

A photograph of a linear accelerator (LINAC) machine, a common piece of equipment in radiotherapy departments. The machine is white and blue, with a large circular gantry and a control panel. The text is overlaid on the image.

# External Beam Radiotherapy for Cancer Cervix

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# Overview of treatment option & outcome

Treatment options and outcome for cervical carcinoma by International Federation of Gynecology and Obstetrics stage

FIGO stage	Treatment options	5-y overall survival (%)
IA1	Simple hysterectomy, radiation therapy	>95
IA1, IA2	Radical hysterectomy, radiation therapy	>95
IB1	Radical hysterectomy, radiation therapy	80–90
IB2, IIA	Chemoradiation therapy, radical hysterectomy	80
IIB	Chemoradiation therapy	65–75
III	Chemoradiation therapy	30–50
IVA	Chemoradiation therapy, exenteration	10–20
IVB	Palliation	<5

# Cancer Cervix: Role of Radiotherapy

- Definitive Radiotherapy
- Post hysterectomy Radiotherapy
- Preoperative Radiotherapy
- Radiotherapy for recurrence

# EBRT in Ca. Cervix

- External Beam RT is an important component of the **total Radio therapeutic management** in cervical cancer, in combination with Brachytherapy or Surgery (in early cases) or chemotherapy (in locally advanced cases)
- The **goal** of EBRT is to destroy tumor cells in the cervix, para-cervical tissue and the regional lymph nodes
- The **therapeutic ratio** is optimized through careful integration of EBRT and Brachytherapy, the dose and intensity of treatment depending upon the disease burden and risk of treatment complications

# Issues in EBRT of Ca. Cervix

- Indications
- Dose of RT
- Field arrangement
- Role of Post-operative RT
- Integration with Brachytherapy and Chemotherapy
- Role of Para-aortic RT
- Altered fractionation schedules in EBRT
- Conformal RT or IMRT

# INDICATIONS

- Early Invasive Cancer (stage IB1 & IIA non bulky )
  - i) An alternative option to surgery
  - ii) The objective is to give radical treatment with an intention to cure
  - iii) Combined with intracavitary RT to deliver tumorocidal dose to the cervix and para-cervical tissue with sparing of bladder and rectum
  - iv) The choice between Radical Surgery and definitive RT still remains controversial, largely dependent upon institutional protocol apart from other clinical factors



## Indications: stage IB2 & IIA (Bulky tumours)

- In bulky tumours, EBRT is given before I/C RT to decrease the size of central tumour and improve the geometry of the I/C application
- As these tumours are technically resectable, many centers also advocate surgery as the primary treatment
- A large majority of such pts (80-85%) require post-op RT however, due to high incidence of parametrial extension and nodal involvement, to minimise chance of pelvic recurrence

## stage IB2 & IIA (Bulky tumours) cont'd

- Although randomized studies report similar overall survival, complications are more in those having initial surgery as they are exposed to the risk of both treatments
- EBRT followed by Hysterectomy: advocated by many clinicians due to slightly increased chance of central disease recurrence, but no diff. in overall survival
- Improved survival found however, in several prospective randomized trials (GOG, RTOG 1999) with concurrent chemotherapy
- **Therefore, EBRT with concurrent CT followed by I/C RT is the standard of care in this group**



## Indications of Locally advanced cervical cancer (IIB-IVA):

- Radiotherapy alone (EBRT followed by Brachytherapy) is the treatment of choice
- EBRT with concurrent chemotherapy showed consistent improvement in local disease control, distant metastasis and survival (5 randomised prospective trials, 1999)
- After publication of these trial results and an associated NIH alert, concurrent cisplatin based chemo-radiation is accepted as the standard of care in this group

For early disease (FIGO I and II A), Surgery and RT have equivalent outcome.

What to follow?

## Early disease : Surgery vs. RT?

**Surgery is preferred for young patients ...**

- **Better maintenance of vaginal pliability and mucosal lubrication**
- **Avoidance of further shrinkage of vagina**

**Radiotherapy is preferred if ...**

- **Presence of involved nodes in imaging**
- **Poor tumor differentiation**
- **Barrel shaped cervix**

## Early disease : Surgery vs. RT?

- Few prospective randomized studies
- Equivalent outcome with 80-90% 5 yr survival reported for either surgery or RT
- However, in most of the studies surgery was followed by external RT if the tumour involved the parametria, surgical margins, deep stroma or lymph nodes
- No significant differences found in the rate of relapse or survival between the two arms
- But the overall incidence of grade 2 or 3 complications was higher in surgery arm

# Dose of EBRT

- **Microscopic disease in parametria / L. Nodes (stage IB & IIA non-bulky or early IIB cases) : 45 - 50 GY**
- **In extensive parametrial involvement or gross lymphadenopathy (advanced cases): 10-15 GY additionally through Parametrial Boost (with midline shielding)**
- **When combined with Brachy: sequence varies depending upon the disease burden in the central and peripheral components as also the institutional protocol**

## Dose of EBRT (cont'd)

- **Most commonly EBRT initially (45-50 Gy with midline shielding after 40 gy) followed by Brachytherapy**
- **However in early non bulky cancer with no or minimum parametrial involvement Brachytherapy may be given first followed by EBRT**
- **In many institutions, Brachytherapy given in the middle of EBRT as soon as the cervical disease regresses to allow I/C insertion (usually after 20-25 gy)**

Radiotherapy or Concomitant  
Chemoradiation?



- **Traditionally definitive radiotherapy alone has been the standard of care .**
- **In 1999, NCI issued an alert that chemotherapy should be added to primary radiotherapy, based on data from 5 cooperative group randomized trials that showed ↑OS (10% absolute survival benefit) for cisplatin based chemoradiation over radiation alone for FIGO 1B2 to IVA patients (Level 1).**
- **Chemoradiation is preferred to radiation alone (when indicated) for FIGO I to IIA patients treated by primary surgery also.**  
**(Level 1).**

# Cancer Cervix: Definitive Radiotherapy Modalities

- EBRT (Cobalt / High MV X-ray/ IMRT)
- Brachytherapy (LDR vs. HDR)

(Relative contribution of EBRT and BT depends on stage)

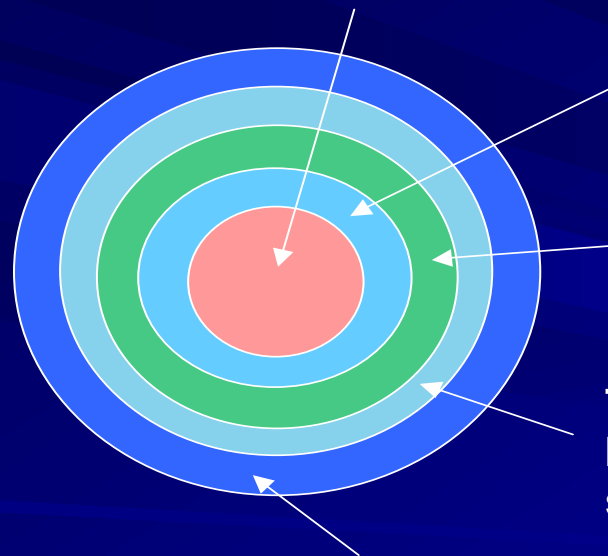
# Basic Steps for EBRT

- Pre-treatment imaging
- Target localization
- Image based individualized planning in 3D-TPS
- Simulation
- Treatment execution  
(To keep hemoglobin level  $> 12\text{gm}\%$  for better tumor response)

# Careful selection of target volume

## Volumes – ICRU 50

**Gross Tumor Volume (GTV)** -- The palpable or visible/demonstrable extent and location of the malignant growth



**Clinical Tumor Volume (CTV)** – GTV + subclinical microscopic malignant disease which has to be eliminated

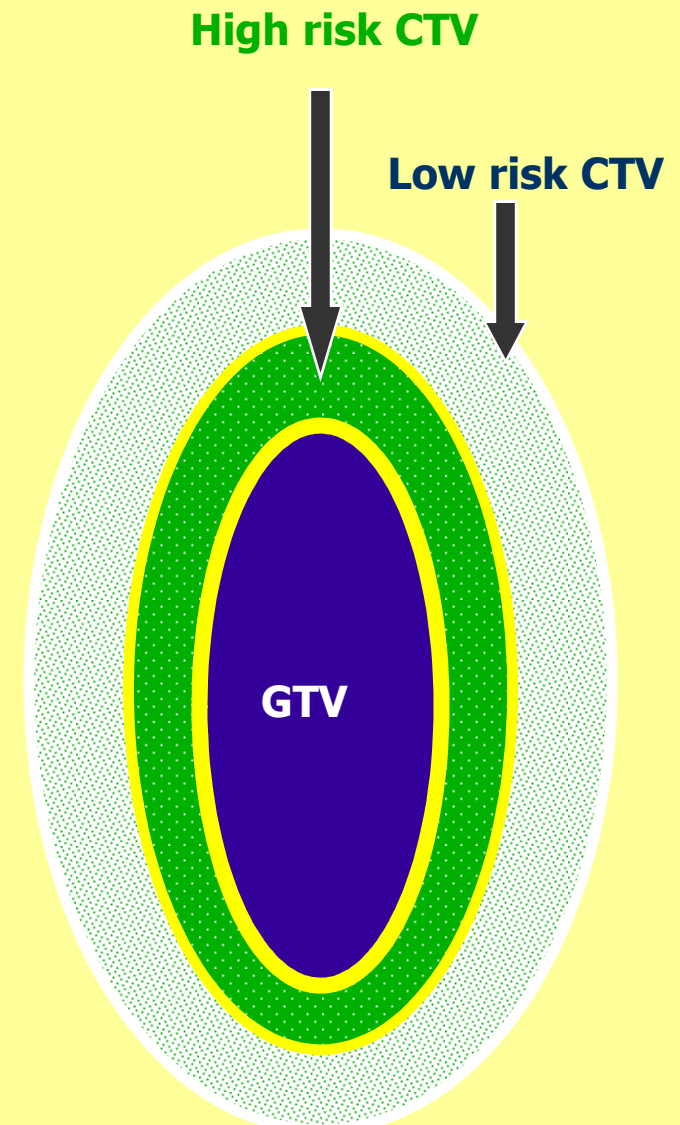
**Planning Target Volume (PTV)** – the volume of tissue receiving the prescribed irradiation (in BT,  $PTV = CTV$ )

**Treated Volume (TV)** – the volume encompassed by an isodose surface that has been specified by the radiation oncologist (= min target dose)

**Irradiated Volume (IV)** – the volume that received a significant dose regarding tissue tolerance

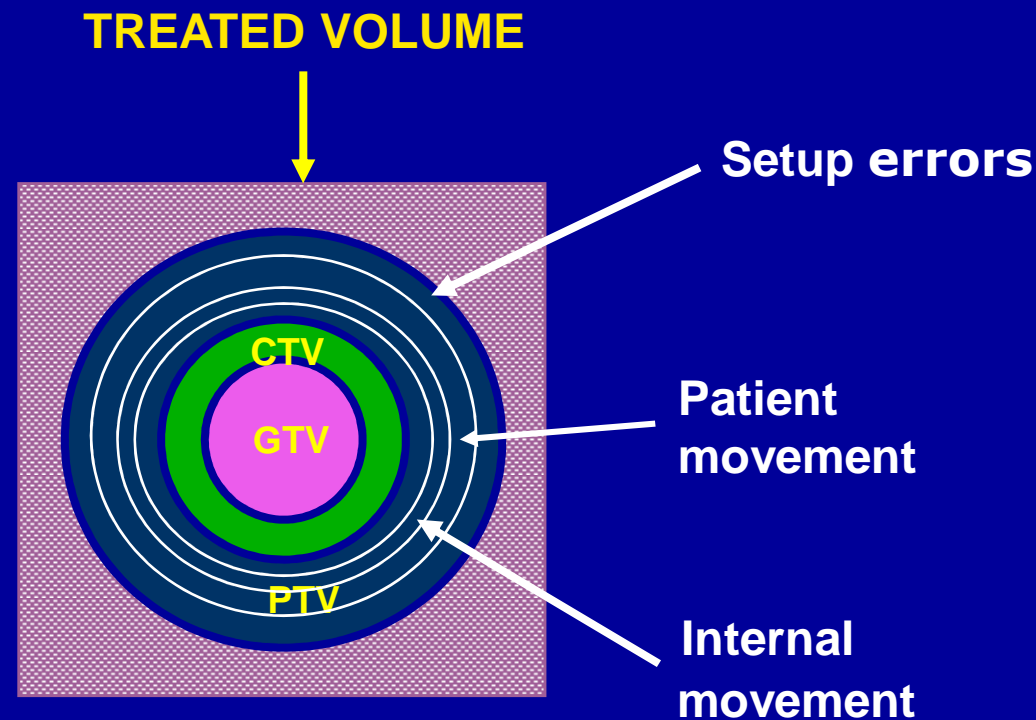
# High risk vs low risk CTV

- There are areas of high density and low density microscopic disease surrounding tumor (GTV)
  - GTV:  $10^{9+}$  cells
  - High risk CTV:  $10^{5-6}$  cells
  - Low risk CTV:  $10^{2-4}$  cells
- Treat GTV by surgery or by EBRT.
- Use brachytherapy to treat HR CTV
  - high risk microscopic areas
  - areas of residual tumor bulk after Sx
- Use EBRT + chemotherapy to eradicate low risk CTV



# Target Volume

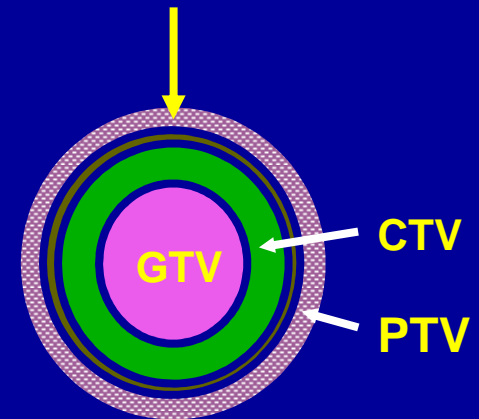
## Determination of Target Volumes: EBRT vs. BRACHY



### EBRT

- Margin over CTV to account for:
  - Internal movements
  - Patient movement
  - Setup errors

**TREATED VOLUME**



### BRACHY

- Margin over CTV to account for:
  - positional errors
  - catheter movement
  - tapering of isodose curve

# Targets for EBRT

- Entire cervix
- Uterus and tubes
- Upper third of vagina
- Entire vagina in selected cases
- Parametrial tissues (cardinal, uterosacral and pubocervical ligaments)
- Pelvic nodes (external and internal iliac, in selected cases up to common iliac)
- Inguinal nodes in selected cases.
- Para-aortic nodes in selected cases.



# Organs at Risk

- Rectum and sigmoid
- Urinary bladder
- Intestine

*Success of RT demands optimum coverage of targets and sparing (as much as possible) of critical normal structures.*

*For this, proper delineation and contouring of these structures are mandatory.*



**CT (preferably MRI) based planning.**



Fig. 1. Delineation of the regions of interest on a T2-weighted magnetic resonance image: Bladder, pink; bowel, green; rectum, yellow; primary gross tumor volume, red; primary clinical target volume, blue; left nodal gross tumor volume, purple; left nodal clinical target volume, light blue; right nodal clinical target volume, orange.

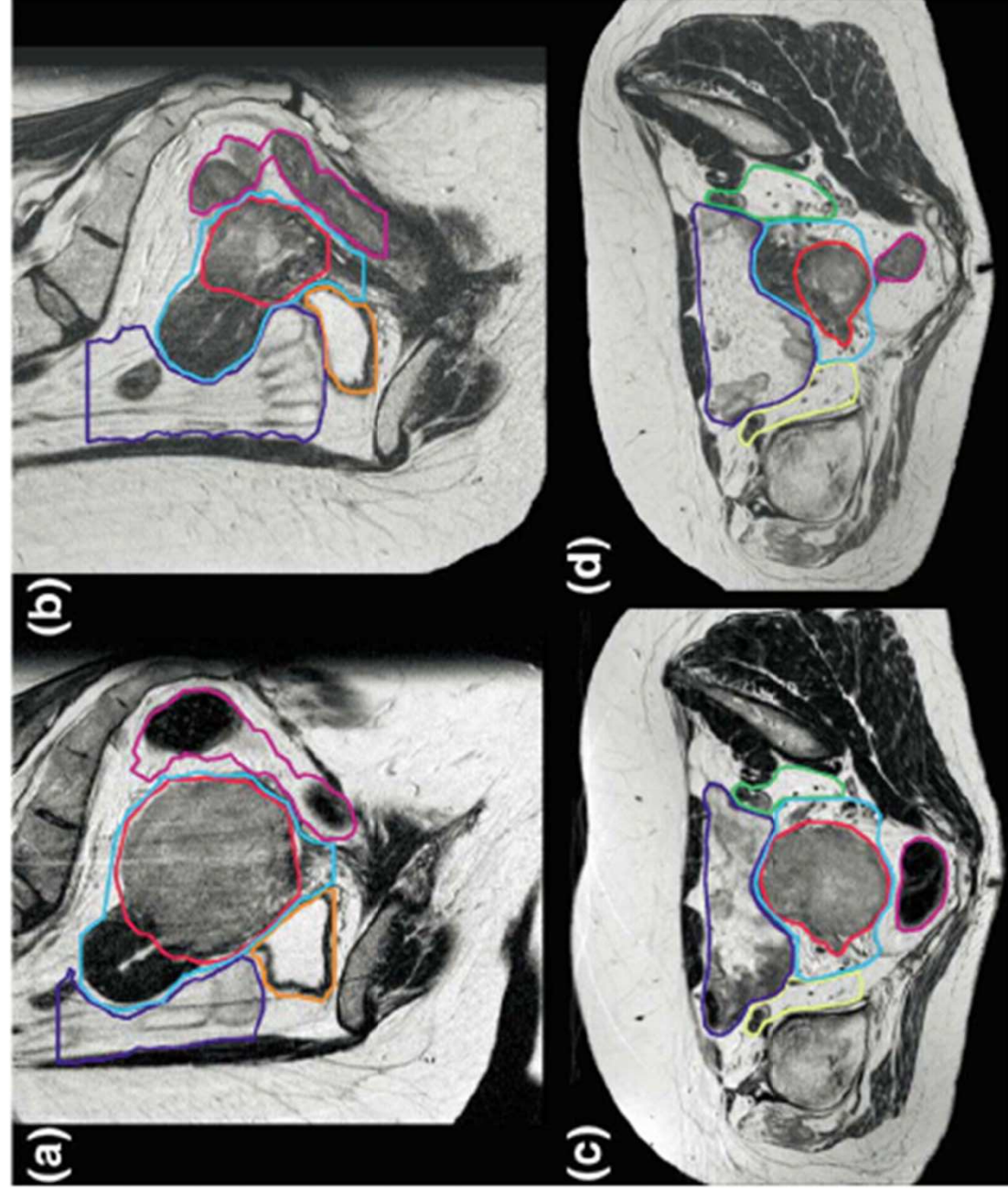


Fig. 2. Delineation on magnetic resonance images (an example of 1 patient). (a) Pretreatment sagittal, (b) intratreatment sagittal, (c) pretreatment axial, and (d) intratreatment axial: Bowel, dark blue; rectum, pink; bladder, orange; primary gross tumor volume, red; primary clinical target volume, light blue; left nodal target volume, green; right nodal clinical target volume, yellow.

# Technique of EBRT

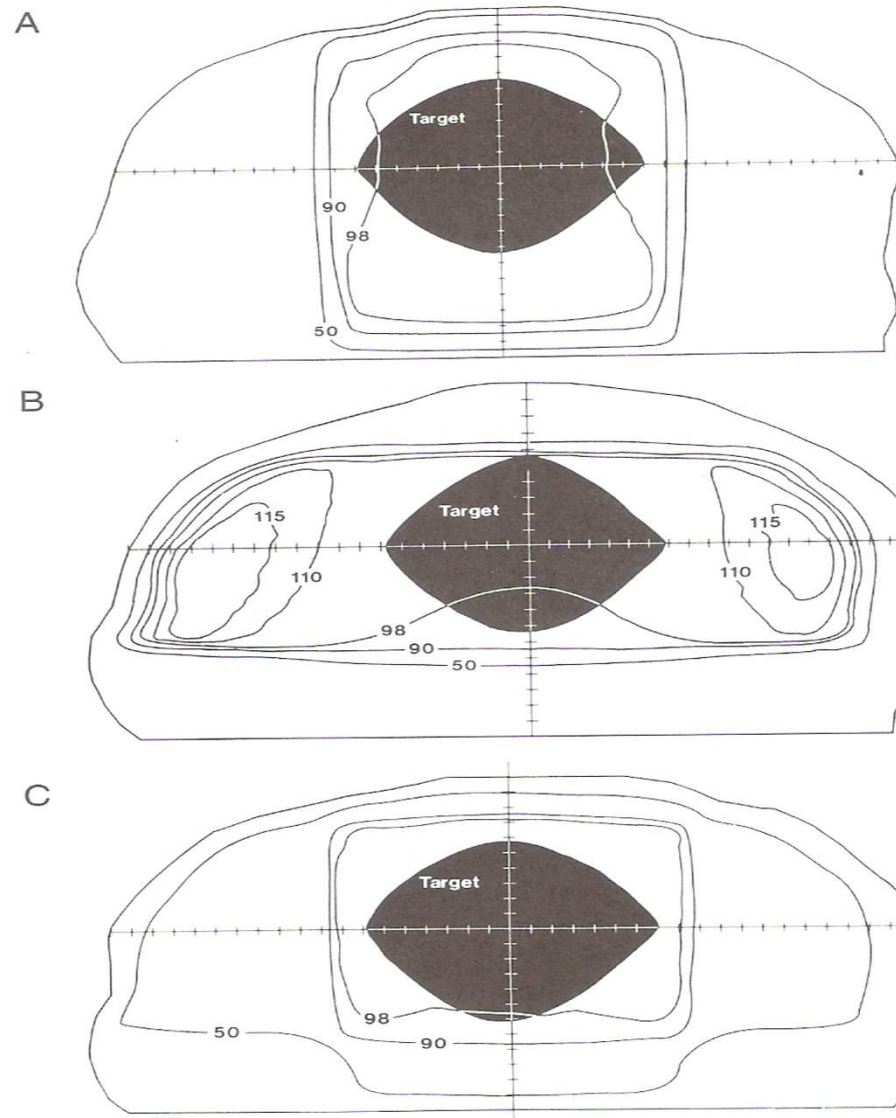
# Machine

- Cobalt or 6-MV Linear Accelerator for non-obese patients (AP Distance < 18cm).
- 10-16 MV Linear Accelerator, if AP distance is higher. may be treated by Cobalt with 4-field.
- IMRT is currently under investigation to determine if toxicities can be decreased by reducing the dose to OARs and if higher dose can be safely administered to metastatic nodes.

# Portals for WPRT

- Traditional AP/PA portals
- 4-field (AP/PA + two lateral) box for homogenous dose distribution with less dose to normal tissue.
- Rotation with or without skip
- Arc





**Best target coverage with minimum dose to normal tissue with 4-field ©, compared to AP/PA (A) or parallel opposed lateral portals (B).**

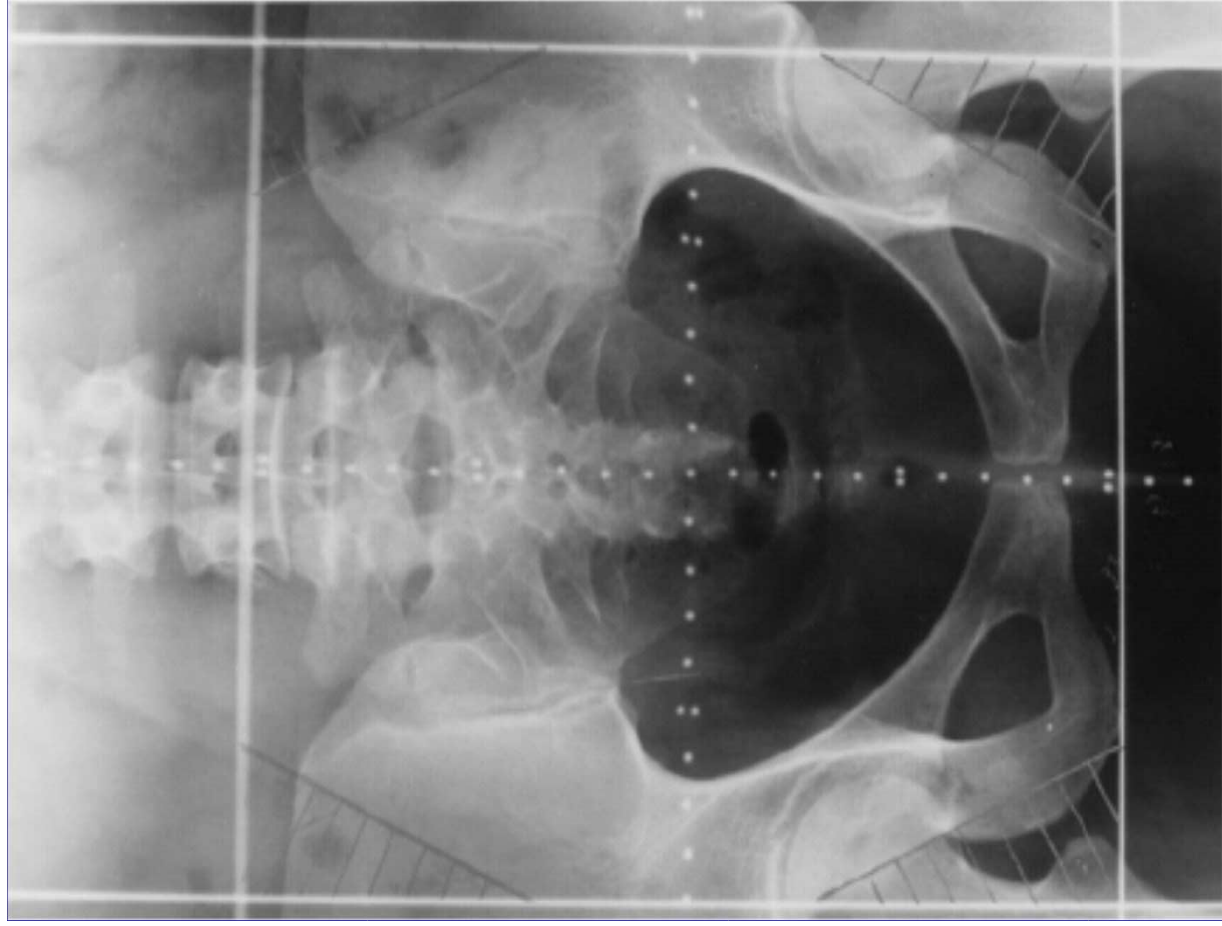
# Conventional Field Borders

## For AP/PA Portal

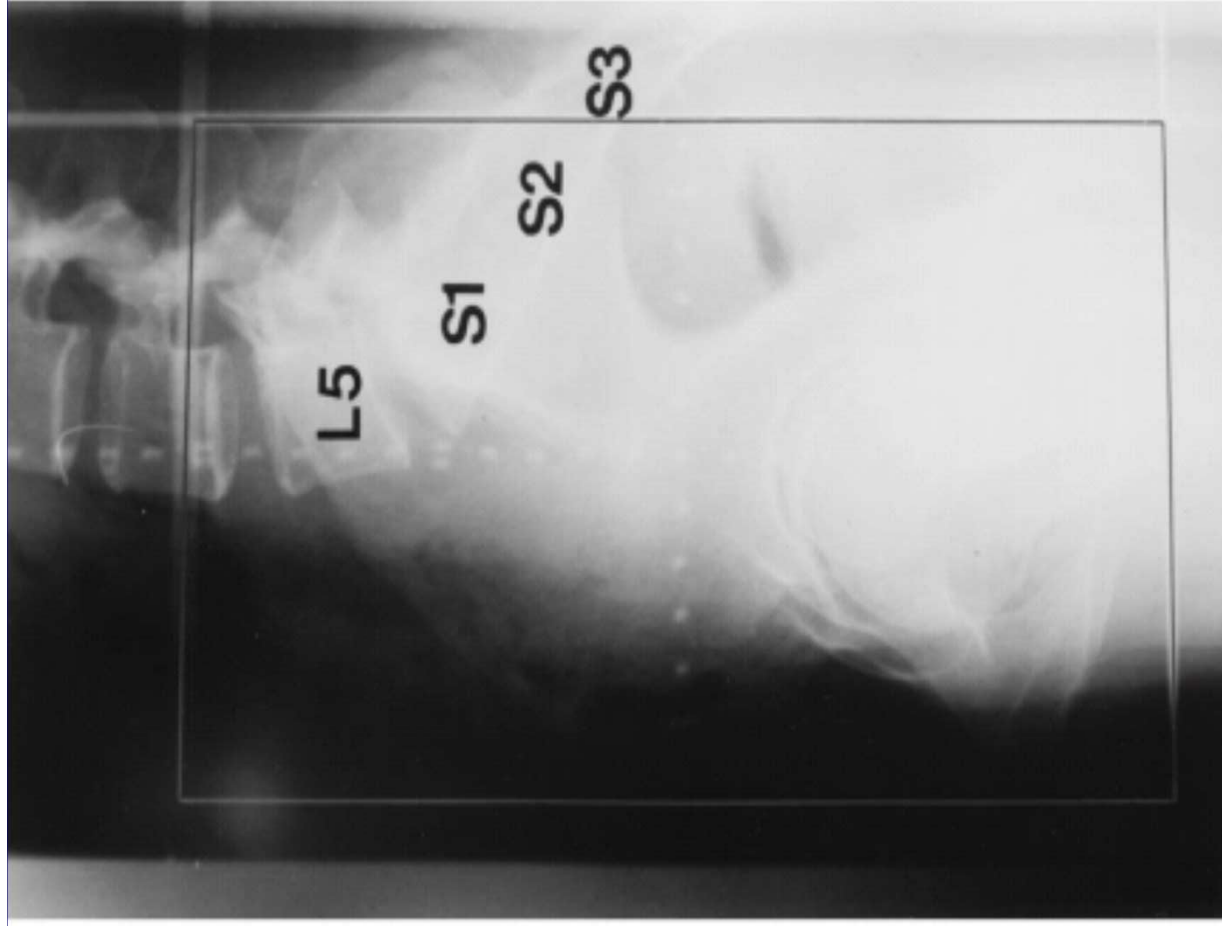
- Superior: L4 - L5 inter space.
- Inferior: Inferior border of obturator foramen (if no vaginal extension).
- Lateral borders: 2 cm margin lateral to bony pelvis.

## Additional Field Borders for 4-Field Box

- Anterior margin of lateral portals: In front of Pubic symphysis .
- Posterior margin of lateral portals: Should extend to sacral hollow, traversing S2/S3 inter space



(a)



(b)

Fig. 1. (a) AP simulation film of the pelvis showing superior, inferior, and lateral borders. (b) Lateral simulation film of the pelvis illustrating lateral portals of the "box" technique. Anterior border over pubic symphysis; posterior border at S2-S3 interspace.

## Superior Border: L4/L5 junction

- Intraoperative retroperitoneal measurements taken at the time of radical hysterectomy reveal both common iliac bifurcations are cephalad to lumbo-sacral prominence in 87% patients. (Greer et al , Gynecol Oncolgy, 1990; 39; 421-424)
- To include all of the ext. iliac and hypogastric L/Nodes , upper border should be at L4/L5
- It must be extended to L3/L4 if common iliac node coverage is indicated.

## Inferior Border

- Depends on vaginal extension of tumor.
- If no vaginal extension: Inferior border of obturator foramen should be inferior border of the field.
- If vaginal involvement: Entire length of vagina down to introitus is to be treated. (If disease extends to lower 1/3 of vagina, inguinal nodes should also be treated).

# Width of AP/PA Portal

- 2 cm beyond the widest point of the inlet of true pelvis to provide adequate coverage of pelvic nodes.
- Ext. Iliac nodes have a mean maximum separation of 14.5 cm and are not adequately treated by standard 15cm wide portals. Width of AP/PA portals should be measured, for treatment planning by CT scan.
- Can be assessed by simple expedient of measuring the separation between femoral arteries at the level of inguinal ligament.



# Merits and Demerits of 4-Field Box

- **Objective: Homogenous dose distribution with less dose to normal tissue, particularly intestine.**
- Anterior margin should be placed at the cortex of symphysis pubis (to cover ext. iliac nodes). Posterior margin should cover at least 50% rectum in IB disease and should extend to sacral hollow with more advanced disease (as cardinal and uterosacral ligaments extend to sacral hollow and to sacrum itself).
- **Chance of missing the PTV, unless MRI-based planning.**
- Ideal for early disease and for P/O EBRT. But for locally advanced disease it should be considered only after 30 – 40 Gy through AP/PA portal.



## Some examples of missing the target with 4-Field plan ...

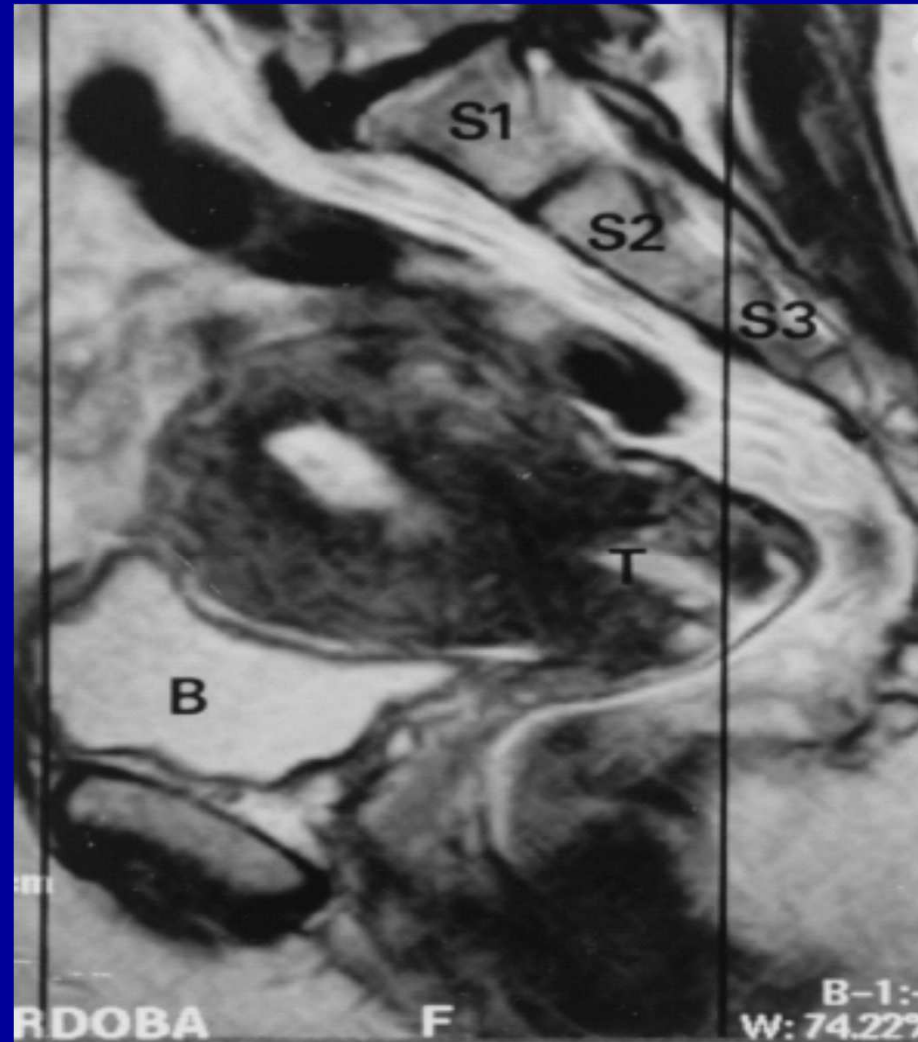


Fig. 2. Posterior border fails to encompass the tumor volume.

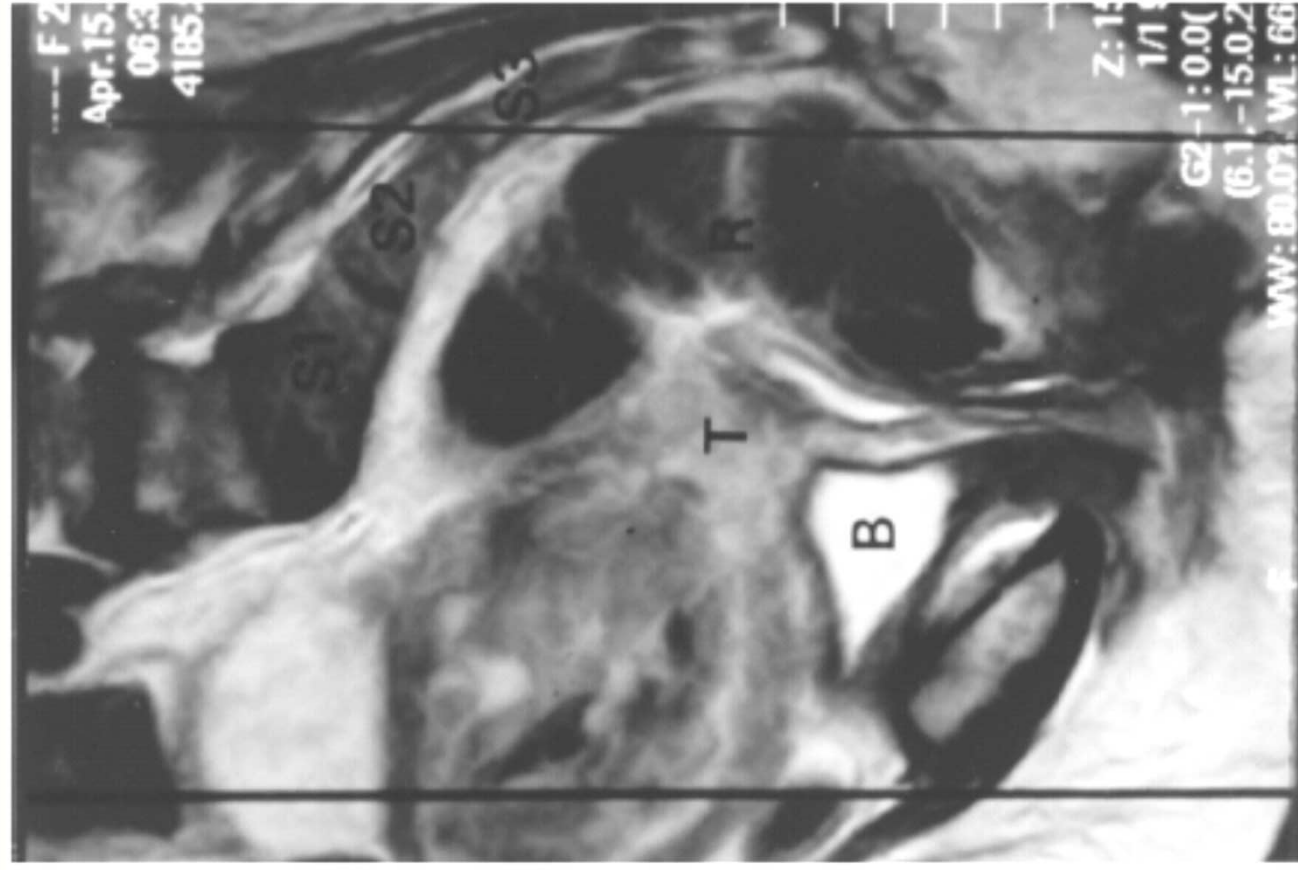


Fig. 3. Uterus in anteverted position. Anterior border traverses the uterus fundus. Pyometra present.

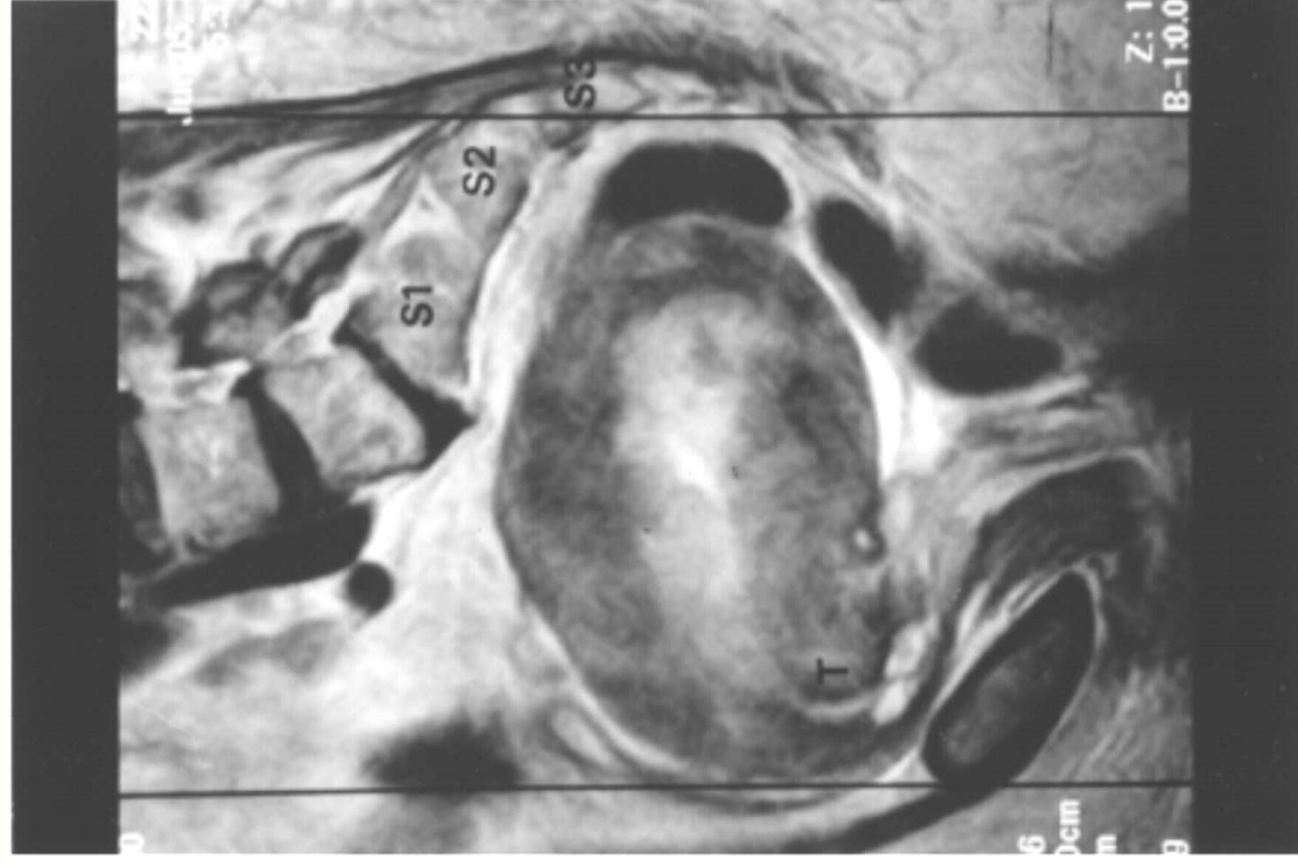


Fig. 4. Anterior border of lateral portal without any margin for the cervical tumor. T = Cervical tumor.

## CLINICAL INVESTIGATION

## Female Genitalia

### ANATOMIC STUDY OF THE PELVIS IN CARCINOMA OF THE UTERINE CERVIX AS RELATED TO THE BOX TECHNIQUE

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LUIS ROSSI, M.D.,<sup>‡</sup> AND DANIEL VENENCIA, PH.D.\*

## CONCLUSION

From this study, we can conclude that the high failure rate of the anterior and posterior borders of the lateral field of the "box" technique to encompass the tumor volume and its microscopic extension is in relation not just to clinical stage, but to the impact of other parameters, such as uterine flexion and associated pathology. This suggests that it is not possible to design standard borders based on conventional bone references or field size according to clinical stage. Therefore, in the light of the present knowledge, if the "box" technique is used, it should be designed based on sagittal MRI.

## EBRT Dose

- Depends on Stage
- Early disease: ↓EBRT Dose + ↑ HDR Contribution
- Most institutions prefer to deliver 45-50 Gy to whole pelvis.
- TD (EBRT + BT): 80 -85 Gy (LDR equivalent) to point A

## Role of Para-aortic RT

- Considered within target only if found involved in staging investigations
- If Para-aortic nodes present or suspected: 45-50 Gy to the P-A area + 5 Gy boost to the enlarged nodes through reduced lateral or rotational portals (preferably MRI based planning)
- Para-aortic RT given either with an extended field covering both pelvis and para-aortic region or through a separate portal

## Extended Field EBRT: Para-aortic node

- Upper border is usually D12 - L1 inter space.
- Lower border is top of pelvic field
- Usually in continuity with WPRT (long 'spade shaped' field)
- Parallel opposed AP/PA portal. 4-Field may be employed , but beam weighting must ensure that kidneys receive <20Gy.
- RTOG trial (IB2-IIB cases): 5 yr survival **67% with pelvis + PA field vs 55% with pelvis only** (p=0.02)
- A contemporary **European trial failed to show any significant diff. in 4 yr. DFS** but para-aortic nodal recurrence was significantly less in those getting para-aortic RT



## Pelvis EBRT : Midline Block

- Considered for early disease.
- Some institutions prefer to limit the whole pelvis dose for early disease and to perform first intracavitary application after 20 Gy, with further EBRT delivered with central block (4-5 cm wide mid-plane)
- Careful attention to the complex matching between reference isodose (from brachytherapy) and the edge of midline block is mandatory.
- If a midline block is inserted **before 40 Gy, it should not extend to top of pelvic field**, because it will shield external iliac and pre-sacral nodes.
- Should be avoided if utero-sacral ligament involvement is suspected.
- **No consensus as yet regarding use of mid line block**

# Parametrial Boost

- Considered in IIB or IIIB disease.
- After completion of whole pelvis EBRT (45 – 50 Gy), parametrium is boosted by additional 10 GY, while midline structures are shielded.
- PMB is achieved by placement of a 4cm rectangular midline shielding of 5 HVL at anterior and posterior portals.



# Sequencing of EBRT and BT

- EBRT  $\rightarrow$  BT
- BT  $\rightarrow$  EBRT
- EBRT + BT (Concomitant)

**Traditionally EBRT is delivered  
before BT , if ...**

- Bulky lesion (To improve geometry of intracavitary application)
- Exophytic, easily bleeding tumors
- Tumors with necrosis or infection
- Parametrial involvement

## **BT is delivered before ...**

- Narrow vaginal apex in elderly patients
- Less than 1 cm tumor
- Parametrium uninvolved

# Concomitant EBRT + HDR BT



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## CLINICAL INVESTIGATION

## Cervix

### THE AMERICAN BRACHYTHERAPY SOCIETY RECOMMENDATIONS FOR HIGH-DOSE-RATE BRACHYTHERAPY FOR CARCINOMA OF THE CERVIX

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JEFFREY D. DEMANES, M.D.,|| AND DANIEL PETEREIT, M.D.,‡ FOR THE AMERICAN BRACHYTHERAPY SOCIETY

The ABS recommends keeping the total treatment duration to less than 8 weeks, because prolongation of total-treatment duration can adversely affect local control and survival (33–36). The overall treatment duration would be unduly prolonged if the HDR was started only after completion of EBRT, because multiple insertions are required for HDR. The recommendation is therefore to interdigitate the implants during the EBRT (but EBRT is not given on the day of HDR). Typically, if the vaginal geometry is optimal, HDR brachytherapy is started after 2 weeks of EBRT. HDR is then continued once a week, with the EBRT being given the other 4 days of the week. If, due to large tumor volume, it is necessary to delay the start of HDR brachytherapy, it is advisable to perform two implants per week after the EBRT has been completed, to keep the total treatment duration to less than 8 weeks.

# Adjuvant Radiotherapy after Radical Hysterectomy

# Post-operative EBRT

## Indications:

- Positive pelvic nodes
- Positive surgical margin
- Deep stromal invasion
- Positive parametria
- Inadequate information regarding surgery and H/P ???

Dose: 45 to 50 Gy in conventional fractionation

***Concom Chemoradiation found to be more beneficial than RT alone in IA2, IB and IIA disease after radical hysterectomy in these situations.***

# Altered Fractionations:

## Rationale

- To increase therapeutic ratio
- To increase tumor control
- To decrease normal tissue reactions
- Combination of both

# Altered Fractionations

Accelerated Fractionation	Hyper fractionation	Accelerated Hyperfractionated Radiotherapy
<ul style="list-style-type: none"><li>• <b>Overall treatment time shortened (either by increasing fraction size or decreasing weekend gap e.g. 6F/week)</b></li><li>• <b>Decreased opportunity for accelerated repopulation</b></li></ul>	Multiple small fractions cause relative sparing of normal tissue and thus higher total dose can be achieved.	Combines the useful elements of both accelerated fractionation and hyperfractionation



*Most of the altered fractionation  
studies are for patients  
not receiving  
concomitant chemotherapy*

Table 4. Altered fractionated radiotherapy without chemotherapy in cervical cancer

Investigator	Patients (n)	Eligibility	EBRT	Point A dose of ICBT	OTT	Toxicity	Survival
Grigsby <i>et al.</i> (25)	81	IB2-IVA	60 Gy/50 fr/5 wk (1.2 Gy/fr, b.i.d.), central shielding at 24–48 Gy	Point A dose not reported	Not reported	5-y Grade 4 toxicities: 5% (IB2-IIIB) 12% (IIIA-IVA)	5-y OS: 48%
Kavanagh <i>et al.</i> (26)	22	IIIA, IIIB, IVA	45 Gy/25 fr/5 wk (whole pelvis) + 14.4 Gy/9 fr/3 wk (concomitant boost to gross tumor)	30.6 Gy (LDR)	Median, 46 d	5-y severe toxicity (requiring colostomy): 37%	5-y OS: 54%
Chun <i>et al.</i> (24)	31	IB2 ≥ 5 cm II, III ≥ 4 cm	18 Gy/10 fr/2 wk followed by 18 Gy/12 fr/6 d (1.5 Gy/fr, b.i.d.) followed by 9 Gy/5 fr/1 wk (with central shielding) followed by 6–14 Gy to parametrium	28 Gy (HDR, median)	61%: 43–49 d 29%: 50–56 d 10%: ≥ 57 d	Grade 1 at rectum: 4 patients Grade 2–5: none	2-y OS: 87%
Viswanathan <i>et al.</i> (27)	15	IIB, IIIB	60 Gy/50 fr/5 wk (1.2 Gy/fr, b.i.d.)	30 Gy (LDR)	Not reported	5-y bowel toxicity: 72%	5-y tumor control: 48%
MacLeod <i>et al.</i> (28)	61	IIB, III, IV, postoperative recurrent tumor	57.5 Gy/46 fr/4.6 wk (1.25 Gy/fr, b.i.d.)	25 Gy (LDR, median)	Not reported	5-y severe toxicity (requiring surgery): 27%	5-y OS: 27%



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## CLINICAL INVESTIGATION

# ACCELERATED HYPERFRACTIONATED RADIOTHERAPY FOR CERVICAL CANCER: MULTI-INSTITUTIONAL PROSPECTIVE STUDY OF FORUM FOR NUCLEAR COOPERATION IN ASIA AMONG EIGHT ASIAN COUNTRIES

**Conclusion:** The results of our study have shown that accelerated hyperfractionated RT achieved sufficient pelvic control and survival without increasing severe toxicity. This treatment could be feasible in those Asian countries where chemoradiotherapy is not available. © 2007 Elsevier Inc.

## CLINICAL INVESTIGATION

## Cervix

### SIX FRACTIONS PER WEEK OF EXTERNAL BEAM RADIOTHERAPY AND HIGH-DOSE-RATE BRACHYTHERAPY FOR CARCINOMA OF THE UTERINE CERVIX: A PHASE I/II STUDY

In summary, the results suggest that six fractions per week of EBRT and HDR brachytherapy is an effective treatment for patients with a carcinoma of the uterine cervix and can be used as a possible alternative to concomitant chemoradiotherapy in elderly patients or in patients with

co-morbidity. However, these findings are not conclusive as a result of the small sample size and the relatively short follow-up period. Further multicenter, controlled, randomized phase III trials will be needed to prove the benefit of the shortening of overall treatment time by increase of the weekly number of fractions.

## Altered Fractionation: Take Home Message....

- Better local control compared to conventional fractionation
- But margin of benefit is less, compared to concomitant chemoradiation; i.e.  
 $CT+RT(\text{Conventional}) > HFRT \text{ or } Acc.RT > RT(\text{Conventional})$
- Should be considered only for patients who cannot afford / tolerate Chemo.
- Concom. Chemotherapy + HFRT or Acc.RT should be avoided because of toxicity.

Average volume in cc	Conventional	Conformal	IMRT
Bowel	626 (115–1370)	427 (52–742)	232 (24–531)
Bladder	101 (15–403)	90 (15–355)	60 (14–198)
Rectum	89 (38–182)	70 (33–150)	58 (30–130)

*Abbreviation:* IMRT = intensity-modulated radiotherapy.

\* Average volumes of the critical organs of all patients receiving 95% of the prescribed dose (range between brackets).

# Radiation Toxicity

## Acute Reactions

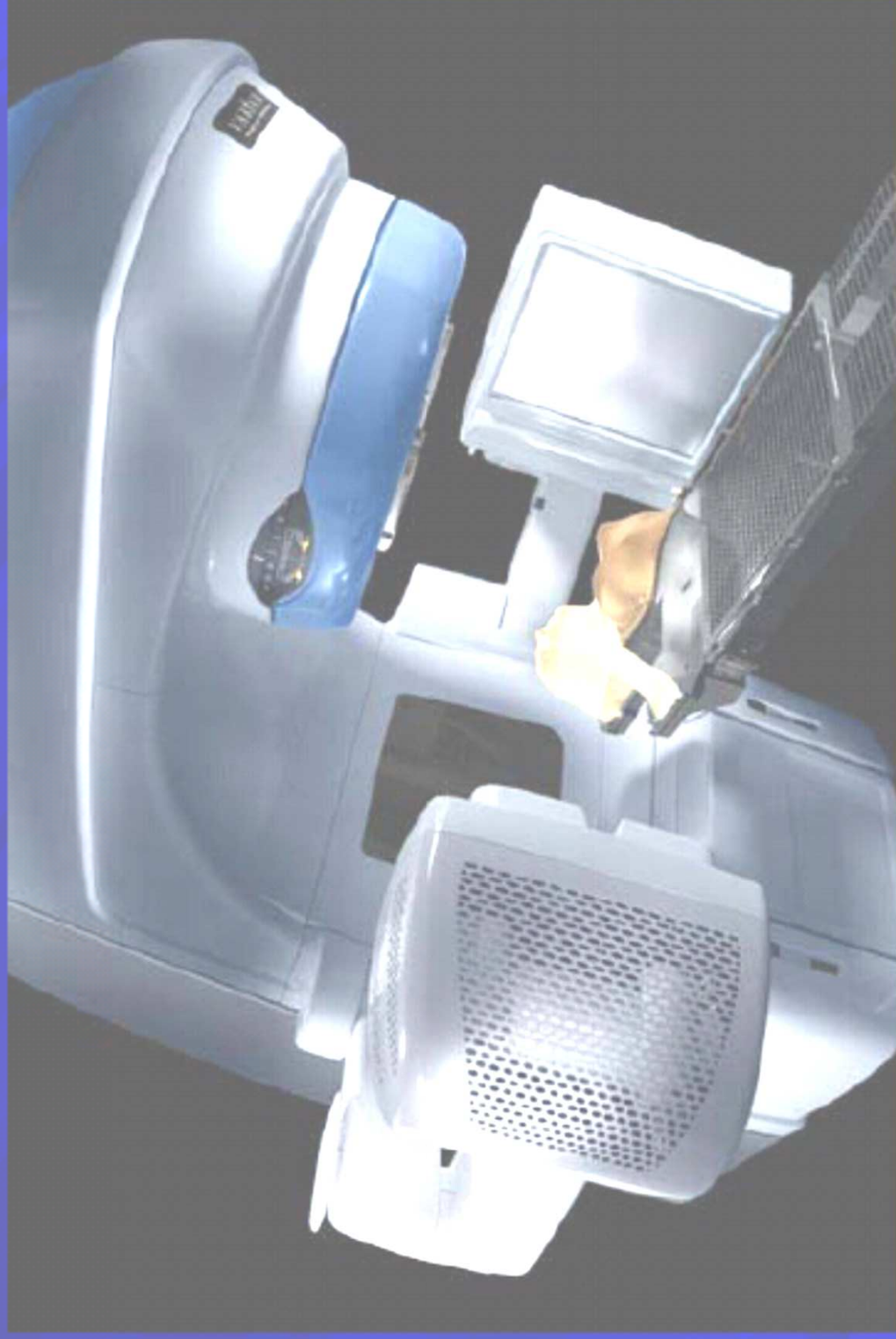
- G.I. Toxicity: Diarrhoea, Abdominal pain, Rectal discomfort and bleeding.
- UTI
- Skin

## Late Reactions

- Proctitis
- Cystitis
- Fistula
- Vaginal Stenosis
- L.S. Plexopathy.



But the revolution continues.....**IGRT**



Varian Trilogy Machine (UCSD 2005)



# EBRT – TAKE HOME MESSAGE

- Should be rational selecting individual case
- Ideal set up – MRI, identify target volume, spare normal tissue as much as possible
- Dose – 45 – 50 Gy AP-PA (Linac), 4 field (Co<sub>60</sub>) with midline shield after calculating Brachy dose to reduce toxicity
- Success of treatment depend - careful balance between EBRT & Brachytherapy
- Complete total treatment by 8 weeks
- Weekly check up during radiation for Hb and toxicity



Thank you

