

An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

#### **Gynecologic Cancer InterGroup Cervix Cancer Research Network**

## Hypofractionated RT in Cervix Cancer Anuja Jhingran, MD



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- Hypofractionated RT in Cervix Cancer: Clinicaltrials.gov
  - 919 cervix trials
  - 134 hypofractionated RT trials
  - Prostate, breast, NSCLC, GBM
  - 0 cervix trials with hypofractionation

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HDR = LDR

# HDR versus LDR intracavity brachytherapy for locally advanced uterine cervix cancer

Liu et al Cochrane Review 2014

Study or subgroup	HDR N/N	LDR n/N	Risk Ratio M - H, Fixed, 95% CI	Weight	Risk Ratio M - H, Fixed, 95% CI			
1 Locaregional Techima 1993	21/86	15/55	-	22.9 N	0.90 [0.51, 1.58]			
Patel 1994	51/236	47/246	-	57.7 %	1.13 [0.79, 1.61]			
Hareyama 2002	11/61	9/71		10.4 N	1.42 [ 0.63, 3.20 ]			
Lertzanguansinchai 2004	7/112	7/109		8.9 N	0.97 [ 0.35, 2.68 ]			
Subtotal (95% CI)	495	481	•	100.0 %	1.09 [ 0.83, 1.43 ]			
To the events: 30 (BDDs, 78 (LDD) Historogannity: Chill = 0.96, df = 3 ( $P$ = 0.81); $P$ =0.0% Test for overall effect: $2 = 0.64$ ( $P$ = 0.52)								
2 Paraarotic lymph node metast Teshima 1993	tasis 9/86	8/55	-	56.9 N	0.72 [0.30, 1.75]	_ I		
Hareyama 2002	6/61	8/71		43.1 %	0.87 [ 0.32, 2.38 ]			
Subtotal (95% CI)	147	126	+	100.0 %	0.79 [ 0.40, 1.53 ]			
Heterogeneity: ChiP = 0.08, df Test for overall effect Z = 0.71	0 = 1 (P = 0.78); P = ( (P = 0.48)	0.0%				_ I		
3 Combined local and distant Patel 1994	6/236	3/246	-	59.2 %	2.08 [ 0.53, 8.24 ]	_ I		
Lertsanguansinchai 2004	5/112	2/109		40.8 %	2.43 [ 0.48, 12.28 ]			
Subtotal (95% CI) Tetal counts: 11 (HDR), 5 (LDR)	348	355	-	100.0 %	2.23 [ 0.78, 6.34 ]			
Historogansity: $Chi^2 = 0.02$ , $df = 1$ ( $P = 0.85$ ); $P = 0.06$ Test for overall effect: $Z = 1.50$ ( $P = 0.13$ )								
4 Distant Techima 1993	12/86	8/55	_	14.7 %	0.96 [ 0.42, 2.20 ]			
Patel 1994	15/236	21/246	-	31.0 %	0.74 [0.39, 1.41]			
Hareyama 2002	15/61	17/71		23.7 %	1.03 [0.56, 1.88]			
Lertranguansinchai 2004	25/112	20/109	-	30.6 X	1.22 [0.72, 2.06]			
Subtotal (95% CI)	495	481	+	100.0 %	0.99 [ 0.72, 1.35 ]			
Total events: 67 (HDP), 66 (LDP) Heterogenety: ChiP = 1.38, dt = 3 ( $P$ = 0.71); P = 0.05 TestBor overall effect Z = 0.08 ( $P$ = 0.94)								
0.01 0.1 1 10 100 Favours experimental Favours control								

Palliation: Select Trials

- IAEA Trial Hoskin et al, 2015
  - 8 Gy vs 4 Gy
  - ORR 80% vs 68%, (p=0.0015)
  - Retreatment rates: 14% vs 22%, (p=0.01)
- RTOG 9714 Hartsell et al
  - 8 Gy vs 30 Gy in 10
  - Pain relief and narcotic use equivalent
- RTOG 7905
  - 10 Gy x 3 with misonidazole, too toxic
- RTOG 8502 Spanos et al
  - 3.7 Gy bid x 3 q 2-4 weeks
  - CR 10%, PR 22%, no change 24%, Progression 10%, Unknown 34%
- TATA Memorial Hosp.
  - 10 Gy x 3

#### Cervix Cancer Education Symposium, January 2016, Bangkok, Thailand

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## Monthly palliative pelvic radiotherapy in advanced carcinoma of uterine cervix

- Mishra et al J Cancer Res Ther. 1(4):208-12, 2005
- •N=100
- •10 Gy x 3
- –Median field size: 15 x 15 cm
- –Brachy 30 Gy after fx 2, or 10 Gy after fx 3
- •68% IIIB, 20% with metastatic disease
- •61 received 2<sup>nd</sup> fx, 33 received 3<sup>rd</sup> fx
- •Control of bleeding, discharge and pain were 100%, 49% and 33%, respectively



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#### Monthly palliative pelvic radiotherapy in advanced carcinoma or uterine cervix

Mishra et al J Cancer Res Ther. 1(4):208-12, 2005





Figure 3: Radiotherapy fraction vs. pain relief



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# Short-course palliative radiotherapy for uterme cervicar cancer.

Kim et al Radiat Oncol J. 2013 Dec;31(4):216-21.

- N=17
- 20-25 Gy @ 5 Gy per fraction
- ORR 94% for vaginal bleeding control
- ORR 67% for pelvic pain

## Palliative RT: Trial Example



## 5 Gy x 5

- endpoints (short term):
  - PRO's
  - Pain relief, bleeding, narcotic usage

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## Definitive Treatment: Hypofractionation EBRT

- 45-50.4 Gy, Is this optimal?
- Dose per fraction: 1.8-2.0 Gy?
- Central blocks?
- Guiding principle: Mitigating late toxicity

Afr. J. Med. med. Sci. (2000) 29, 253 - 258

#### Comparative evaluation of hypofractionated radiotherapy and conventional fractionated radiotherapy in the management of carcinoma of the cervix in Ibadan, Nigeria

OB Campbell<sup>1</sup>, IB Akinlade<sup>1</sup>, A Arowojolu<sup>2</sup>, IA Babarinsa<sup>2</sup>, RI Agwimah<sup>3</sup> and IF Adewole<sup>2</sup> <sup>1</sup>Department of Radiotherapy, <sup>2</sup>Department of Obstetrics & Gyneacology, University College Hospital, Ibadan and <sup>3</sup>Department of Physics, University of Ibadan, Ibadan, Nigeria.

- 63% of cancers were cervix cancer, wait time was 3 months to get on treatment
- Randomized trial, Univ College Hosp, Ibadan, Nigeria
  - Hypofrac. group (n=230, 50 Gy in 15 fractions in 5 weeks)
  - Control group (n=250, 50 Gy in 25 fractions in 5 weeks)
- Both groups received a single 30 Gy implant
- Survival and response were similar
- Late reactions were observed in 42.6% of hypofrac. group and 12.8% of control group



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## Definitive Treatment: Hypofractionation Brachytherapy

- Standard regimens
  - 5-6 Gy x 5
  - 7 Gy x 4
  - 8 Gy x 3
  - 9 Gy x 2
- 2 LDR implants preferable to 1
- Guiding principle: mitigating late toxicity



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## **Definitive CRT: Trial Example**



### ENDPOINT: RFS

## Hypofraction: BED and EQD2

Dose	Dose per fraction	Alpha/Beta	BED	EQD2
45	1.8	3	72.0	43.2
44	2.0	3	73.2	44.0
37.5	2.5	3	68.8	41.3
30	3.0	3	60.0	36.0
45	1.8	10	53.1	44.3
44	2.0	10	52.8	44.0
37.5	2.5	10	46.9	39.1
30	3.0	10	39.0	32.5
Brachy				
30	6.0	3	90.0	54.0
28	7.0	3	93.3	56.0
24	8.0	3	88.0	52.8
18	9.0	3	72.0	43.2
30	6.0	10	48.0	40.0
28	7.0	10	47.6	39.7
24	8.0	10	43.2	36.0
18	9.0	10	34.2	28.5

45/1.8 + 30/6 = **97.2 EQD2** vs 37.5/2.5 + 24/8 = **94.1 EQD2** for alpha/beta 3 <u>30 fractions vs 18 fractions</u>



Outcomes: Non-inferiority to External Beam & Brachy for 2-year survival; Equivalence for Toxicity/QoL Analysis: Stratify on Stage and Node Involvement Data: Standardized; Tissues (Genetics; HPV type); Blood (Nutritional Status) Sites: Brazil and Mexico; Minimum requirement---CT image of Abdomen and Pelvis and Chest x-ray

## IAEA trial

- Clinical Research Project

   Multinational
- Accrual complete, data initially analyzed
- 2 x 2 design
  - ChemoRT vs RT,
  - Brachy: 9 Gy x 2 vs 7 Gy x 4

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## Hypofractionation: Where do we go from here?

- Goal: Improve care delivery, not improving OS
  - May need public funding
- Culturally sensitivity and practical
- Integration with chemo: watch out for acute toxicity (q weekly vs q 3 week)
- Remember: Our standard need not be the standard elsewhere
  - Some countries have no cervical cancer care