Hypofractionated RT in Cervix Cancer

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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

Palliative Radiation Therapy

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

Monthly palliative pelvic radiotherapy in advanced carcinoma of uterine cervix

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

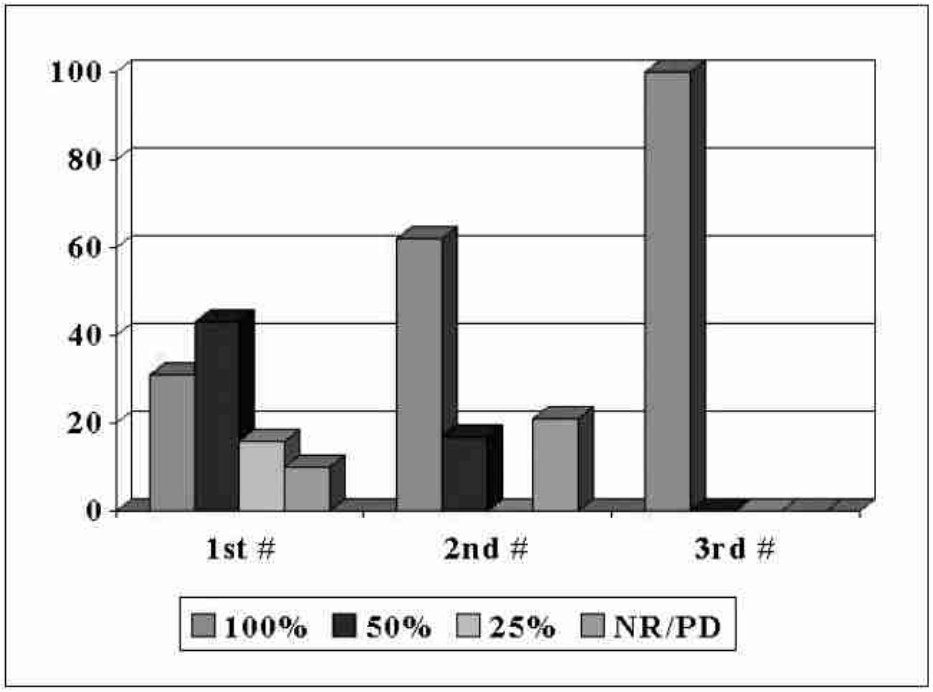


Figure 1: Radiotherapy fraction vs. control of bleeding

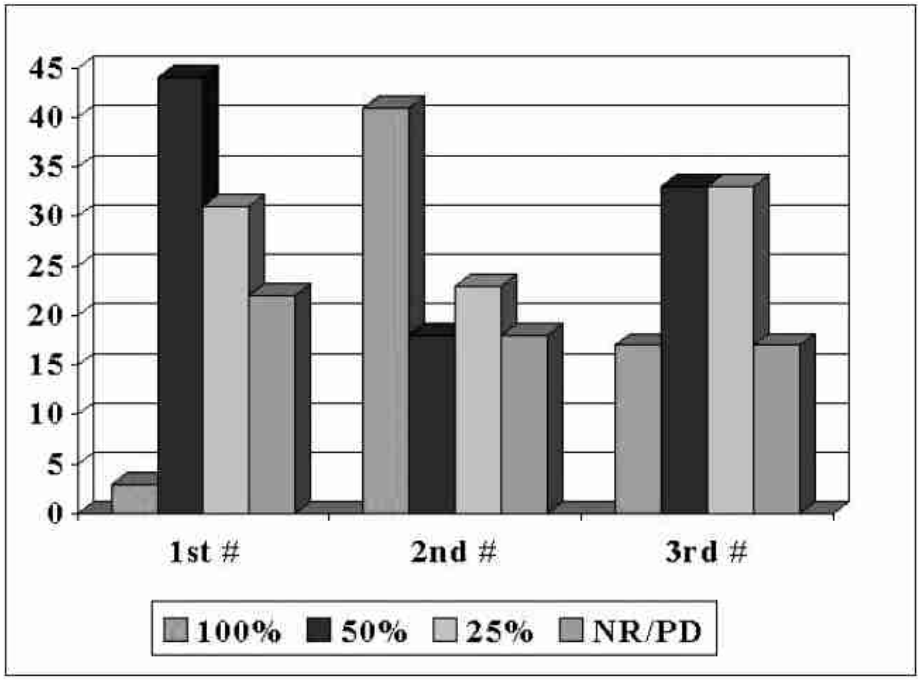


Figure 3: Radiotherapy fraction vs. pain relief

PROs?

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

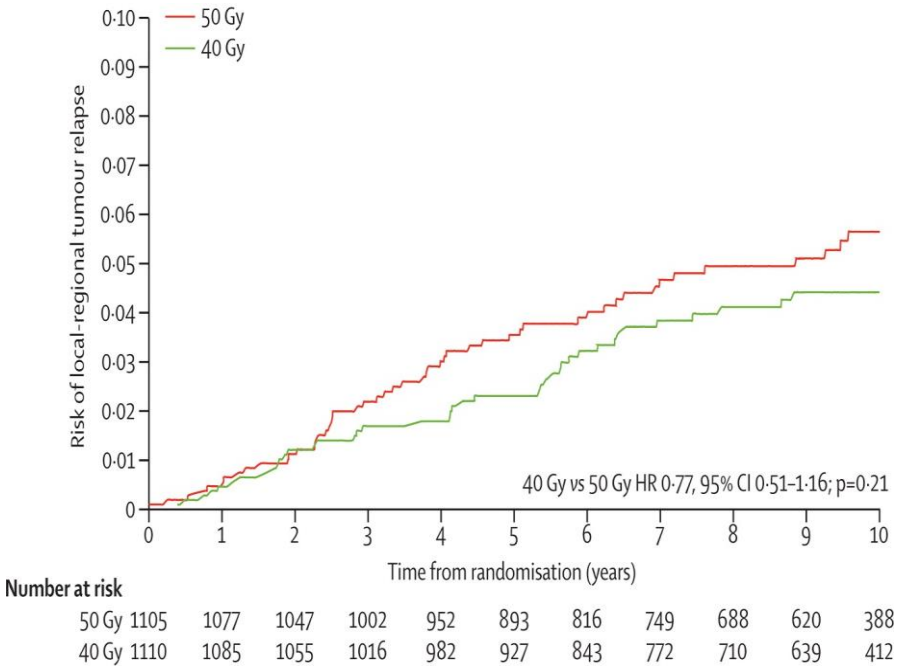
Definitive Hypofractions

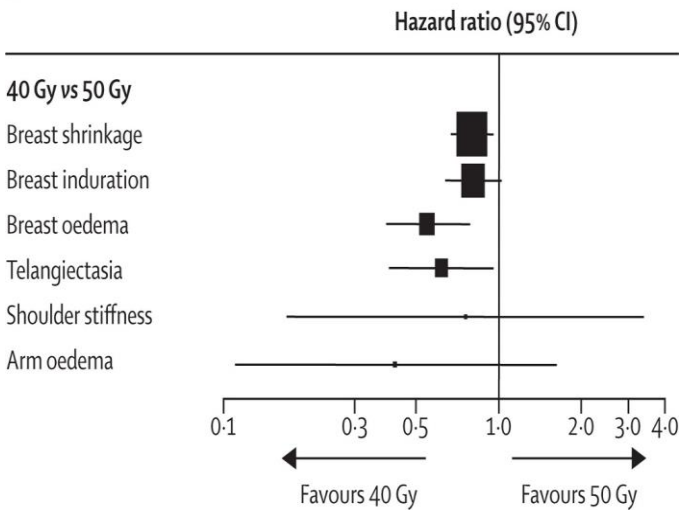
Definitive Treatment: Hypofractionation EBRT

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

Hypofractionated WBI

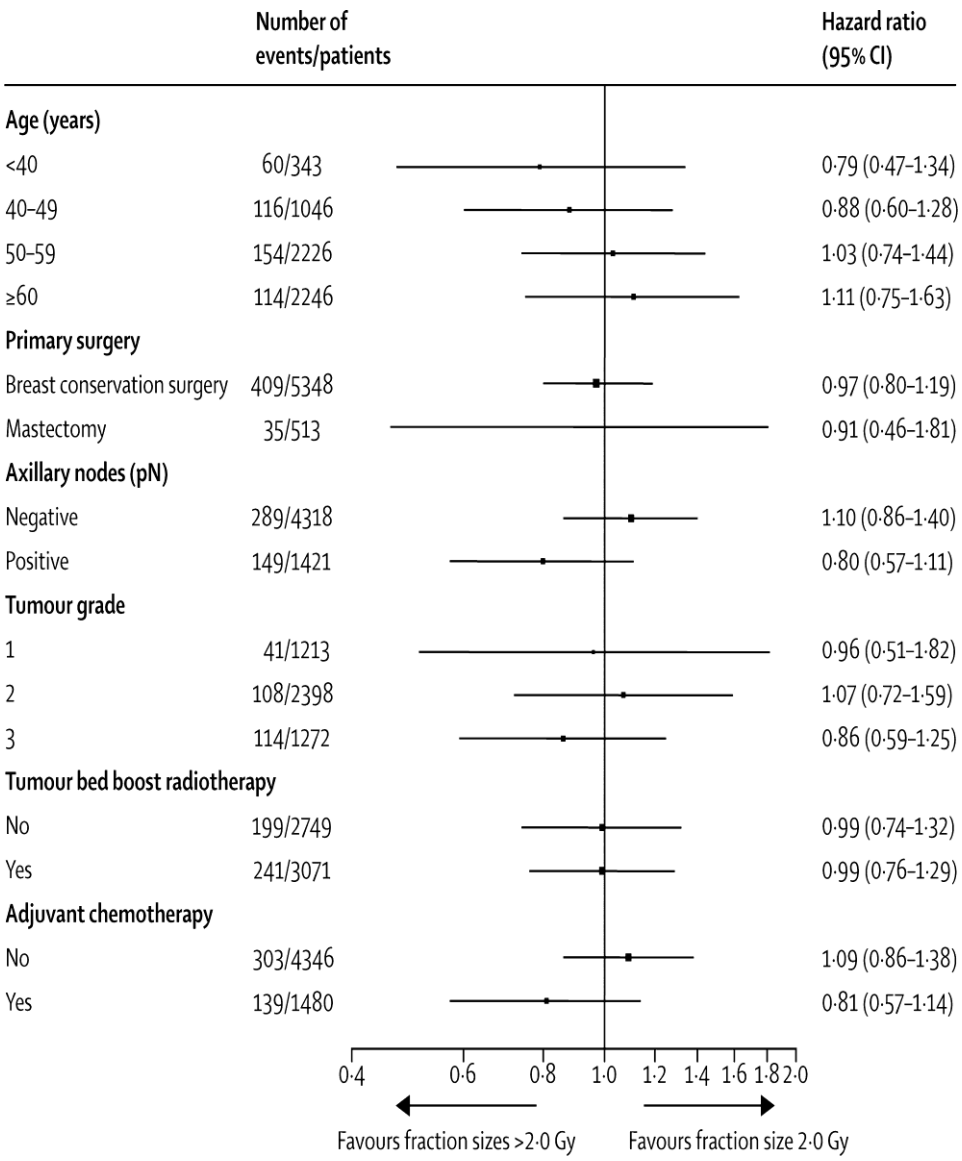
START B





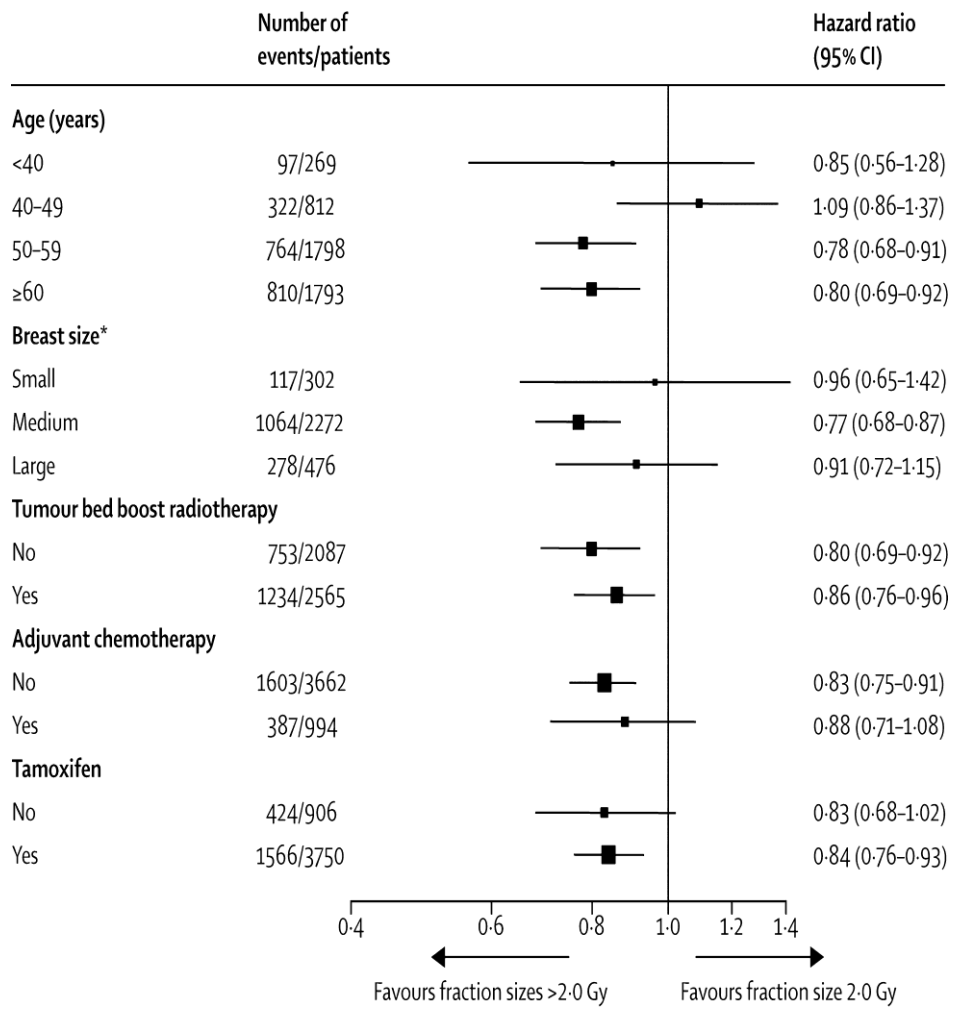
Haviland et al, Lancet Oncol 14:108

Meta-analysis for local-regional relapse



Haviland et al, Lancet Oncol 14:108

Meta-analysis for complications



Haviland et al, Lancet Oncol 14:108

MD Anderson trial

	Dose to Whole Breast/ # Fractions	Dose to Tumor Bed Boost/ #Fractions	Total Days of RT
CF-WBI	50Gy/25fx	10Gy/5fx Margin ≥2mm 14Gy/7fx Margin <2mm	30-32
HF-WBI	42.56Gy/16fx	10Gy/4fx Margin ≥2mm 12.5Gy/5fx Margin <2mm	20-21

Shaitelman et al., JAMA Oncology 94:338-48, 2016

MD-Reported Acute Grade ≥ 2 Toxicity Recorded Weekly During RT

	CF-WBI	HF-WBI	p-value
Any Acute Grade ≥ 2	77.9%	46.4%	**<0.001**
Any Acute Grade ≥ 3	5.4%	0.0%	**0.006**
Fatigue	16.7%	8.7%	**0.020**
Pruritis	6.7%	4.3%	**<0.001**
Breast Pain	8.7%	5.1%	**0.003**
Dermatitis	69.1%	36.2%	**<0.001**
Hyperpigmentation	20.1%	8.7%	**0.007**
Shoulder Arthralgia	0.7%	1.4%	0.23
Breast Edema	2.7%	0.7%	0.22

Shaitelman et al., JAMA Oncology 94:338-48, 2016

MD-Reported Grade ≥ 2 Toxicity at 6 month follow up

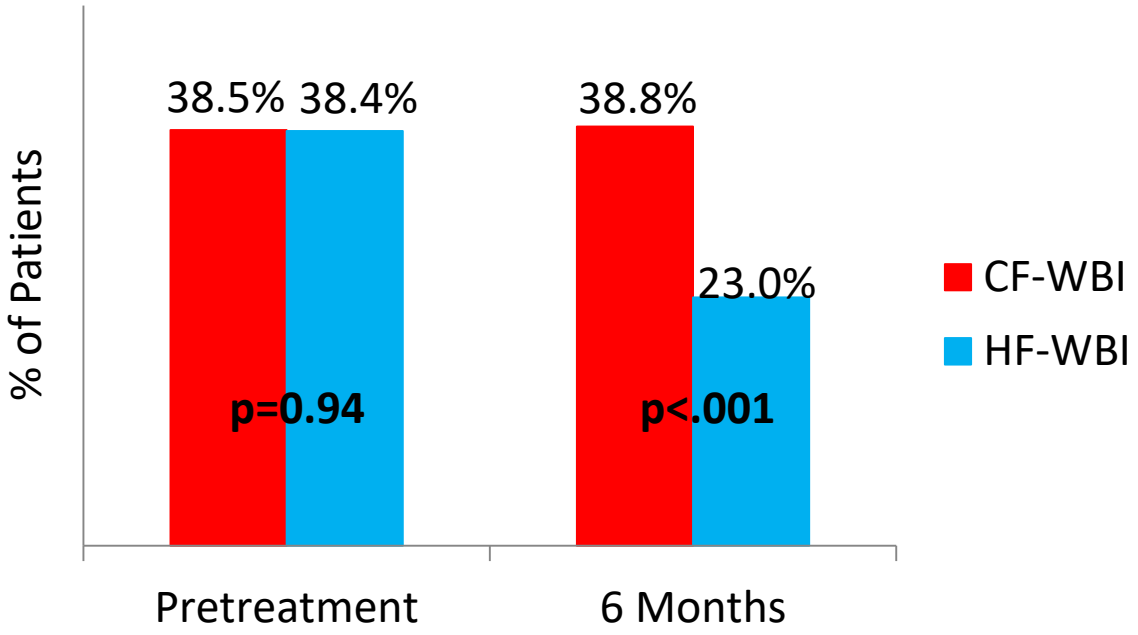
	CF-WBI	HF-WBI	p-value
Fatigue	6.4%	0.0%	**0.009**
Hyperpigmentation	7.8%	11.4%	0.12
Skin Induration	1.4%	0.8%	0.38
Dermatitis	0.7%	0.0%	0.64
Telangiectasias	0.7%	2.4%	0.22
Skin Ulceration	0.0%	0.0%	n/a
Wound Complications, Non-Infectious	0.0%	0.0%	n/a
Breast Infection	0.7%	0.7%	0.36
Wound Infection	0.0%	0.0%	n/a
Upper Extremity Edema	0.0%	0.0%	0.92
Breast Edema	5.0%	1.6%	0.08

Shaitelman et al., JAMA Oncology 94:338-48, 2016

6 Month Patient FACT-B Scores

	CF-WBI	HF-WBI	p-value
Mean Physical Wellbeing Score	24.7	25.4	0.07
Q1. Lack of energy: somewhat or worse	38.8%	23.0%	**<0.001**

Patient Reported somewhat or worse lack of energy

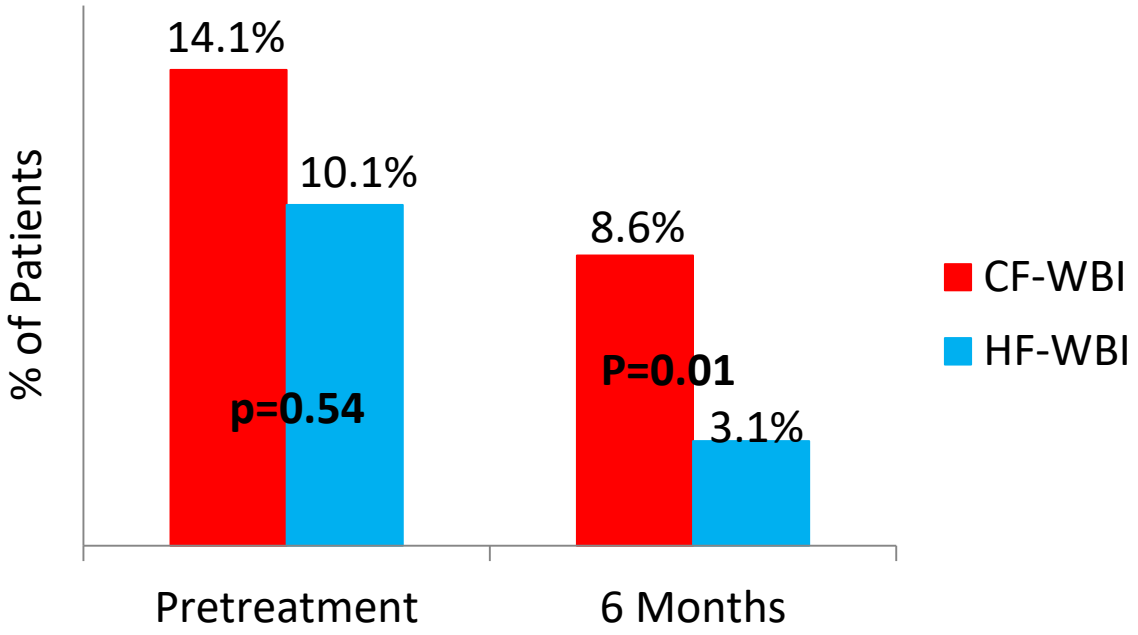


Shaitelman et al., JAMA Oncology 94:338-48, 2016

6 Month Patient FACT-B Scores

	CF-WBI	HF-WBI	p-value
Mean Physical Wellbeing Score	24.7	25.4	0.07
Q3. Somewhat or worse trouble meeting family needs	38.8%	23.0%	**<0.001**

Patient Reported somewhat or worse trouble meeting family needs



Shaitelman et al., JAMA Oncology 94:338-48, 2016

Summary

- For women who need whole breast irradiation without addition of a third field to cover the regional nodal basins, hypofractionated-whole breast irradiation should be the preferred standard of care
  - Evidence is robust
  - Less expensive and more convenient
  - Less acute toxicity
  - Less fatigue – a benefit that lasts through at least 6 months post-treatment
  - With 40 Gy in 15 fractions, better cosmetic outcome and soft tissue toxicity
- An acceptable standard of care for nearly all patients with early breast cancer treated with breast conserving surgery.

Phase III Randomized Trials –Moderate Hypofx
2.4- 4 Gy per day, 52-72 Gy, 19-30 txs

Study	Median FU, mo	Risk, GS, or NCCN	Technique	Regimen	BED, Gy	*n*	Outcome	Toxicity
Lukka et al. [15]	68	60% GS ≤6 31% GS 7 9% GS 8–10	3DCRT No IGRT	52.5 Gy/20 fx	62	466	5 yr FFBF 40% (NS)	Gr ≥3 2% (NS)
				66 Gy/33 fx	66	470	5 yr FFBF 43%	Gr ≥3 1%
Yeoh et al. [17]	90	n.s.	2D/3DCRT No IGRT	55 Gy/20 fx	66.8	108	7.5 yr FFBF 53% ($p < 0.05$)	Late GU; HR: 1.58 (95% CI, 1.01–2.47) favoring hypofractionation
							34%	
Dearnaley et al. [18]	51							Gr ≥2 GU 0% (NS) Gr ≥2 GI 1% (NS)
								Gr ≥2 GU 2% Gr ≥2 GI 4%
								Gr ≥2 GU 2% Gr ≥2 GI 4%
Kuban et al. [14]; Hoffman et al. [19]	60						%	5 yr Gr ≥2 GU 16% (NS) 5 yr Gr ≥2 GI 10% (NS)
							2%	5 yr Gr ≥2 GU 17% 5 yr Gr ≥2 GI 5%
Arcangeli et al. [12,13]	70						%	3 yr Gr ≥2 GU 16% (NS) 3 yr Gr ≥2 GI 17% (NS)
			100% 9 mo ADT				*p ss for GS ≥4 + 3	
				80 Gy/40 fx	80	85	5 yr FFBF 79%	3 yr Gr ≥2 GU 11% 3 yr Gr ≥2GI 14%
Pollack et al. [16]	68	34% GS ≤6 47% GS 7 19% GS 8–10	IMRT IGRT	70.2 Gy/26 fx	84	151	5 yr BCDF 23% (NS)	5 yr Gr ≥2 GU 13% ($p = 0.16$) 5 yr Gr ≥2 GI 9% (NS)
				78 Gy/36 fx	78	152	5 yr BCDF 21%	5 yr Gr ≥2 GU 13% 5 yr Gr ≥2 GI 9%

Outcomes and complication rates "similar" to conventional fx
85-90+ % PSADF LR/IR

RTOG 0415- 1115 pts
Non-inferior BF, sl ↑ complications

Koontz, Eur Urol 68:683, 2015

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[1], IB Akinlade[1], A Arowojolu[2], IA Babarinsa[2], RI Agwimah[3] and IF Adewole[2]

[1]Department of Radiotherapy, [2]Department of Obstetrics & Gyneacology, University College Hospital, Ibadan and [3]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

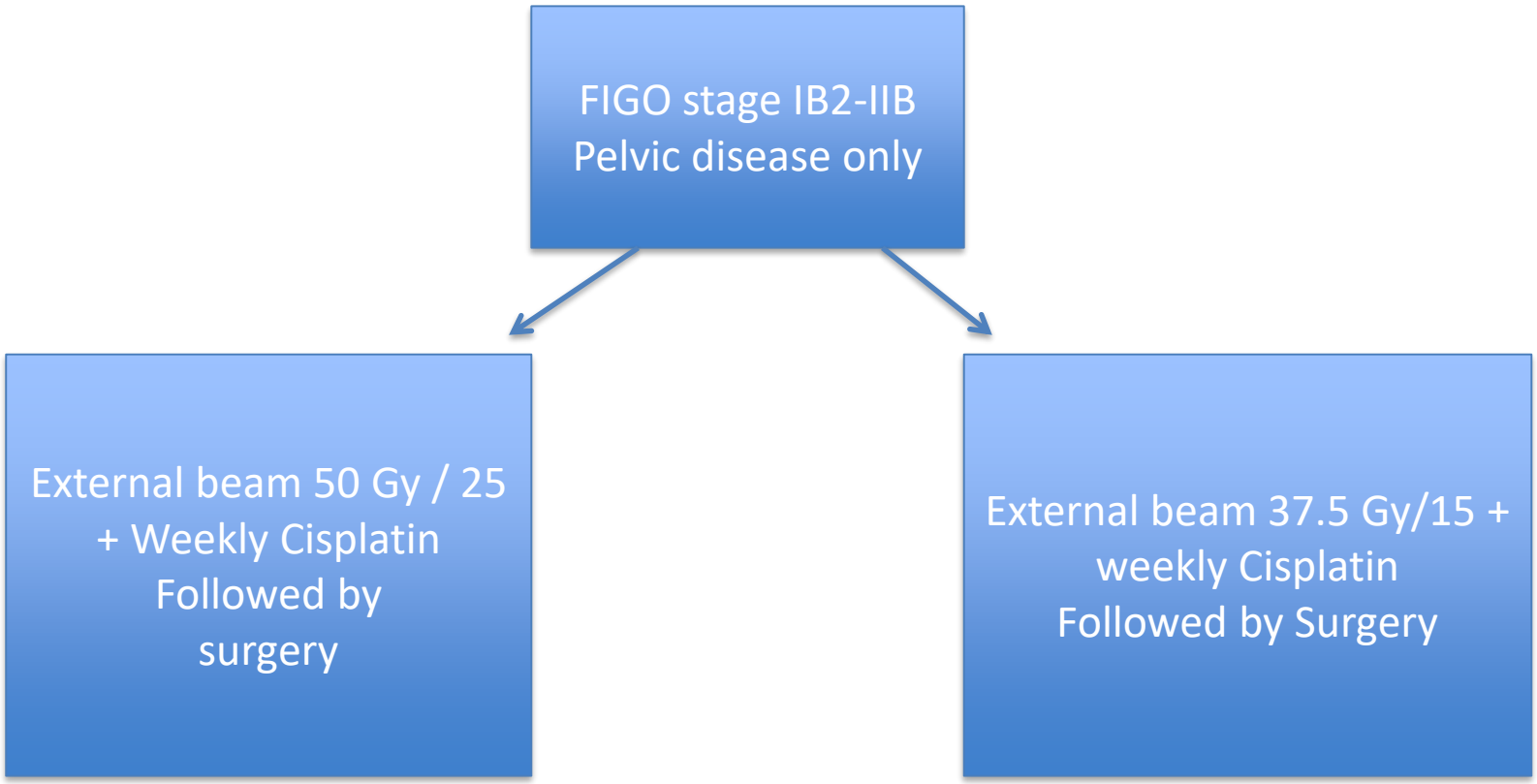
Hypofraction: BED and EQD2

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>

Definitive Trial: Phase II - No brachytherapy



Definitive Trial: No brachytherapy

- Surgery:
  - Radical hysterectomy 4 -6 weeks after radiation with removal of only abnormal nodes at that surgery and sampling of pelvic and para-aortics
  - If positive para-aortics – treatment with radiation therapy
  - No surgery – if progression of disease

Definitive Trial: No brachytherapy

- Chemotherapy:
  - Weekly cisplatin – will give 5 courses in both arms
- Endpoints:
  - Primary: PRO –patient reported outcome(EPIC) and Cervix Subscale from FACT
  - Secondary: relapse free survival, overall survival, complications: including days in hospital after surgery and blood transfusion, pathological response

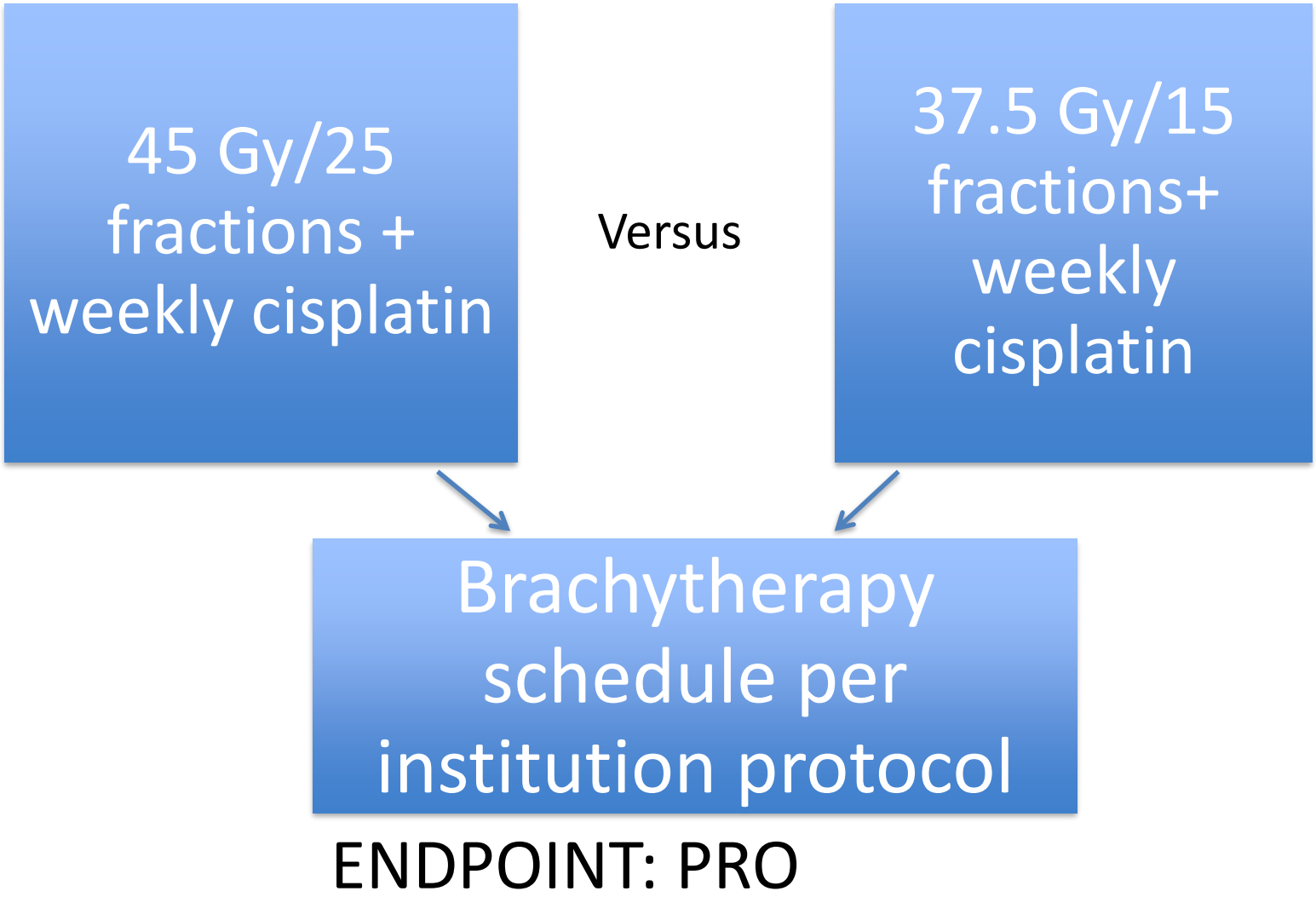
Definitive Trial: No brachytherapy

Time Point	Purpose
Before RT	Baseline
2 weeks after RT start	Compare early acute toxicity
End of RT/chmotherapy (at 5 weeks in both arm)	Maximum difference in acute toxicity
4-6 Weeks after RT (before surgery)	Compare resolution of acute toxicity
6 months after RT	Compare toxicity after surgery
1 year from the start of RT	Early chronic toxicity
2 years from the start of RT	Long term toxicity

Definitive Trial: No brachytherapy

- Early stopping rules – after 10 enrolled patients/per center and then every 50 enrolled patients
- If increase toxicity seen – then terminate trial

Definitive CRT: Phase II Randomize



ENDPOINT: PRO

Definitive Trial: brachytherapy

- Chemotherapy: weekly cisplatin?
- Endpoints:
  - Primary: PRO – Expanded prostrate cancer index composite (EPIC) and Cervix Subscale from FACT Secondary: relapse free survival and overall survival and chronic complications

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)

Thank You