



**Gynecologic Cancer InterGroup
Cervix Cancer Research Network**

Hypofractionated RT in Cervix Cancer

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Cervix Cancer Education Symposium, January 2016, Bangkok, Thailand



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

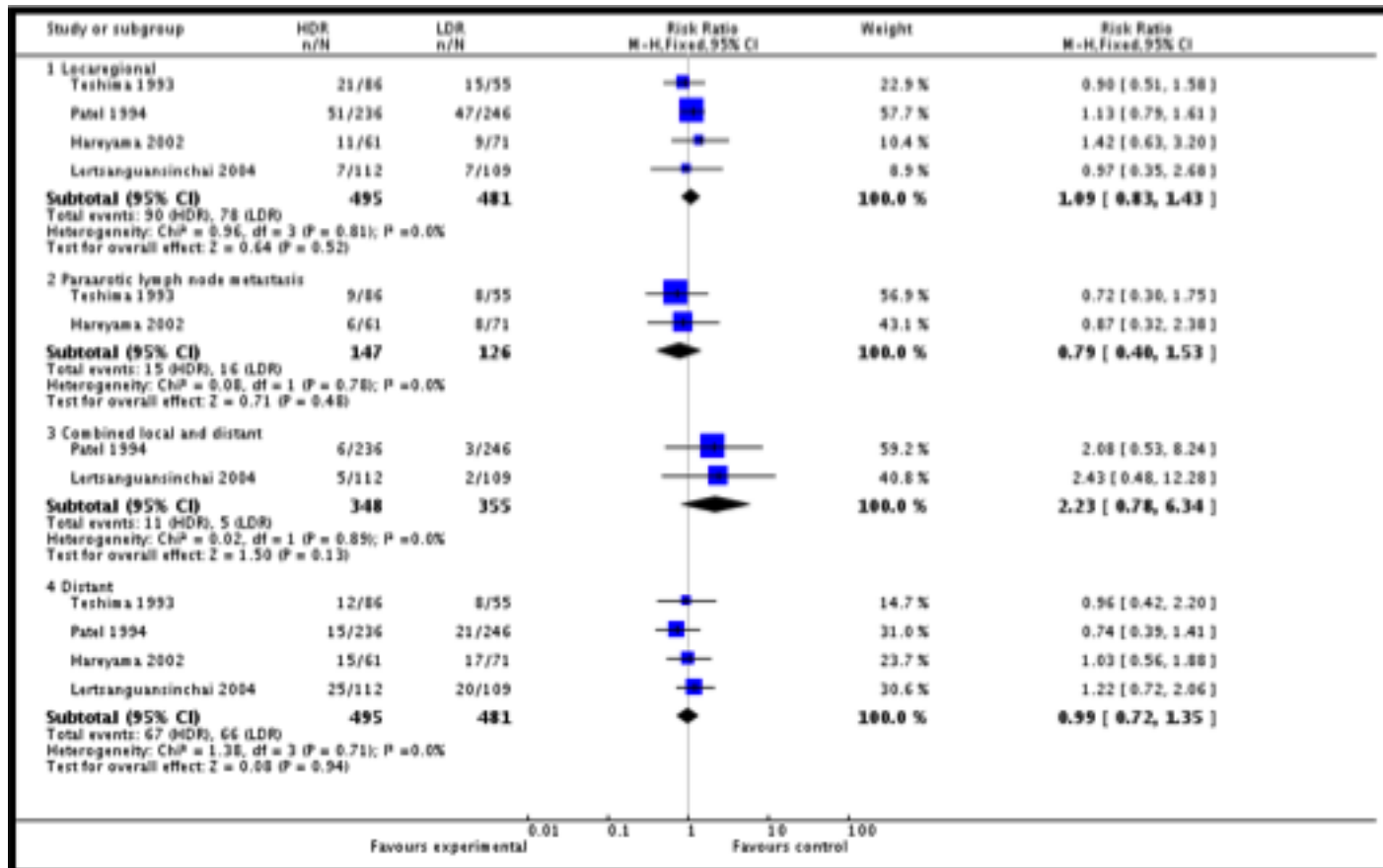
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HDR = LDR

HDR versus LDR intracavity brachytherapy for locally advanced uterine cervix cancer

Liu et al Cochrane Review 2014



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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

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 2nd fx, 33 received 3rd fx
- Control of bleeding, discharge and pain were 100%, 49% and 33%, respectively

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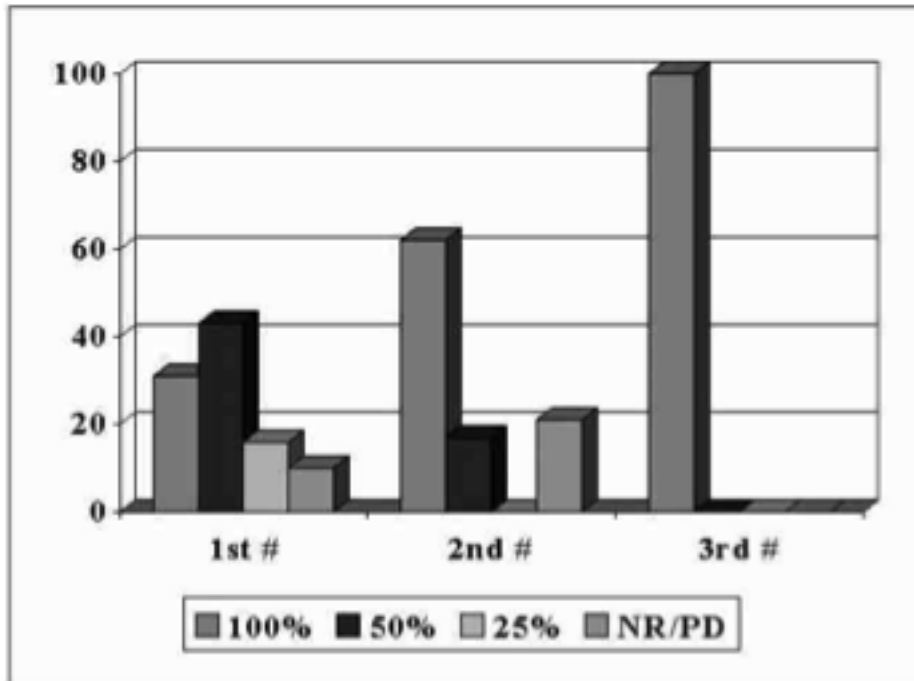


Figure 1: Radiotherapy fraction vs. control of bleeding

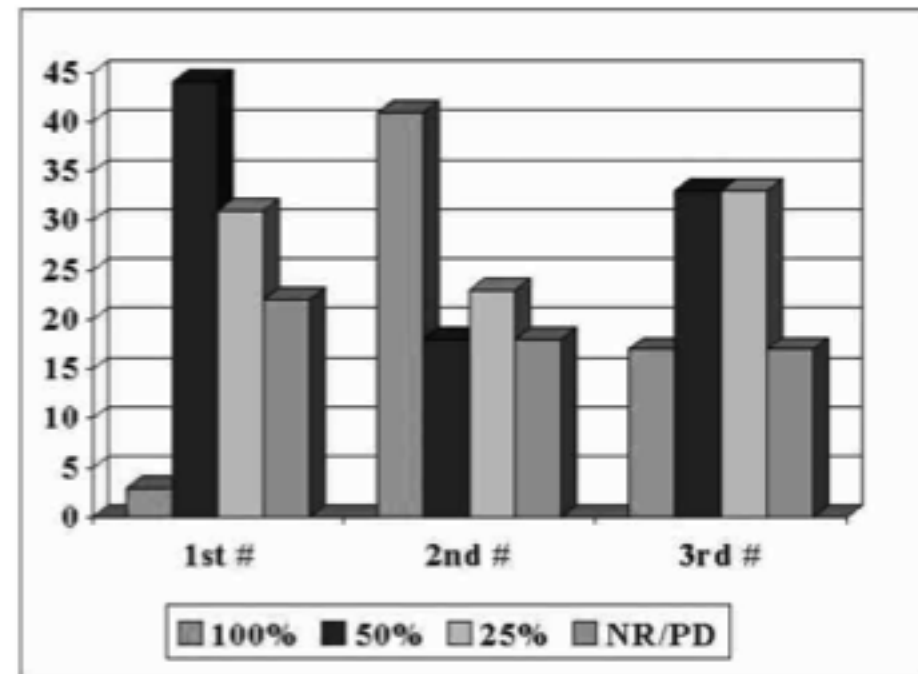


Figure 3: Radiotherapy fraction vs. pain relief

Short-course palliative radiotherapy for uterine cervical 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

10 Gy x 2 q month

5 Gy x 5

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



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

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

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³Department 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

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

Definitive CRT: Trial Example

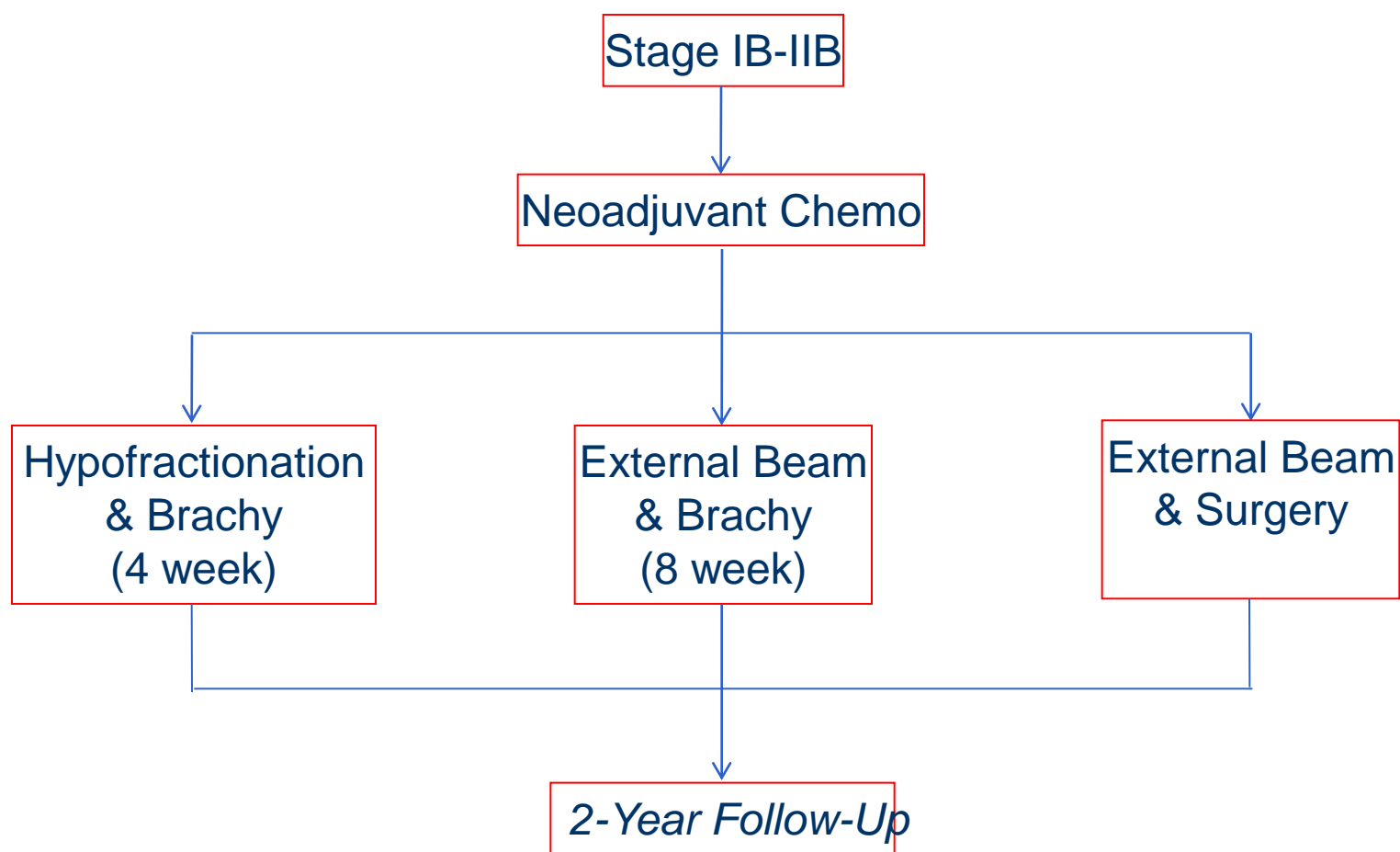


ENDPOINT: RFS

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
30 fractions vs 18 fractions



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

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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