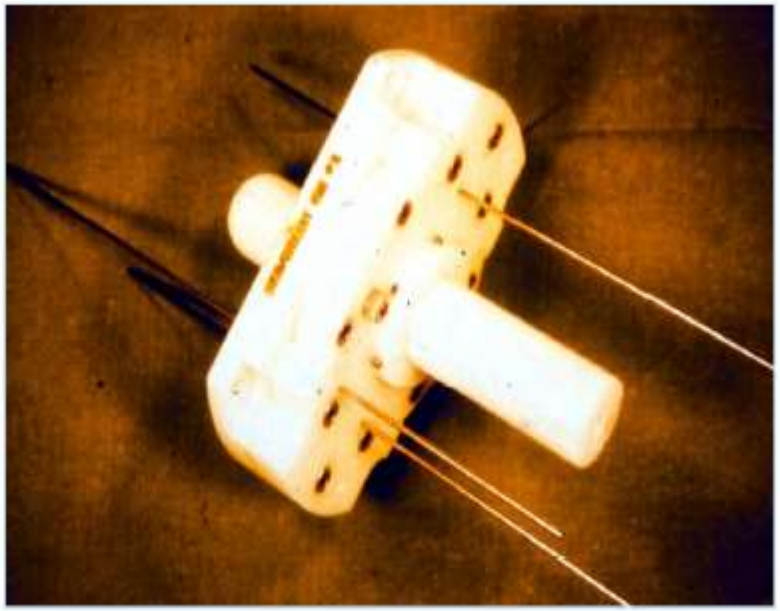
Modern day Remote Afterloading HDR Brachytherapy machine

Modern-day Intracavitary Applicators

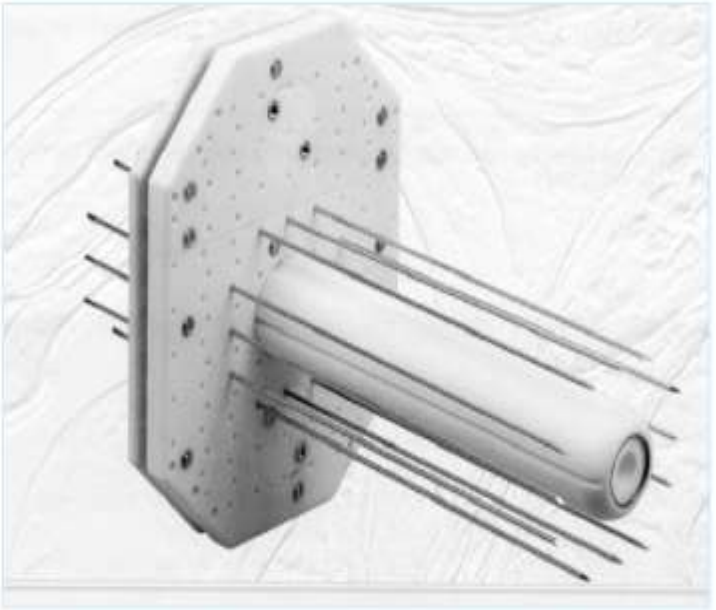
Classical interstitial techniques

Perineal Templates

Syed

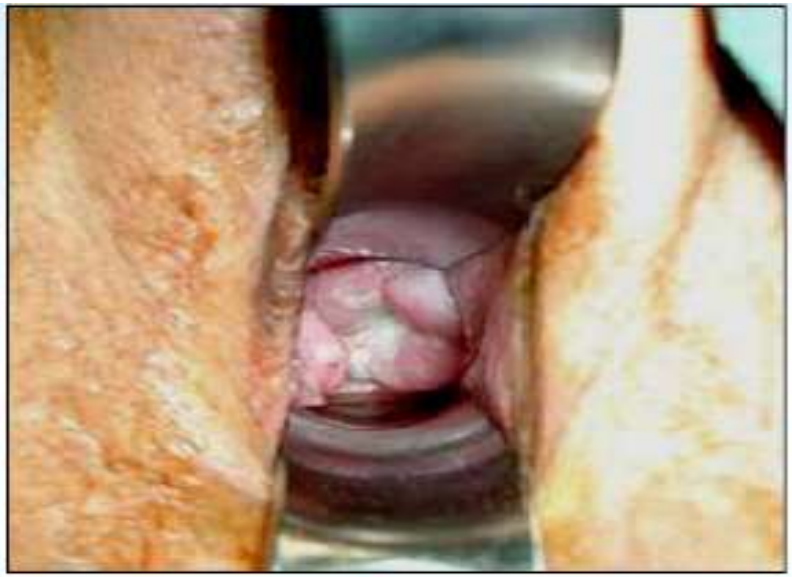


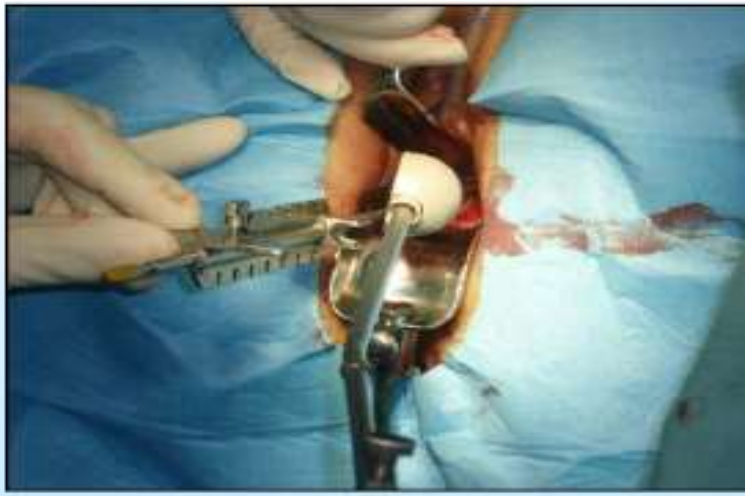
MUPIT



Instruments

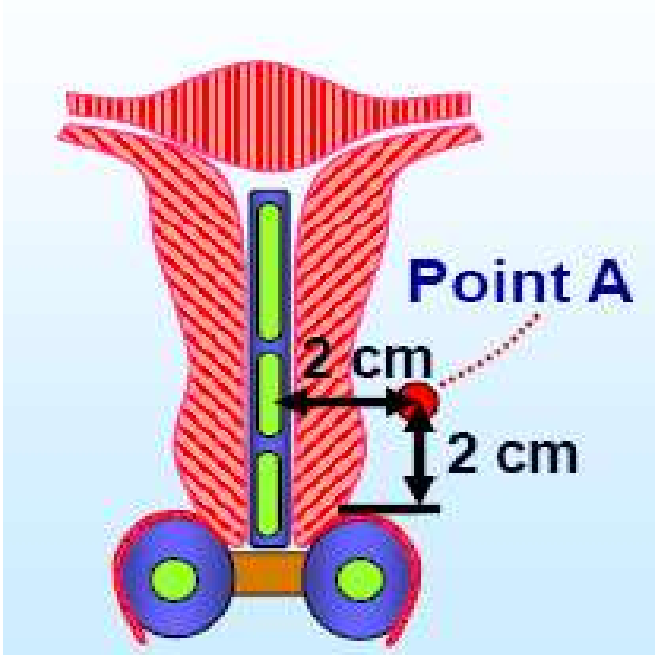
Preparation

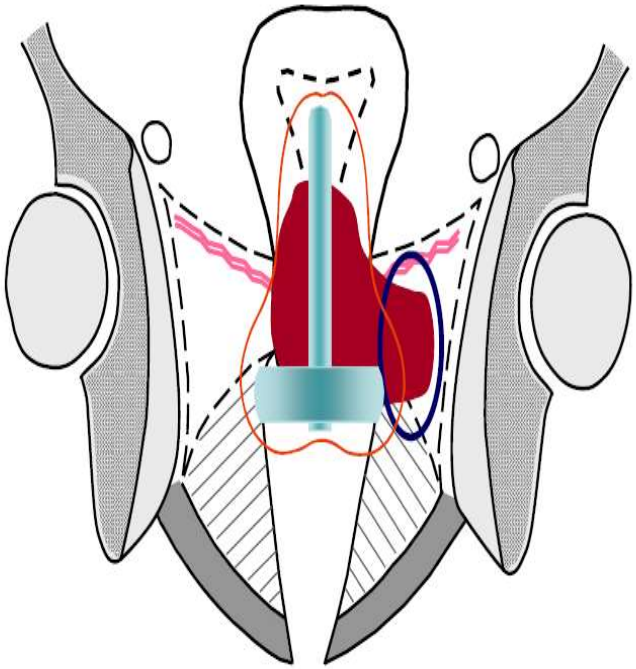


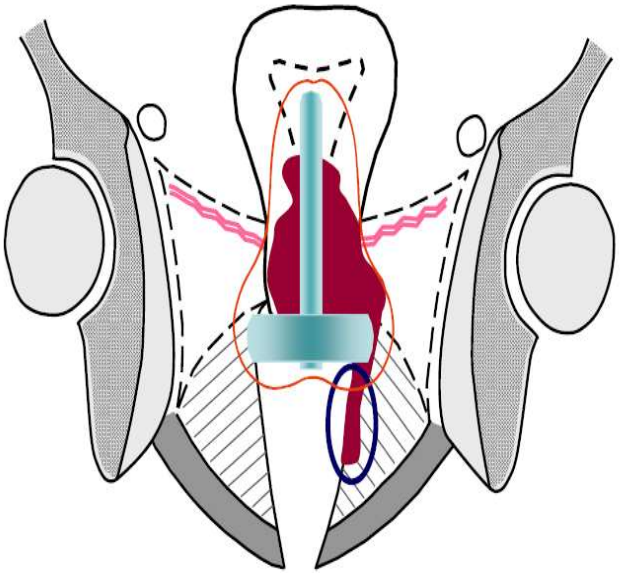




Packing of vagina


At completion of packing


Point A
2 cm
2 cm





- Commonly used radioisotopes are Iridium^{192} & Cobalt^{60} for high-dose rate (HDR) brachytherapy & Cesium^{137} for low-dose rate (LDR) brachytherapy

- Tiny bead, kept in lead-shielded container within brachytherapy machine

- Treatment is delivered by remote afterloading: the hollow applicators are connected to the brachytherapy machine by transfer tubes. The radiation bead is sent through these tubes inside the patient's body to deliver treatment & returned back to the machine thereafter.

- Thus, there is no radiation exposure to the medical/paramedical staff.

- Dose was classically prescribed to Point A
- This is the point where the uterine artery & ureter cross
- It was once erroneously thought that the radiation tolerance of this region is the limiting factor in radiation dose
- Dose schedule of 7Gy/# x4# OR 8Gy/# x 3# OR 9Gy/# x2# used. Usually one # /week
- Plan is optimised by computerised planning to reduce dose to rectosigmoid & urinary bladder

GEC-ESTRO recommendations

ELSEVIER

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Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group☆ (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV

Christine Haie-Meder[a,*], Richard Pötter[b], Erik Van Limbergen[c], Edith Briot[a], Marisol De Brabandere[c], Johannes Dimopoulos[b], Isabelle Dumas[a], Taran Paulsen Hellebust[d], Christian Kirisits[b], Stefan Lang[b], Sabine Muschitz[b], Juliana Nevinson[e], An Nulens[c], Peter Petrow[f], Natascha Wachter-Gerstner[b]

ESTRO project

Recommendations from gynaecological (GYN) GEC ESTRO working group (II): Concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy—3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology

Richard Pötter[a,*], Christine Haie-Meder[b], Erik Van Limbergen[c], Isabelle Barillot[d], Marisol De Brabandere[c], Johannes Dimopoulos[a], Isabelle Dumas[b], Beth Erickson[e], Stefan Lang[a], An Nulens[c], Peter Petrow[f], Jason Rownd[e], Christian Kirisits[a]

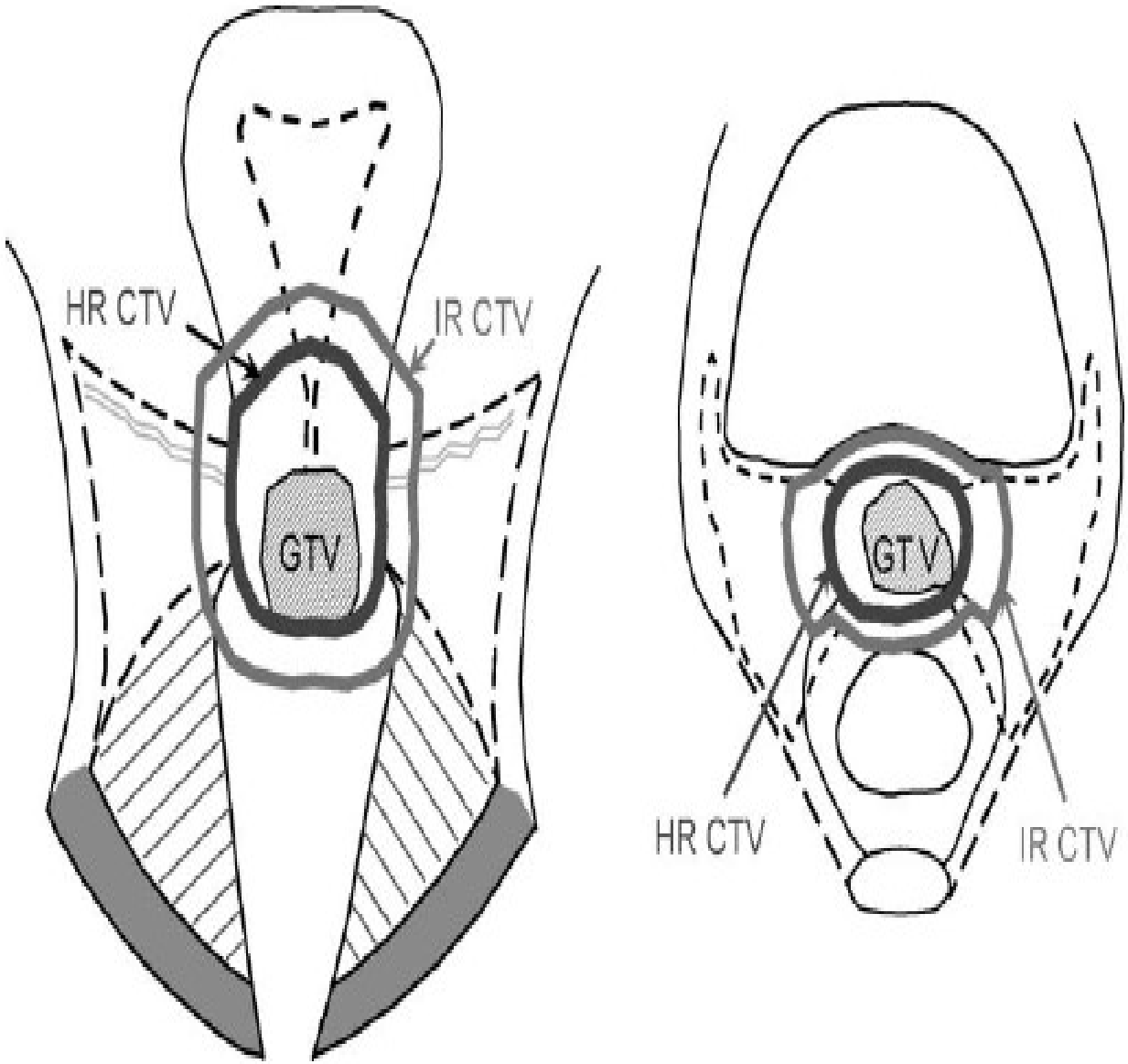
GEC-ESTRO recommendations

Target definition

2 CTVs

A first target related to the extent of GTV **at diagnosis** :
with an intermediate dose prescribed to this target (60 Gy)
Intermediate risk CTV

A second target related to the extent of GTV **at time of BT** :
taking into account tumour extent at diagnosis.
with a high dose prescribed to this target (80-90 Gy)
High risk CTV


HR CTV
IR CTV
GTV
GTV
HR CTV
IR CTV

What's different?
Target

Point - based dosimetry

- Dose prescribed according to maximum tolerance of normal structure (crossing of uterine artery & ureter)
- Dose prescription point is unrelated to actual size and shape of the tumor
- Dose prescription considers the stage, but not the extent of response of the tumor

Volume-based dosimetry

- Dose prescribed according to minimum dose to the tumor
- Dose prescribed directly to the residual tumor at the time of brachytherapy
- Dose prescription considers both stage and extent of response of the tumor (adaptive radiotherapy)

What's different?
Organs at Risk

Point-based dosimetry

- Constraints applied to hypothetical points derived from planar X rays
- Doses at reference points may not reflect actual high-dose regions
- Reference points are poorly correlated with clinical endpoints (rectal bleeding,etc)

Volume-based dosimetry

- Constraints applied to organ volumes as visible on sectional imaging (CT/MRI)
- Allows accurate assessment of organ volumes receiving high dose
- Good correlation between dose-volumes and clinical endpoints (Dose to 2cc rectum>75-80Gy=rectal bleeding)

Brachytherapy –common toxicities

- Pain/soreness locally
- Bleeding PV (oozing)
- Hematuria (in some cases, after interstitial brachytherapy)
- Post-spinal headache

2D radiotherapy : dose at points and outcome

MORBIDITY RATES AFTER RADIOTHERAPY (EBRT+BT)

	STAGE				
	IB	*IIA*	*IIB*	*IIIB*	*IVA*
Total no. of patients	415	137	391	326	23
G2 complications	51 (12%)	14 (10%)	65 (17%)	38 (12%)	3 (13%)
G3 complications	26 (6%)	23 (17%)	57 (15%)	45 (14%)	2 (9%)

G3 morbidity > 10% ~ all stages

„Refinements in brachytherapy techniques are necessary to improve the present results“

Perez CA in Perez/Brady 1998

3D radiotherapy:dose to volumes and morbidity

Results-Vienna

LENT/ SOMA	G1 n	G2 n	G3 n	G4 n
BLADDER	7	11	1	2
RECTUM/ SIGMOID	2	7	2	2
SMALL BOWEL/COLON	5	0	0	0
VAGINA	78	36	5	0

Post-operative radiotherapy

Intermediate risk: RT alone

- Bulky disease >4cm
- Deep stromal invasion >1cm
- LVSI+

High risk: Chemoradiation

- Positive margins
- Nodal metastases
- Parametrial extension

- EBRT:

- Same dose-schedule as for EBRT for radical radiotherapy

- Brachytherapy:

- Vaginal cylinder
- 6Gy/# x 2# , once weekly
- Prescribed to vaginal mucosa at 5mm from applicator surface
- OPD basis
- No anaesthesia required

- Interstitial brachytherapy for gross residual disease

Late toxicities (>3 months)

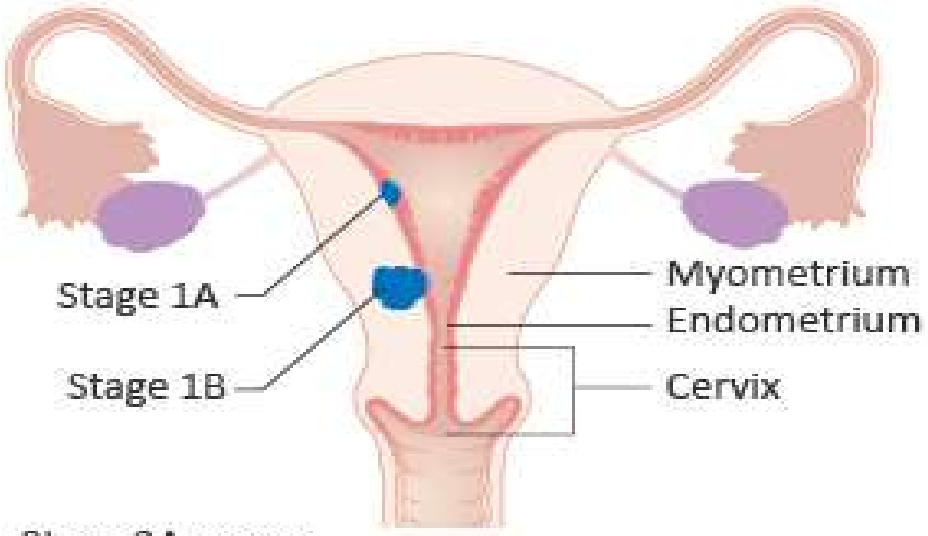
- Radiation proctitis: may cause rectal bleeding. Some require transfusion. Managed by APC LASER coagulation/ steroid enema/hyperbaric oxygen therapy

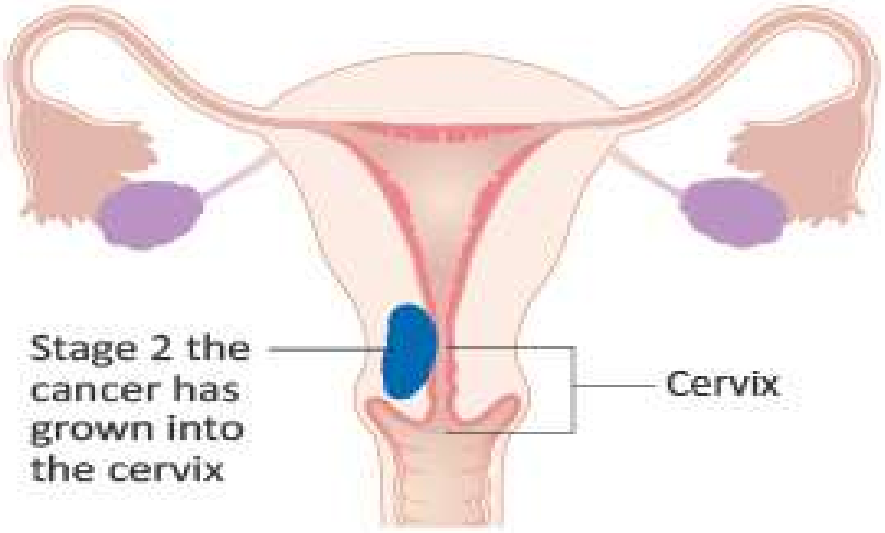
- Radiation cystitis: urinary frequency & dysuria, rarely hematuria. Managed by LASER fulguration/ formalin instillation

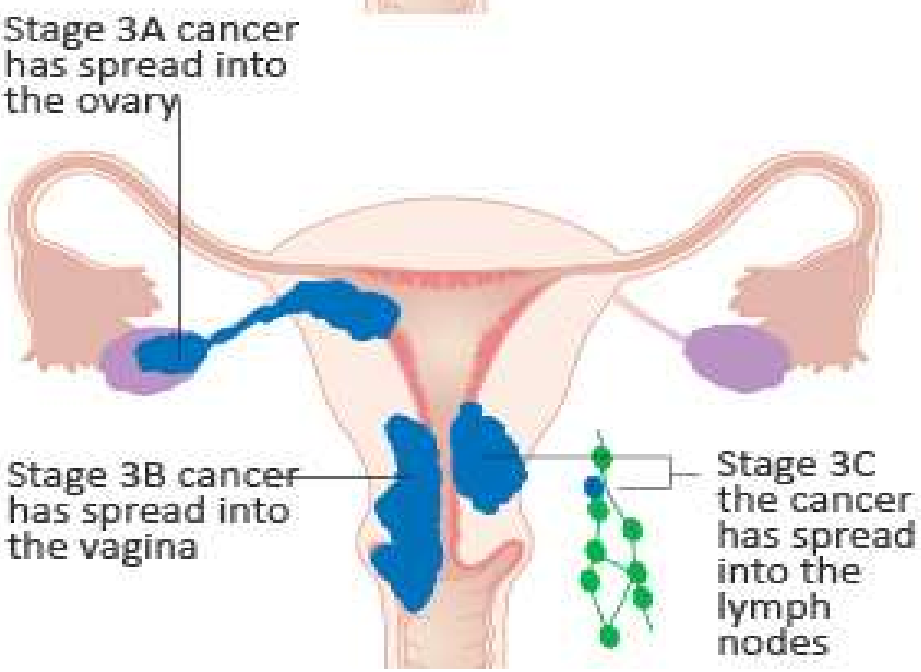
- Vaginal fibrosis: synechiae may form. May cause dyspareunia.

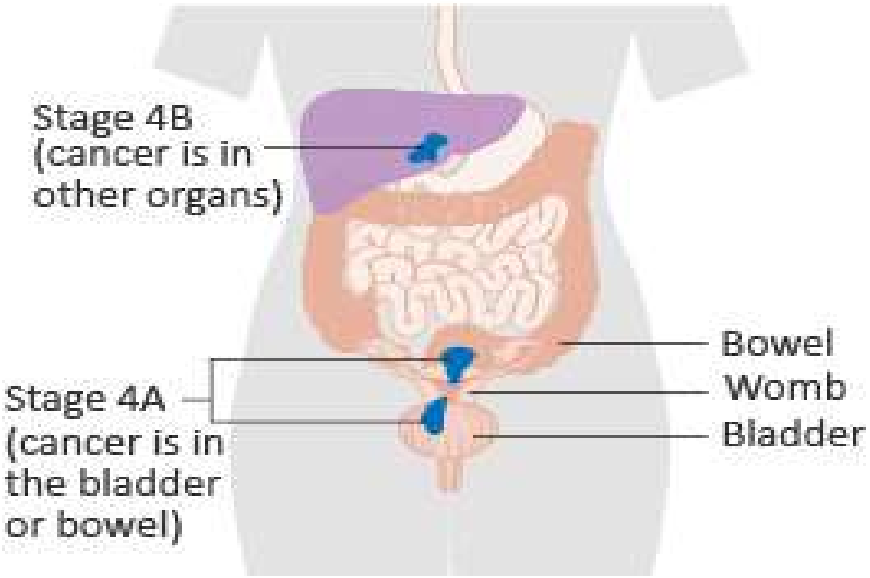
Staging-Endometrial Cancer

- IA: endometrium/<50% thickness of myometrium
- IB: >50% thickness of myometrium
- II: extends to cervical stroma
- IIIA: extends outside uterus into serosa/adnexae
- IIIB: extends outside uterus into vagina/parametria
- IIIC: pelvic or para-aortic Lnpathy
- IVA: extends to mucosa of urinary bladder/rectum
- IVB: distant metastases


Stage 1A
Stage 1B
Myometrium
Endometrium
Cervix


Stage 2 the cancer has grown into the cervix
Cervix


Stage 3A cancer has spread into the ovary
Stage 3B cancer has spread into the vagina
Stage 3C the cancer has spread into the lymph nodes


Stage 4B (cancer is in other organs)
Stage 4A (cancer is in the bladder or bowel)
Bowel
Womb
Bladder

Endometrial Cancer
ESMO-ESGO-ESSO Consensus Guideline (2016)

- Low risk: IA, gr 1-2,LVSI-: observation
- Intermediate risk: IB, gr 1-2, LVSI-: vaginal brachytherapy
- High-intermediate risk: IA, gr 3/IB, gr 1-2, LVSI+/: pelvic EBRT
- High risk: IB, gr 3/II/III: pelvic EBRT + chemotherapy

Thank You