Carcinoma Cervix

Treatment policies

External Beam Radiation Therapy

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Introduction

Global scenario

- **2nd commonest malignancy in women**
- **4,50,000 new cases annually**
- **2,10,000 deaths**

(Ferlay et al. Cancer incidence and mortality worldwide, 1998)

India

- **20-50% of all cancers in women**
- **1,00,000 new cases yearly**

TMH

- **22% of all cancers recorded (1997 registry)**

Pre-treatment Evaluation

I Establish tissue diagnosis

II Staging of disease

III Systemic evaluation

Pre-treatment Evaluation

I. **Diagnostic:**

Biopsy

Colposcopic guided biopsy

Endo cervical curettage

Cone biopsy

II. **Staging:**

Pelvic Examination / EUA

Chest x-ray

Cystoscopy, Proctoscopy } if

IVP, Ba-enema } indicated

Pre-treatment Evaluation

- **Haematological & biochemical parameters**

- **Optional studies:**
  - **USG,**
  - **CT Scan / MRI**
  - **PET**

Joint Clinic

Principles of Treatment

Plan treatment to include (clinical):

- **Disease at the primary site**
- **Local extension to parametria & vagina**
- **Regional spread to pelvic nodes**
- **Spread to para- aortic nodes**
- **Possible systemic spread**

Factors for Treatment

- **Age of the patient**
- **Stage of disease**
- **Tumour histology**
- **Wish to preserve ovarian function & fertility**
- **Choice of treatment options**

Disease Spectrum

- **Premalignant**
- **Preinvasive**
- **Microinvasive**
- **Invasive**

Carcinoma In Situ

Treatment

- **Conization of cervix**
- **Total abdominal hysterectomy**
- **Vaginal hysterectomy**
- **LAVH** (Laparoscopically Assisted Vg Hysterectomy)

Pelvic lymphadenectomy: No role

Carcinoma-in-situ
Is Hysterectomy Justified?

- **18 out of 5442 women (0.3%) with CIS treated by conization later developed invasive cancer.**

Vs

- **38 out of 8995 women (0.4%) with CIS treated by hysterectomy later developed invasive cancer of vagina**

Hysterectomy not justified based on current evidence.

FIGO Staging 1985
Revised Staging for Stage I FIGO 1994

Stage I **Carcinoma strictly confined to cervix**

Stage Ia **Microscopic lesion**

Ia1 **Minimal microscopically evident stromal invasion up to 3mm and horizontal spread up to 7mm**

Ia2 **Stromal invasion 3.1 to 5mm and horizontal spread up to 7mm**

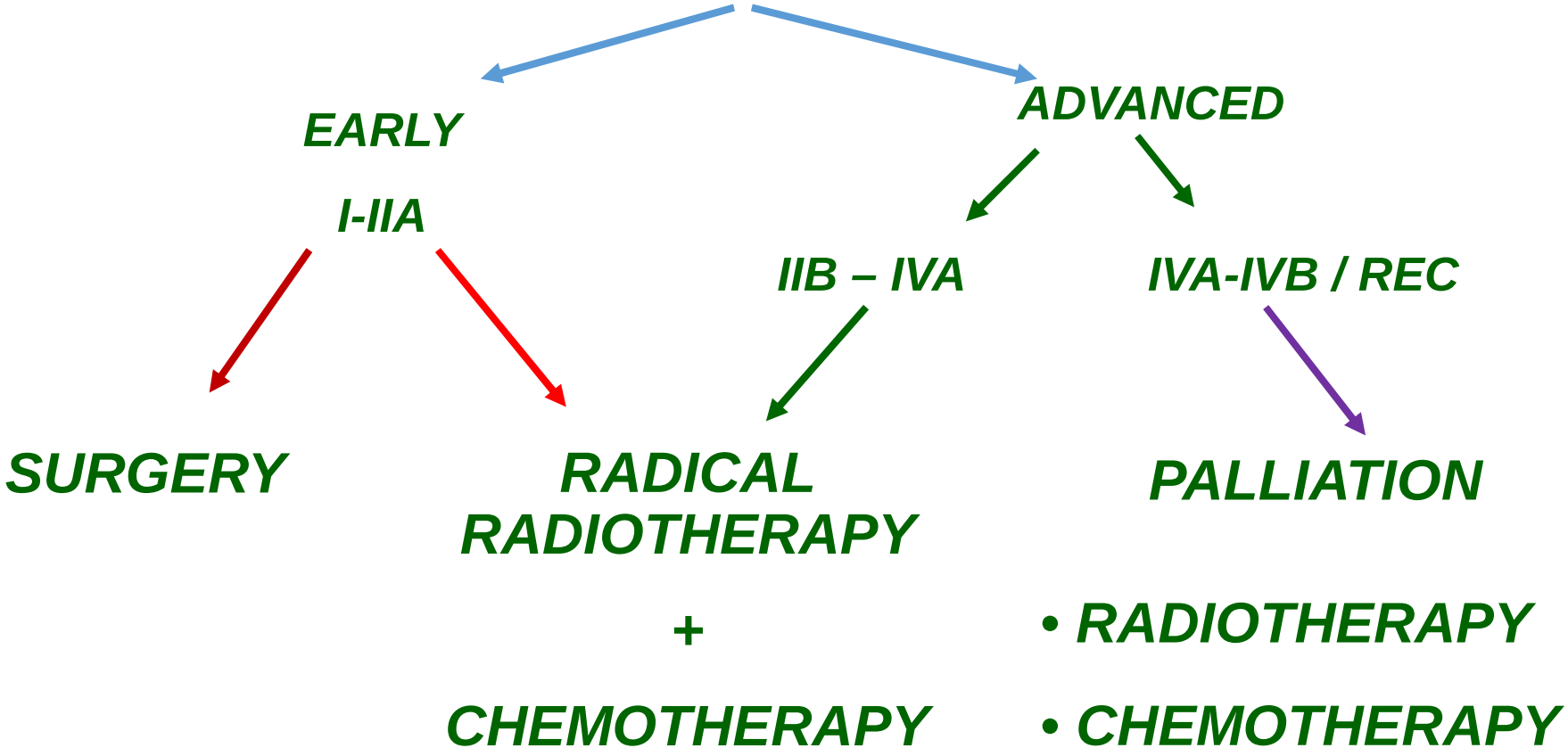
Stage Ia Natural History

- **Lymph node metastases related to:**
  - **Depth of stromal invasion**
  - **Lympho-vascular space invasion**
- **Incidence of lymph node metastasis:**

Stage Ia1	**0.5%**
Stage Ia2	**3.5%** (Averette 1976)
	3.9% (Simon 1986)
	5 - 8% (Literature)

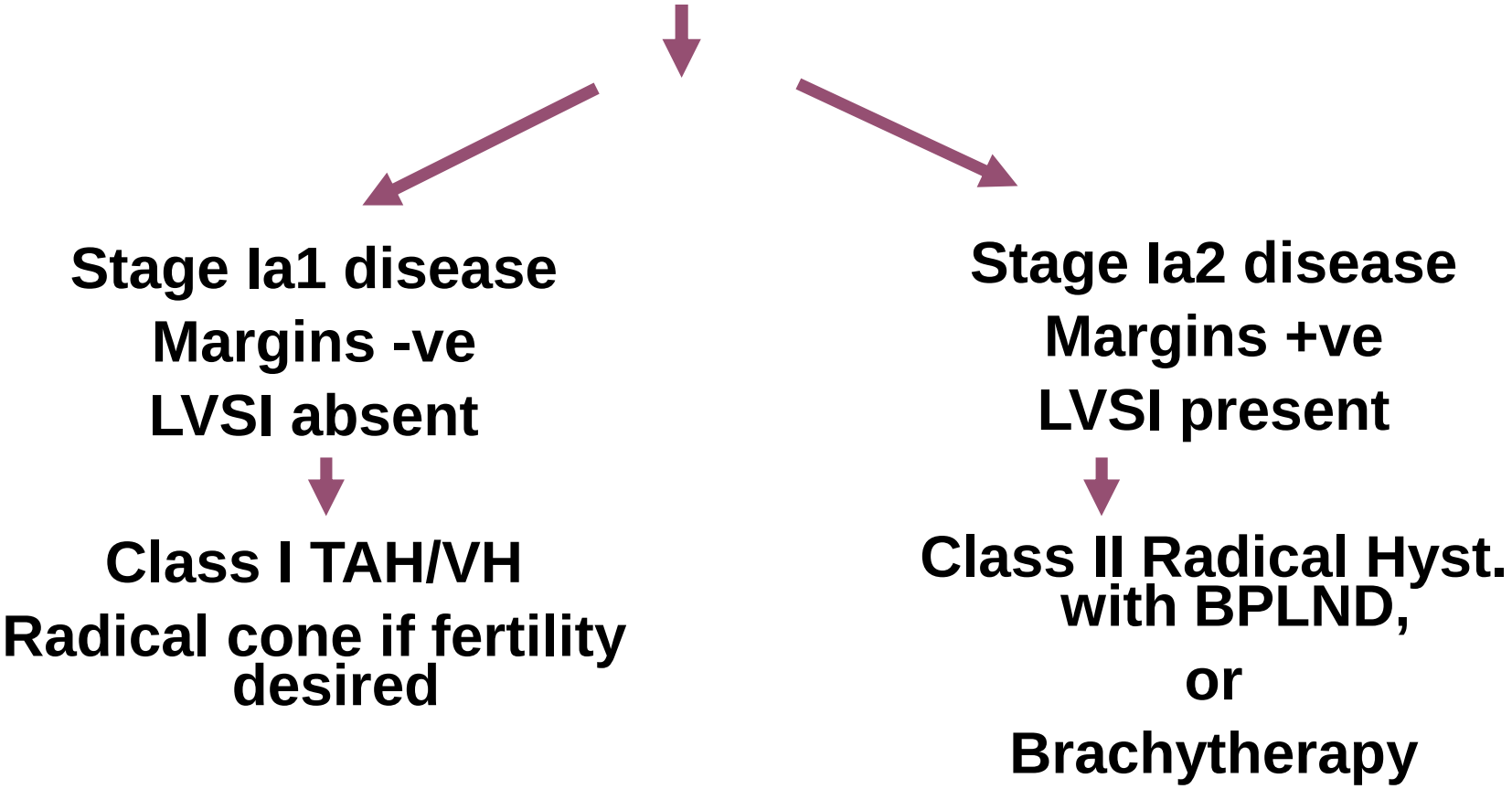
Rationale: To identify a subgroup with a negligible risk of LN mets & who may be treated with less than radical therapy (SGO 1993)

FIGO STAGING



Stage-Ia Treatment

Non-visible Lesion
Cone Biopsy



Stage Ib

Lesions of greater dimensions than Stage Ia whether seen clinically or not

Stage Ib1- Lesion < / = 4 cm

Stage Ib2- Lesion > 4 cm

STAGE Ib & IIa TREATMENT

Class III radical hysterectomy
With BPLND
Or
Radical radiation therapy
(Ext + Brachy)

Choice of treatment determined by age, menopausal status, ovarian preservation, co-morbid conditions, patient's wish & availability of expertise in surgery & RT
(NIH Guidelines 1997)

Stage Ib and IIa
Radical surgery vs Radical RT

Non randomised data:

Both Rx modalities are comparable vis-à-vis locoregional control & 5 yr survival

(Roddick 1971, Newton 1975, Hoskins 1987)

Randomised data:

(Morley and Seski 1976; Landoni et al 1997)

Stage Ib & IIa Treatment
Surgery Vs. Radiation Therapy
(N=343)

- **Prospective RCT: 169 received Radical surgery & 158 received Radical RT**
- **108 in the surgery arm also received adjuvant RT (64%) while 61(20%) received only Surgery**
- **25-26% recurrence in both the arms**
- **5 year survival: DFS 83% surgery, 74% RT (p=NS)**
- **Morbidity: 28% in surgery arm and 12% in RT arm (mainly chronic bladder dysfunction and hydroureteronephrosis: May be related to RT)**

Landoni 1997

Stage Ib & IIa : Treatment
Surgery Vs. Radiation Therapy

- **Both radical surgery & radical RT equally good options of management: No survival benefit with either modality**
- **Combination of surgery & RT has the worst morbidity.**
- **Optimum therapy for each patient should take into account factors such as menopausal status ,age, patient's wish, medical illness, histology type & cervical diameter.**

- **Adjuvant RT: Does it impact survival or only adds morbidity?**

Landoni 1997

Radical Hysterectomy: Survival

Author	Year	No	5 y Surv%
Park	1973	126	91.0
Morley	1976	156	87.2
Hoskins	1976	47	89.4
Sall	1979	219	90.0
Lerner	1980	48	91.7
Powell	1984	103	90.3
Kenter	1989	213	87.3
Lee	1989	343	87.2
Ayhan	1991	270	80.1
Hopkins	1991	213	92.5
AFTER 1970		1738	87.9

Advantages Of Radical Surgery

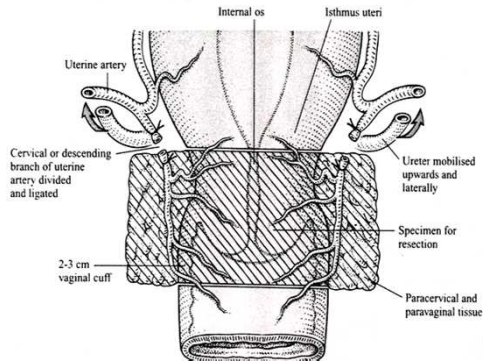
- **Accurate surgicopathologic staging**
- **High risk group for adjuvant therapy identified**
- **Preserves ovarian function**
- **Maintains better vaginal function**
- **Most complications are early and can be corrected**
- **Treatment period is short**
- **Pelvic rec can be succesfully cured by RT**

Role Of Lymphadenectomy

- **Accurate surgicopathological staging**
- **Prognostication**
- **High risk group identified**
- **Therapeutic in presence of micro mets**
- **Decreases mortality from persistent disease**
- **Aids central disease clearance**
- **Extent: Obturator LND adequate if -ve Else: PLND**

No evidence of survival benefit in RCTs

Trachelectomy



- **Fertility preserving radical surgery pioneered by Dargent (1994)**
- **Eligibility : Stage Ib1 < 2 cms lesion in young women desirous of fertility preservation**
- **Combined with open / lap PLND**
- **Relapse rate 3.4% (4/130 in 4 series)**

No RCT comparing trachelectomy with Rad Hysterectomy

Prognostic Factors for Relapse After Radical Hysterectomy

Positive nodes	**}**	**High**
Positive cut margins	**}**	**risk**
Positive parametria	**}**	
Deep stromal invasion	**}**	
Large tumour diameter	**}**	**Intermediate**
LVSI	**}**	**risk**

Stage Ib/IIa
Impact of Lymph Node Metastases

	Survival (%)	Relapse (%)
LN -ve	**95.8**	**-**
LN +ve		
Pelvic	**63.5**	**32**
PA	**40.8**	**57**
Pelvic+PA	**18.4**	**73.7**

Early Stage Carcinoma Cervix- Primary Surgery
Intermediate Risk : Role of Adjuvant therapy

GOG 92 : RCT (Gynae Oncol 73 ;177-83: 1999)

Outcome	*No Adj RT N = 140*	*Adj RT N = 137*	*p value*
2 yr RFS	*79%*	*88%*	*.008*
2 yr OAS	*79%*	*87%*	*.008*
Pelvic rec	*21%*	*13%*	
Dist mets	*7%*	*2%*	

ADJUVANT PELVIC RT IS BENEFICIAL

"Grade A"

Early Stage Carcinoma Cervix- Primary Surgery
High Risk : Role of Adjuvant therapy

Intergroup 0107 : RCT (Gynae Oncol 73 ;177-83: 1999)

Outcome	*PO RT N = 116*	*PORT+CTRT N = 127*	*p value*
4 yr RFS	*63%*	*80%*	*.001*
4 yr OAS	*71%*	*81%*	*.001*
Pelvic rec	*17%*	*6%*	
Dist mets	*11%*	*3%*	

CHEMORADIATION SHOULD BE STANDARD OF CARE

"Grade A"

Stage IB2 : Approaches

- **Surgery**
- **Radiation therapy**
- **Surgery + Radiation therapy**
- **Radiation therapy + Surgery**
- **Neoadjuvant chemo + Surgery**
- **Concurrent chemoradiation**

Stage Ib2: Role of Extrafascial Hysterectomy after RT

	RT(80Gy)	RT(75Gy+EFH)
5y survival	61.4%	64.4%
Rec rate	43.3%	34.5%
Local rec	25.8%	14.4%
Distant rec	8.9%	15.9%
Adv events	54.8%	62.1%

No improvement in survival with addition of adjuvant hysterectomy

(Keys 1997 GOG:RCT)

Stage Ib2 : Role of NACT

- **NACT + RT vs RT:**

  No difference in survival (13 RCTs)
- **NACT+ Surg vs Surgery + RT**

  Survival benefit at 3y in pts with tumour size >4 cm & >60 cc (Sardi et al 1997)
- **Concurrent chemoradiation better than RT in DFS & OAS in 5 RCTs**

RCT comparing NACT+Surgery vs Concurrent chemoradiation recommended

STAGE III & IV

Stage III	**Carcinoma extends onto the pelvic wall, lower 1/3rd of vagina, hydronephrosis & malfunctioning kidney.**
III a	**Extension to vagina.**
III b	**Extension to parametria.**
Stage IV	**Carcinoma extends beyond the true pelvis, involves mucosa of bladder and rectum**
IV a	**Spread of growth to adjacent organs**
IV b	**Spread beyond pelvis, distant organs**

Locally advanced disease

- **Problems**
  - **Increased local tumour bulk**
  - **High incidence of pelvic & PA node mets**
  - **Potential systemic spread**
- **Options**
  - **Radiation therapy**
  - **Concurrent chemo-radiation**
  - **NACT + RT (7 RCTs : No benefit)**
  - **NACT + Surgery**

Stage IIb & III : Treatment

- **Till recently, radical RT standard of care**

- **Current evidence: Radical RT (Ext + Brachy) with concurrent weekly cisplatin based chemo (40mg/sqm/week)**

Rationale	**Cytotoxic to microscopic disease** **Sensitization effect**
Evidence	**GOG 85, GOG 120, GOG 123, RTOG 90-01, SWOG 8797**
	Meta analysis: **Green et al. 2001** **Lukka et al. 2002**

Locally Advanced Cancer Concurrent Chemoradiation: RCTs

Author	CT	Surv CT+RT	% RT	p	RR death
Morris	PF	73	58	.004	0.52
Keys	P	84	68	.008	0.54
Peters	PF	81	63	.01	0.5
Whitney	PF	50.8	-	.018	0.72
	H	39.8	-		
Rose	P	64	-	.002	0.61
	H	39	-		
	PHF	66	-		0.58

Concurrent Chemoradiation Result of RCTs

- **43 -46 % reduction in risk of death & recurrence**
- **The RR for death and recurrence remarkably similar in all studies**
- **Compelling evidence of survival benefit of 10-15% with concurrent cisplatin chemotherapy**

Concurrent Chemoradiation

“ These 5 major randomized phase III trials show that platinum based chemo when given concurrently with RT prolongs survival in women with locally advanced cervical cancer stages Ib2 - IVa as well as in women with stage I / IIa found to have metastatic pelvic lymph nodes, positive parametrial disease and positive surgical margins at the time of primary surgery ”

Clinical announcement by NCI NEJM Feb1999

Concurrent Chemoradiation Results of Meta-analysis

- **19 RCTs between 1981 and 2000 : 4580 randomised patients**
- **Increase in OAS by 12% & RFS by 16% (absolute benefit)(p=0.0001)**
- **Greater benefit in patients in stages IB2 and IIB**
- **Decrease in local and systemic recurrence (p=0.0001)**

Green JA et al . Lancet 2001; 358:781-786

Stage IVa

Neoadjuvant chemotherapy in suitable cases followed by radiotherapy in responders

Rationale:

High response rates to CT in patients who have not received RT
Downstaging making it amenable to RT or Surgery

Evidence:
9 RCTs and one meta-analysis (Sheung 1998) have shown no benefit in PFS & OAS

Stage IVb

- **Palliative chemotherapy: RCTs**
  Cisplat+Ifosfamide better than cisplat alone
  Cisplat+Paclitaxel better than cisplat alone

- **Palliative care**
  - **Pain relief**
  - **Psychological support**
  - **Role of radiation therapy and surgery needs to be defined**

Pelvic Recurrence & Salvage

- **Post Surgery**
  - **RT and/or Chemotherapy**

- **Post Radiotherapy**
  - **Central recurrence**

    Extrafascial / Rad hysterectomy
    Ant/post/total pelvic exenteration

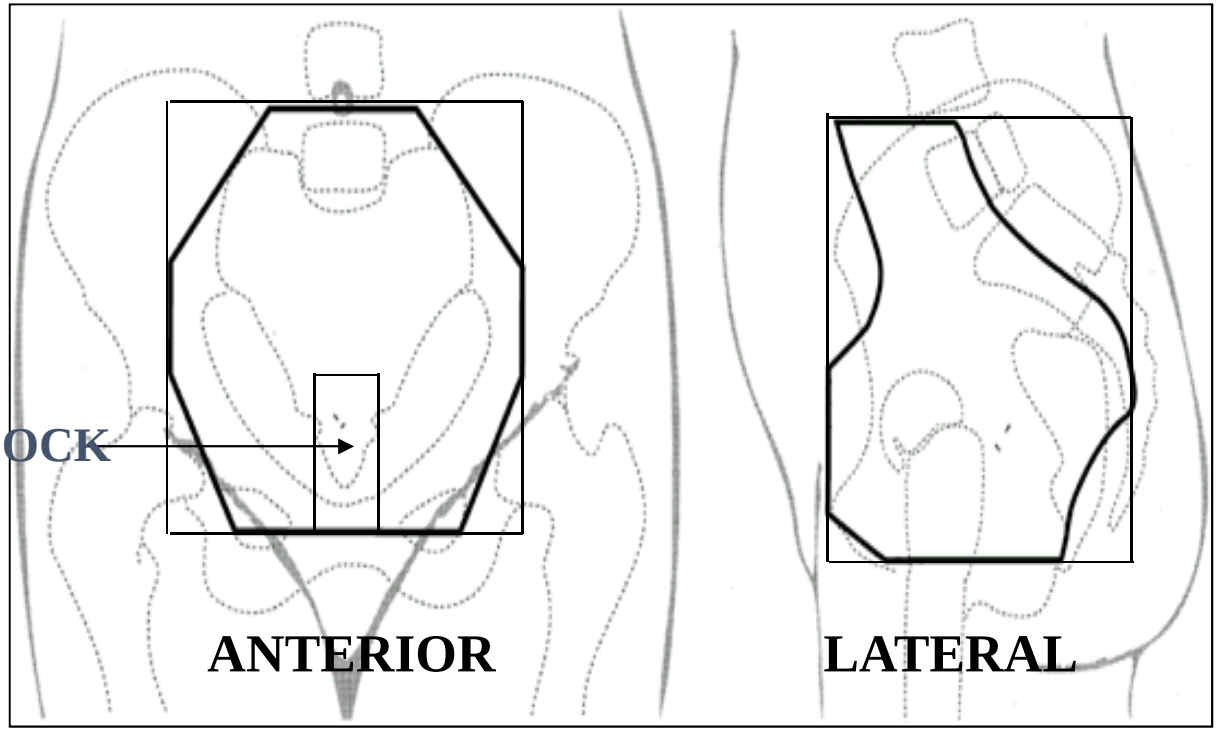
  - **Lateral recurrence & distant mets**

    Palliative chemotherapy
    Re-radiation therapy

Results Of Exenteration

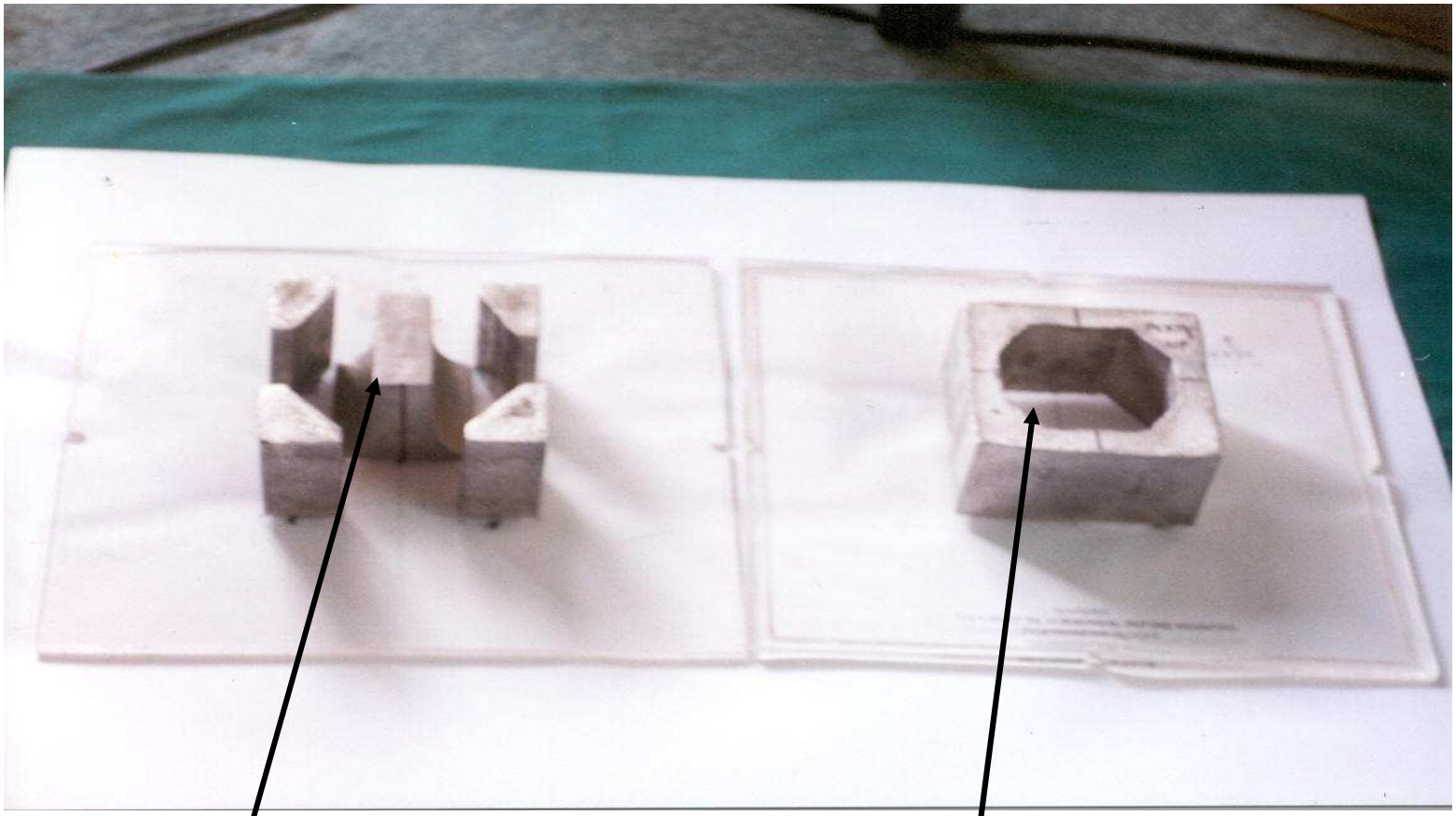
Author	Mortality	Survival
Douglas1957	4.3%	22.0%
Parsons 1964	21.4%	21.4%
Brunschwig 1965	16.0%	20.1%
Brider 1967	10.0%	34.6%
Kreiger 1969	11.0%	37.0%
Ketcham 1970	7.4%	8.2%
Symmonds 1975	8.0%	32.3%
Morley 1976	2.9%	62.0%
Rutledge 1977	13.5%	33.4%
Averette 1984	10.4%	58.0%
	13.5%	33.0%

EXTERNAL BEAM RADIATION THERAPY RECOMMENDATIONS



- **WHOLE PELVIS WITH AP/PA OR FOUR FIELD BOX TECHNIQUE**
- **DOSE DEPENDING ON THE STAGE**
- **BORDERS**

MIDLINE BLOCK/CORNER SHIELDS



- **MIDLINE BLOCK**
- **FOR DOSE ESCALATION**

- **CORNER SHIELDS**
- **TO REDUCE G.I TOXICITIES**

(Level 2 Evidence)

BRACHYTHERAPY

- **BRACHYTHERAPY : INTEGRAL PART OF RADIATION THERAPY**

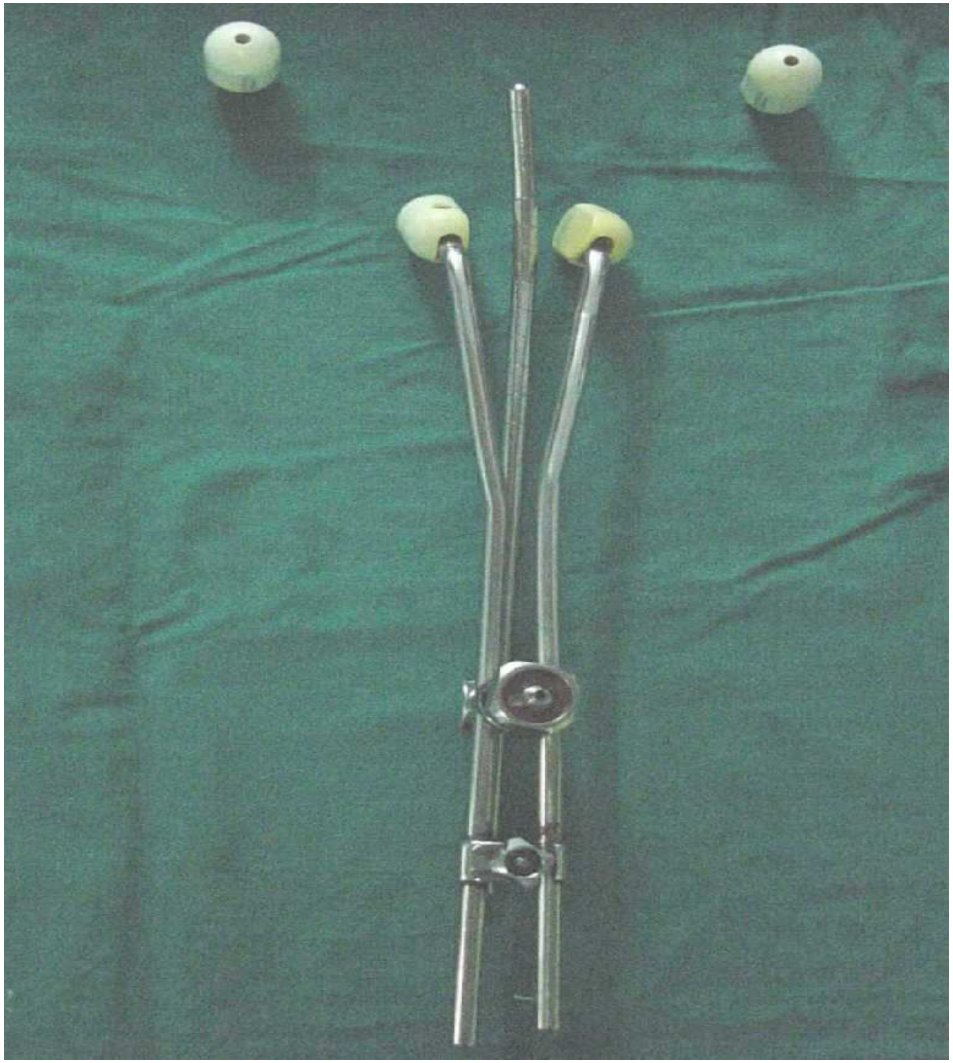
- **PATTRENS OF CARE STUDIES CONFIRM SIGNIFICANT REDUCTION IN RECURRENCES AS WELL AS COMPLICATIONS**

- **PRECISE APPLICATION OF THE CATHETERS ESSENTIAL TO OBTAIN ABOVE RESULTS - *EXPERTISE AND SKILLS***

CANCER 1983,1990, IJROBP 1991,1995, GYNAE ONCOL 1994,1999

INTRACAVITARY- TIME TESTED (> 70 YRS)

INT. COMMISSION ON RAD. UNITS- (ICRU-38) RECOMMENDATIONS



RECOMMENDED TOTAL RADIOTHERAPY DOSES

	EXT. RT PELVIS	ICRT POINT 'A'	TOTAL DOSE 'A'
IA	0	50-60	50-60
IB/IIA	45	30-35	75-80
IIB	45-50	35-40	85
IIIB	50	35-40	85-90

- **RADIOTHERAPY TREATMENT TO BE COMPLETED WITHTIN 8 WEEKS**

IJROBP 1993,1995

Thank You