Concurrent ChemoRT- the new standard of care for barrel/bulky cervical cancer.

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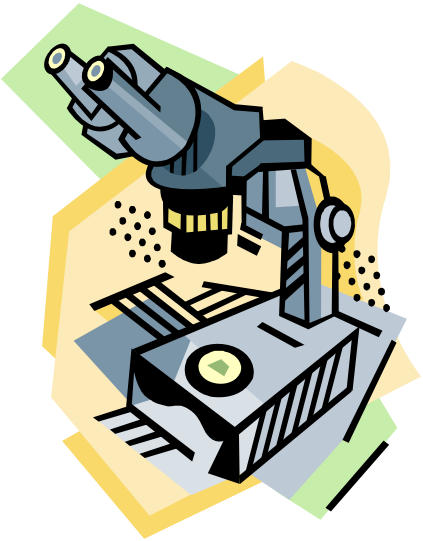
Introduction

- Case presentation
- Definition of barrel/bulky dz
- Management
  - RT alone vs RT+surg
  - Concurrent chemoRT
  - RT technique
- Conclusion.



Case presentation

- 49 yow, post menopausal since 45
- 4/99 - developed clear vaginal discharge, followed by heavy bleeding

- 5/99 – P/E
  - No palpable LNs
  - Normal vaginal wall, cervix showed a 6-7 cm ulcerated tumor, did not involve the lateral surface/fornices
  - An erosive barrel shaped mass involving the entire cervix, neg. for parametrial, ant. pubocervical, retrovaginal, uterosacral ligament involvement
  - Normal cysto/procto exam
  - **Intra-op laparoscope** – normal uterus/tubes/ovaries, lympadenectomy

Case presentation

- Married 13, first pregnancy 23, menopause 45
  - last mammo/pap 4 yrs ago- negative
  - used OCP for 20 yrs, stopped 40
  - No h/o - HTx, previous abnormal cytol, STD, smoke, alcohol
- 5/99 – bx pos. for mod diff keratinizing SCCa of cervix, 0/15 pelvic and 0/10 PA LNs
- CT c/a/p – 6x6 cm infiltrating soft tissue mass in the cervix, neg for any LNs.

Case presentation

Impression

- 49 yow, recent dx of keratinized and moderately differentiated SCCa of cervix, stage IB2 barrel.

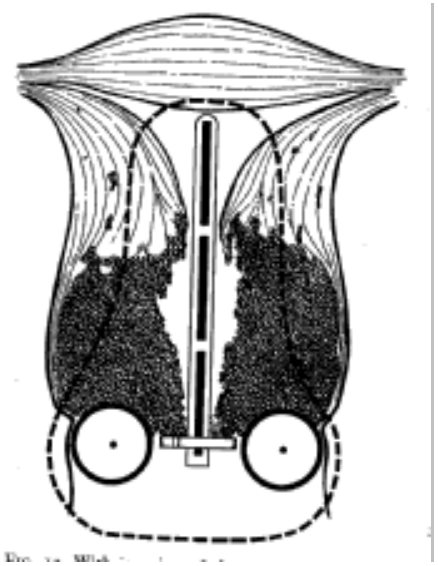
Definition of barrel/bulky dz

Barrel shaped cervix

- Lesion which expands the lower uterine segment by invading the myometrium of the isthmus.
- Tumor cells are too far for brachytherapy.

Bulky tumor

- Cervical cancer with substantial volume is known as bulky dz.
- Division between bulky and non-bulky is variable in the literature 3-6 cm, FIGO cutoff is at 4 cm.



Heyman J 1927

- Discussion on the question of operative or radiological treatment of the cancer of the cervix.
- Reported from several series of operable pts treated either surgically (3659 pts) or by RT (960 pts).
- Results at 5 yrs

	cure(%)	mortality(%)
radical surgery	35.6	17.2
radium therapy	34.9	1.7

- concl:
  - radical surgery would not accomplish more than radiologic treatment.

Turn of the Last Century

For cervical cancers

- Intracavitary radium treatment is effective
- Barrel/bulky pts more central recurrence
- Some cervical cancers are ‘Radioresistant’ !

Durrance et al 1969/MDA

- SCCa cervix stage I, II retrospectively analyzed
  - Stage I $\leq$ 1 cm – ICRT alone
  - Stage I > 1 cm – EBRT+ICRT
  - Stage II favorable – EBRT+ICRT
  - Stage I, II barrel/bulky – EBRT 2000-4000 cGy
    ICRT 4000-5000 mgh x1 appl
    Followed by surgery-Total hysterectomy
- Reslts:

	LR (%)	OS (%)
RT alone	35	64
RT+surg	18	75

- <u>Concl:</u> combined Tx of RT+TH improved LC, OS.

Perez et al 1985/MIR

- 128 pts SCCa Cx all stage barrel retrospectively analyzed
  - RT alone EBRT WP 4000 cGy+ICRT 8000 mgh x2 appl
  - Pre-op EBRT WP 2000 cGy+ICRT 6000 mgh x1 appl
  - Pre-op EBRT WP 2000 cGy+ICRT 6000 mgh x1 appl+PM 3000 cGy

- Reslts:

  @ 5 yrs

	IB		IIA		IIB	
	LR (%)	OS (%)	LR (%)	OS (%)	LR (%)	OS (%)
Rt alone	18	60	25	45	19	58
RT+surg	6	60	25	75 ns	26	

- Concl: higher dose RT alone yielded comparable results.

Keys et al 1997/GOG 71 (abs)

- 282 pts with SCCa Cx bulky IB2 (≥ 4 cm) randomized to RT alone vs RT+EFH.
- RT dose to pt A was 80 Gy in RT alone and 75 Gy in RT+EFH group.
- Results at 5 yrs

	LR	DM	OS	gd 3/4
RT	26	9	61	54
RT+EFH	14 ss	16	64	62

- Cncl:
  - addition of EFH to standard RT reduced LR but did not improve OS.
  - Chemotherapy needed to impact on OS.

Alvarez et al 1991/ UAB

- Retrospective review of 401 pts with stage IB cervical ca treated with radical hysterectomy/pelvic lymphadenectomy.
  - 56 (13%) pts had tumor > 4 cm, 50 (12%) pts had +LN.
  - Tumor diameter/nodal involvement significant in multivariate.
  - Tumor > 4 cm 5 yr OS 40%
  - Tumor > 3 cm and +LN 5 yr OS 15%
- Concl:
  - Bulky tumor/+LN pts need neoadjuvant/adjuvant therapy.

Alvarez et al 1993/ UAB

- Retrospective review of 48 pts with bulky (≥ 4 cm) early stage cervix cancer underwent radical hysterectomy.
- 25% pts received radiation therapy post-op.
- Median f/u 2.8 yrs.
- Pelvic recurrences 40%
- 5 yr OS 73.6%

- concl:
  - Radical hysterectomy/pelvic lymphadenectomy have equal efficacy and morbidity compared with RT alone or RT+EFH in bulky IB/IIA cervix ca.

Sedlis et al GOG 92/1997

- 277 pts with cervix ca with at least 2 of the risk factors LVI, stromal invasion > 1/3, tumor size ≥ 4 cm (- LN) randomized between RH vs RH+RT.
  - RT was given four field technique to WP to 46-50.4 Gy.
  - 30% of the pts had tumor size > 4 cm
  - Results at 2 yrs

	LR	DFS	OS	GR 3/4
Surg alone	28	79	79	2
Surg+RT	15	88	88	6
p value	ss	0.008	ns	

- Concl:
  - Adjunctive RT following radical surgery improves DFS in selected IB cervix ca pts, at a cost of little higher side effect.

Landoni et al 1997/Italy

- 337 SCCa Cx pts with stage IB, IIA prospectively randomized to
  - Radical hysterectomy vs RT alone.
    - RT given EBRT to WP to 45 Gy, ICRT to pt A total 70-90 Gy, pt B > 50 Gy, additional dose to PM by EBRT if necessary, if +PALN EBRT to PA 45 Gy+ 5-10 Gy boost to gross dz.
    - **High risk** pts (surgical stage > pIIA, close margin < 3 mm, cut through tumor, +LN) after RH received EBRT to WP 50.4 Gy +/- PA 45 Gy. Results at 5 yr

	LR (%)		DFS (%)		OS (%)		gd 3/4
	< 4 cm	> 4 cm	< 4 cm	> 4 cm	< 4 cm	> 4 cm	
RH (RT in HR)	10	20	80	63	87	70	28
RT alone	11	29	82	57	90	72	12
p value	ns	ns	ns	ns	ns	ns	ss

- Cncl:
  - Early stage IB, IIA pts have similar DFS and OS treated with RH (RT) or RT alone.
  - Combination of RH+RT high severe morbidity.

Landoni et al 1997/Italy

- Pathological risk factors in surgery group patients by cervical diameter.

	< 4 cm (114 pts)	> 4 cm (55 pts)	p value
Risk factors			
surgical stage >pIIA	19 (%)	35 (%)	0.04
safe stroma < 3 mm	39	45	0.50
cut through	6	22	0.007
pos LN	25	31	0.49
lymph vascular space invol	57	75	0.03
Adjuvant RT	**54**	**84**	**0.0002**

- pts with cervical diameter > 4 cm should receive radical RT ± chemo or
- Neo adjuvant chemo followed by RH.

Thomas GM 2000

Rational for neoadjuvant chemo

- Access of chemo into tumor before local Tx interferes vasculature
- Reoxygenation of tumor after chemotherapy and before RT
- Reduction in clonogenic cells
- Eradication of micromet dz.

Thomas GM 2000

Randomized study of neoadjuvant chemo failed to show any OS benefit

RANDOMIZED STUDIES						
Chauvergne et al[87]	138: CT-RT = 68; RT = 72	IIB	PBM-Chl	35	1.5	2-yr DFS, CT-RT 63% vs RT 60%, P = NS
Tobias et al[614]	66: CT-RT = 32; RT = 34	IIA-IV	BIP	69	6	CR after CT-RT, 75%; RT 56%
Cardenas et al[82]	24: CT-RT = 11; RT = 13	IIB	CEP	73	9.0	CT-RT CR 6/9 vs RT CR 12/13
Souhami et al[566]	107	IB-III	MDBP	—	47 CT-RT; 32.5 RT	5-yr survival in CT-RT 23% vs 39% in RT group
Sundfor et al[585]	CT-RT = 47; RT = 47	IIIB-IVA	CT-RT, P-5FU	80 CT-RT; 82 RT	53 CT-RT; 57 RT	CT-RT 5-yr DFS 70%; RT 57%
Kumar et al[323]	177: CT-RT = 89; RT = 88	IIB-IVA	BIP	72	4.5	DFS at 30 mo 69% in CT-RT vs 67% in RT group; P = NS

Sardi J et al 1997/ Argentina

- 205 pts with bulky (≥ 2 cm) IB cervical ca randomized between
  - RH+post-opRT vs NAC+RH+post-opRT.
  - NAC CDDP 50 mg/m2, Vincri 1 mg/m2, Bleo 25 mg/m2 d1-3 x3 cyl.
- Results at 7 yrs

	LR	DM	all IB	IB1	IB2
RH+RT	17	7	66	77	61
NAC+RH+RT	7	5	81	82	80
p value	< 0.001	ns	< 0.05	-	ss

- Concl
  - NAC can improve OS in bulky (> 4 cm) IB Cx ca.

Chang et al 2000/ Taiwan

- 124 pts with bulky (≥ 4 cm) IB/IIA cervical ca randomized to
  - NAC+RH vs RT alone.
  - EBRT WP 40-44 Gy+ICRT, total pt A dose 70 Gy.
  - NAC CDDP 50 mg/m2 and Vincri 1 mg/m2 d1, Bleo 25 mg/m2 d1-3 x3 cyl.
- Reslts @ 5 yrs

	LR (%)	DM (%)	DFS (%)	OS (%)
NAC+RH	21	9	65	70
RT alone	12	12	51	61
p value			0.76	0.77

- Concl:
  - NAC+RH and RT alone similar efficacy for bulky IB/IIA cx ca.

Thomas GM 2000

Rational for concurrent chemoRT

- Avoid delay RT, prevent accelerated clonogen proliferation
- Interaction between the two agents – 4 Rs
- Independent additive cytogenic effects of chemo

- 5 recent randomized studies showed significantly improved OS.

Thomas GM 2000

Table 1. Estimates of the Relative Risk of Death in Five Clinical Trials of Concurrent Chemotherapy and Radiotherapy.

Study	FIGO Stage*	Treatment		Relative Risk of Death in Comparison Group
		Control Group	Comparison Group	
Keys et al.[1]	IB2	Radiotherapy	Radiotherapy plus weekly cisplatin	0.54
Rose et al.[2]	IIB–IVA	Radiotherapy plus hydroxyurea	Radiotherapy plus weekly cisplatin	0.61
			Radiotherapy plus cisplatin, fluorouracil, and hydroxyurea	0.58
Morris et al.[3]	IB2–IVA	Extended-field radiotherapy	Radiotherapy plus cisplatin and fluorouracil	0.52
Whitney et al.[5]	IIB–IVA	Radiotherapy plus hydroxyurea	Radiotherapy plus cisplatin and fluorouracil	0.72
Peters et al.[6]	IB or IIA (selected postoperatively)	Radiotherapy	Radiotherapy plus cisplatin and fluorouracil	0.5

Keys et al 1999/GOG 123

- 369 pts cervical ca stage IB barrel/bulky, neg LN
  - RT→ TH vs RT+CDDP→ TH
  - RT given EBRT WP 45 Gy+ICRT pt A 30 Gy, pt B 10 Gy
  - CDDP given 40 mg/m2 qwk x6 cycles

- Reslts:

  @ 4 yrs

	LR (%)	DFS (%)	OS (%)	gr 3/4 (%)
RT+TH	21	60	70	13
RT+CDDP+TH	9	76	82	35
p value		0.001	0.008	

- <u>Concl:</u>
  - Elimination of TH from both regimen would not effect OS
  - chemoRT with CDDP should be adequate for stage IB barrel/bulky cervical ca.

Morris et al 1999/RTOG 90-01

- 388 pts cervical ca stage IB, IIA (≥ 5 cm), IIB-IVA
  - Pelvic+PA RT vs Pelvic RT+CDDP+5FU
  - RT given EBRT 45 Gy+ICRT pt A 40 Gy
  - Chemo given CDDP 75 mg/m2, 5FU 4000 mg CVI d1-5 q3wks x3 cycles

- Reslts:
  @ 5 yrs

	LR	DM	DFS	OS
pelvic+PA RT	35	33	40	63
pelvic+CDDP+5FU	19	14	67	76
p value	0.001	0.001	0.001	0.004

- Concl: addition of CDDP+5FU to RT significantly improved DFS/OS in locally advanced cervical ca.

NCI USA 1999

Clinical announcement

‘Strong consideration should be given to incorporation of concurrent chemotherapy with radiation therapy in women who require radiation therapy for the treatment of cervical cancer.’

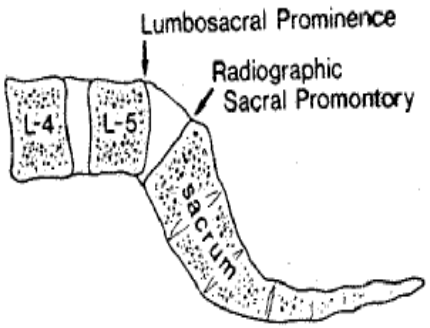
RT technique

- Radiation is the most active curative agent for cervical cancer.
  - EBRT shrinks and improves tumor geometry for optimal brachytherapy to bring tumor cells into the higher dose region of the ICRT.
  - Intracavitary brachytherapy is the most important part of the radiation therapy.
- Concurrent chemo improves pelvic control and contribute to improve OS.

Greer et al 1990

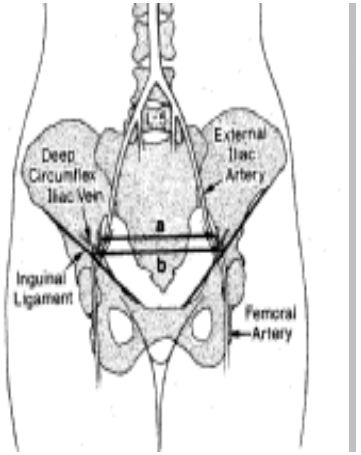
100 pts underwent intra-op pelvic measurements relative to LSP

- Pelvic side wall width at the obturator fossa
- Width of the ext iliac A at deep circumflex iliac vein
- Separation of femoral A at inguinal ligament

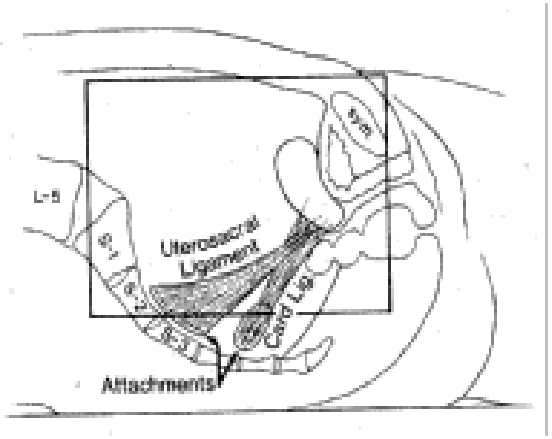


Greer et al 1990

- Reslts:
  - Common iliac bifurcation - 1.5 cm above LS promontory
  - Maximal separation of femoral A - 14.6 cm
  - Cardinal/uterosacral lig post to rectum/sigmoid attached to sacral hollow
  - Radiographically L4-L5 is 3.5 cm sup to LS prominence



- <u>Concl:</u>
  - <u>sup border</u> at L4-L5 to cover mid common iliac LNs
  - AP/PA fields at least 16 cm wide
  - Lateral fields should encompass the ant sacral silhouette.



Kim et al 1994

- 34 pts cervical ca Txed 4 field were analyzed
  - Sup – L4-L5, inf – bottom of obturator/2 cm below tumor, lat – 2 cm beyond bony pelvis, ant – symphysis pubis, post – S2-S3
  - CT defined tumor volume reconstructed on sim film
  - Measurements from tumor volume to the field borders made
- Reslts:

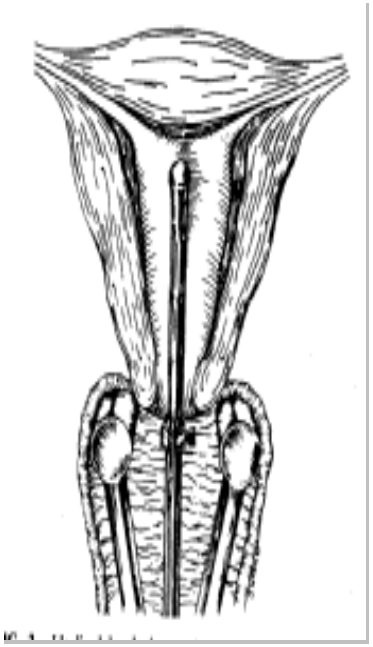
pelvic control

		pelvic	control	
		IB (%)	**IIB (%)**	**IIIB (%)**
adequate margin		100	88	50
inadequate margin		71	50	50

- Concl:
  - Higher LF with inadequate margin
  - Strongly recommend CT planning for 4 fld Tx.

Corn et al 1994

- 66 pts LA SCCa Cx analyzed for brachy parameters
  - Distance between the rt and lt colpostat source and distal tandem source
  - Symmetry of the colpostat placement
  - Implant ideal if all 3 parameters satisfactory

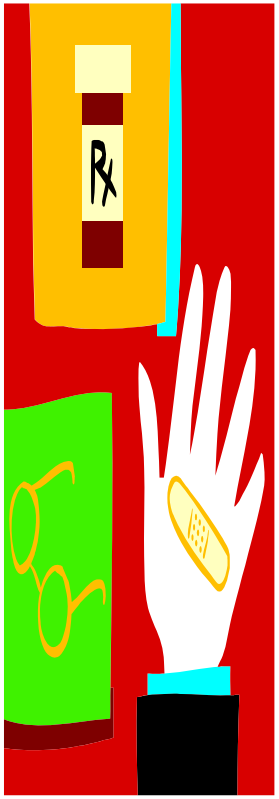


- Reslts:

	LC	OS
ideal+adequate	68	61
unacceptable	35	42
p value	0.02	0.1

- <u>Concl:</u>
  - Technical implant performance influences LC
  - Emphasis of proper implant technique.

Conclusions

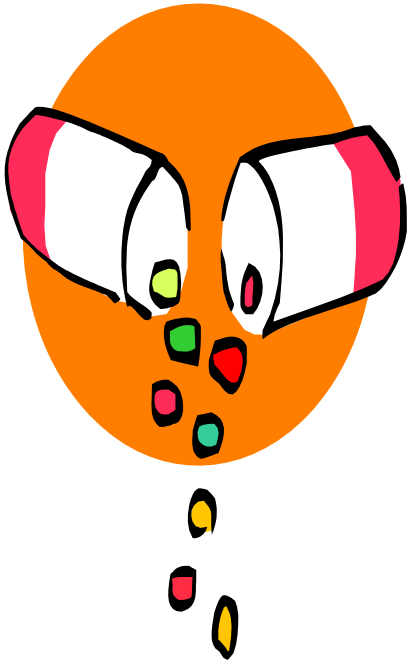


- GOG 71 and Italian Landoni study clearly showed that RT alone is adequate in barrel/bulky cervical cancer pts without causing any decrease in DFS/OS.
- Combination of surgery and RT should not be used as this significantly increases severe morbidity.

Conclusions

- GOG 123 and RTOG 90-01 clearly showed that CDDP based concurrent chemoRT improves DFS/OS for barrel/bulky IB and locally advanced cervical ca and is now the new standard of care.

Conclusions



- Optimal choice of chemotherapy and its schedule remains to be determined as these studies used different chemo regimen and doses.

- Radiation portion of this new standard of care chemoRT regimen must be optimized, in order to benefit from it.

Conclusions

- The report of NAC before surgery is conflicting and should be considered investigational.
- Its use before hysterectomy is currently being studied by GOG.

Conclusions
F/U on our pt

- EBRT WP 4 fld 2880 cGy, followed by
- ICRT pt A 5420 cGy, pt B 1593 cGy, followed by
- EBRT PM AP/PA 1620 cGy after ML block
- Total pt A 8300 cGy, pt B 6093 cGy, max bladder ICRU 7057 cGy, max rectal ICRU 6004 cGy
- Concurrent CDDP 40 mg/m2 qwk x6 cycles
- Tx completed on 7/16/99, total Tx time 7 wks

- Last f/u on 1/28/00- she is clinically NED, has developed bilateral LE lymphedema and complained of depression, for which she is under care now.

Conclusions

- GOG 165, current trial for advanced cervical ca.
- Pts randomized between
  - RT+concurrent CDDP (40 mg/m2/wk) x6 wks vs
  - RT+concurrent protracted IV 5FU (225 mg/m2/d) x5 wks.
- RT technique improved
    - pt A dose is 85 Gy
    - entire sacral hollow included in lat fields
    - overall time reduced to $\leq$ 8 wks
    - PM boost given between intracavitary placements
    - HDR accepted as alternative to LDR.

Conclusion

- GOG current phase III study
- pts with bulky IB2 cervical ca randomized to
  - NAC+RH vs RH alone.
  - Chemo given CDDP 50 mg/m2, Vincris 1 mg/m2 q10d x3 cyl
- Total target 415 pts.

Janeway HH/ 1919

- “Our present evidence indicates that radium destroys the disease at this site (cervix) to a greater distance than the knife is capable of removing it.”

Conclusions

- The end.