Gynecologic Cancer InterGroup
Cervix Cancer Research Network

Hypofractionation for Cervical Cancer

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Cervix Cancer Education Symposium, January 2019

Definitive Treatment: Hypofractionation EBRT

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

Advantages and Concerns

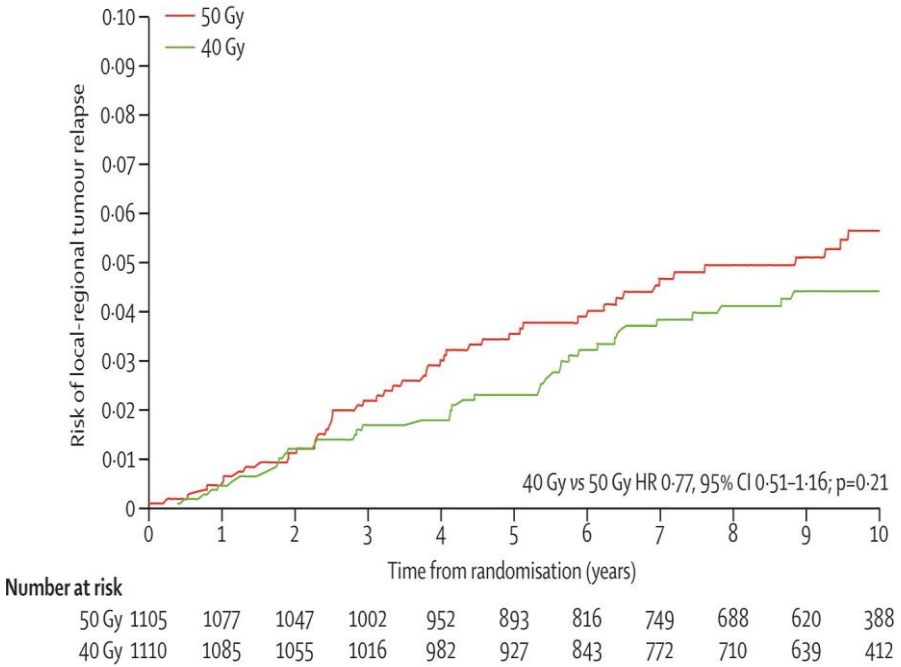
- Shortening fractionation raises concerns
  - Late toxicity in bowel = esp with long term survival
  - Conventional fractionation might be better at reducing local recurrences – especially nodal
- Inherent advantages
  - More convenient
  - Less expensive
  - With intact cervix could shorten treatment time

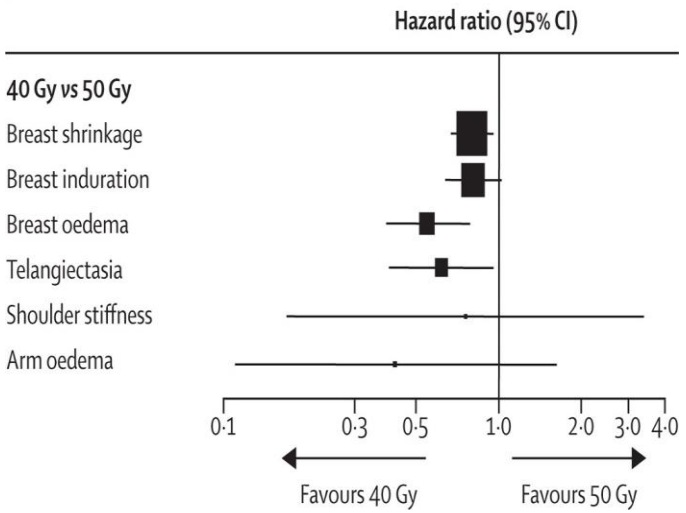
Precedent

- Breast
  - START trials, Canadian hypofractionation
- Rectal
  - Swedish Rectal Trial, Polish Rectal Trial, EORTC, Wash U
- Prostate
  - Extreme hypofractionation
- Pancreas
- SBRT, SRS

Hypofractionated WBI

START B





Haviland et al, Lancet Oncol 14:1086-94, 2013

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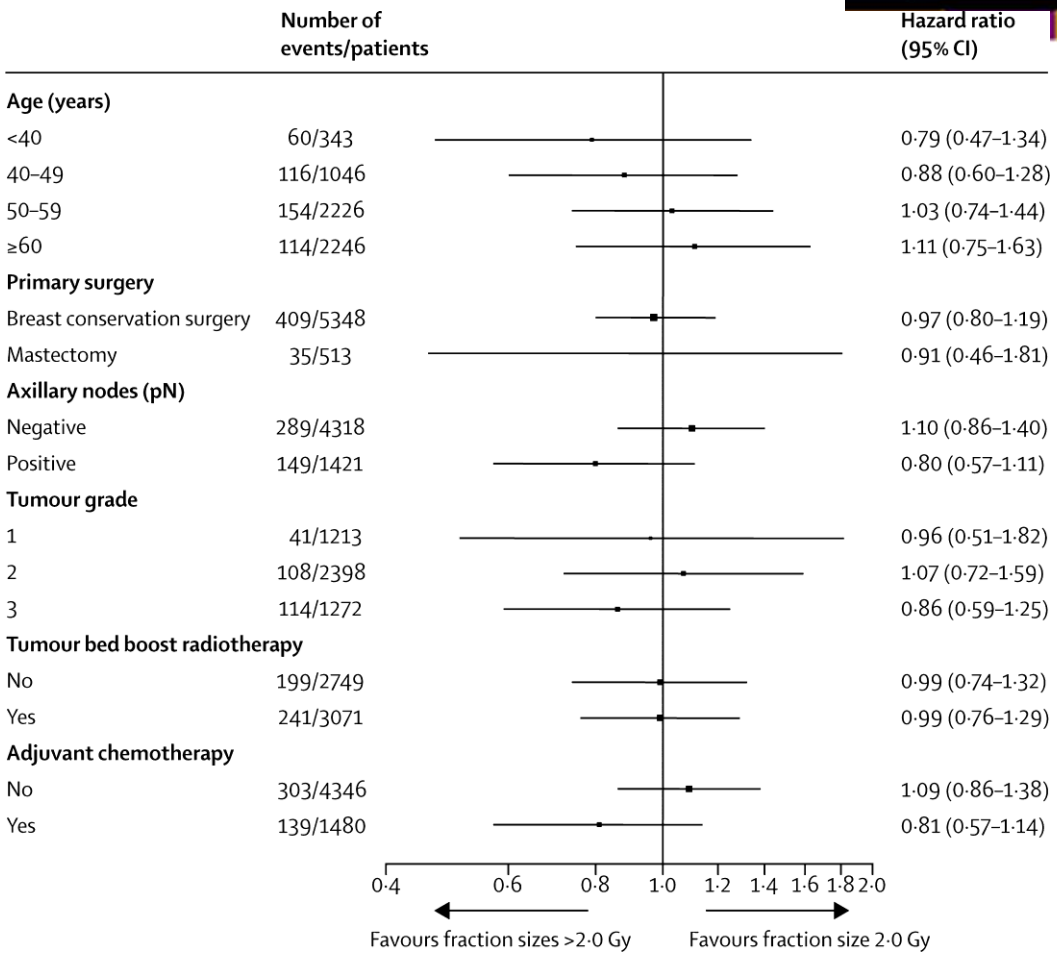
Meta-analysis for local-regional relapse



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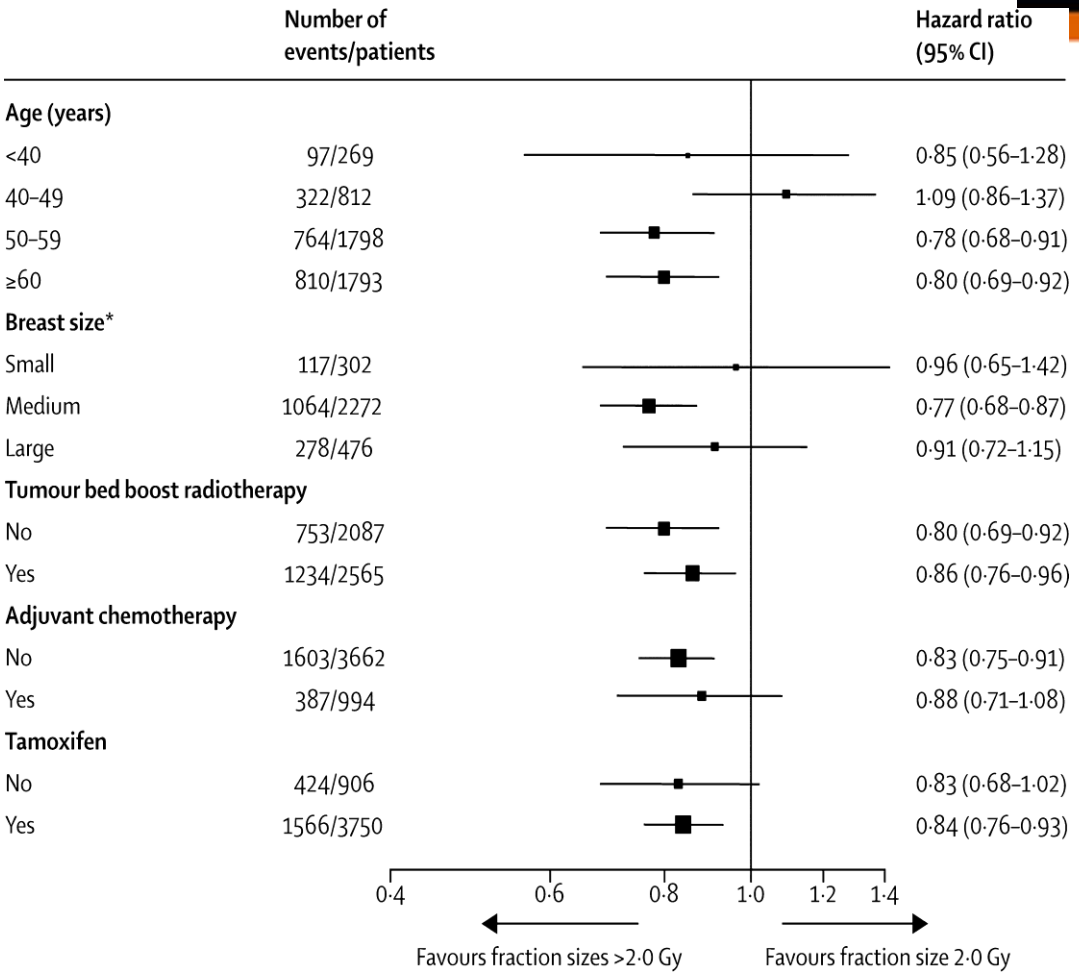
Meta-analysis for complications



Cervix Cancer Education Symposium, January 2019

Haviland et al, Lancet Oncol 14:1086-94, 2013

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MD Anderson trial

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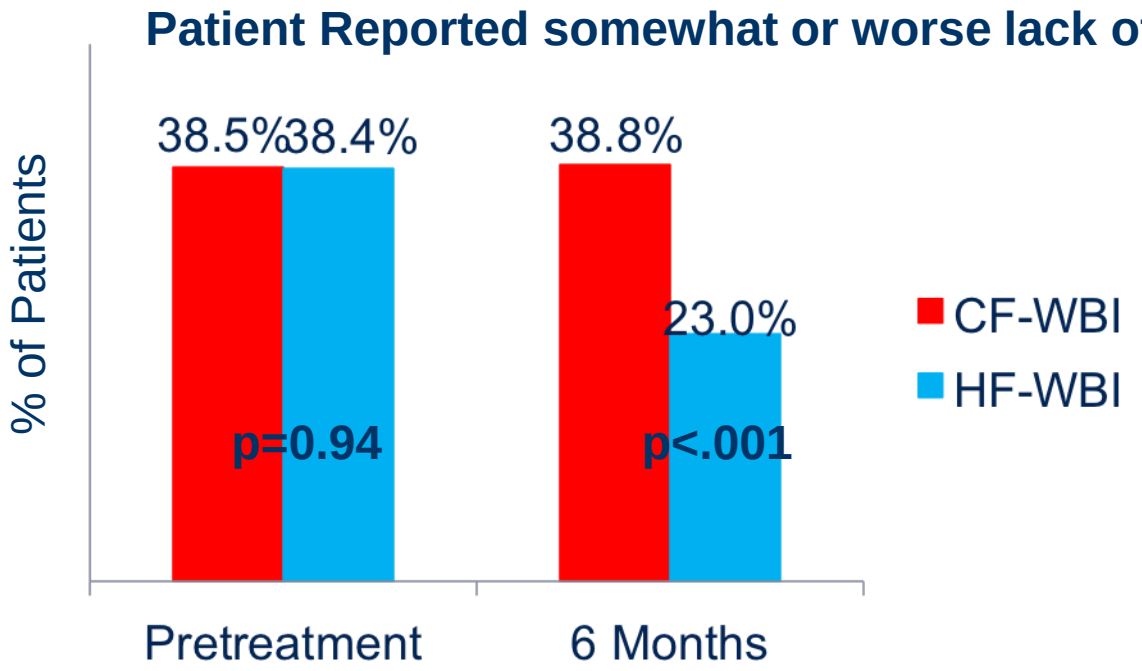
An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

	Dose to Whole Breast/ # Fractions	Dose to Tumor Bed Boost/ #Fractions	Total Days of RT
CF-WBI	50G**MD Anderson trial**/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

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**

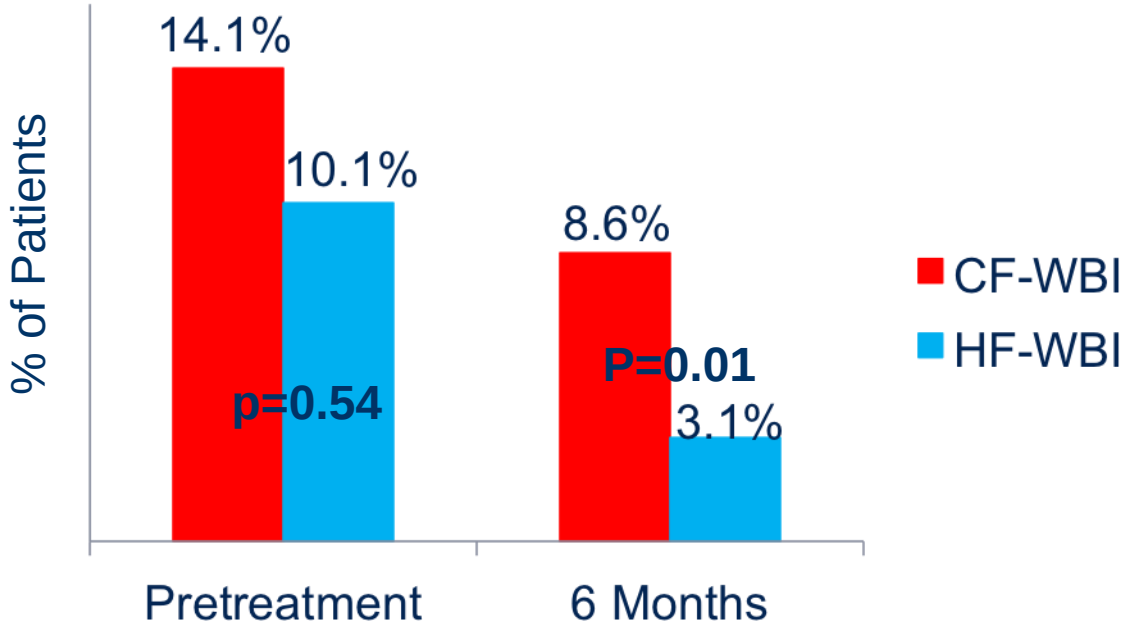


Shaitelman et al., JAMA Oncology 94:338-48, 2016

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.

Long term results of randomized trial of preop short course vs conventional

Bujko K et al Polish Colorectal Study group: *Br J Surg* 2006;93:1215

- Randomized trial, n=316 with median f/u 48 months
  - chemoradiation (FU/leucovorin) 50.4 Gy in 28 fractions preoperatively vs 25Gy in 5 fractions
  - TME 7 days after short course and 4-6 weeks post long course
- cT3T4, treatment goal was sphincter preservation with secondary survival. LR, DM, and late toxicity
- Fields were low pelvis standard bony landmark fields
- If outback chemotherapy was given it was 4 months for standard fractionation and 6 months for short course
- Q 6 month exams and CT X 3 years then yearly
- LR was any recurrence in the RT field

Long term results of randomized trial of preop short course vs conventional

Bujko K et al Polish Colorectal Study group: *Br J Surg* 2006;93:1215

- Acute effects

	Short course	Standard
Gr3/4 acute	3.2	18.2

	Short course	Standard
compliance	97.9	69.2

Long term results of randomized trial of preop short course vs conventional

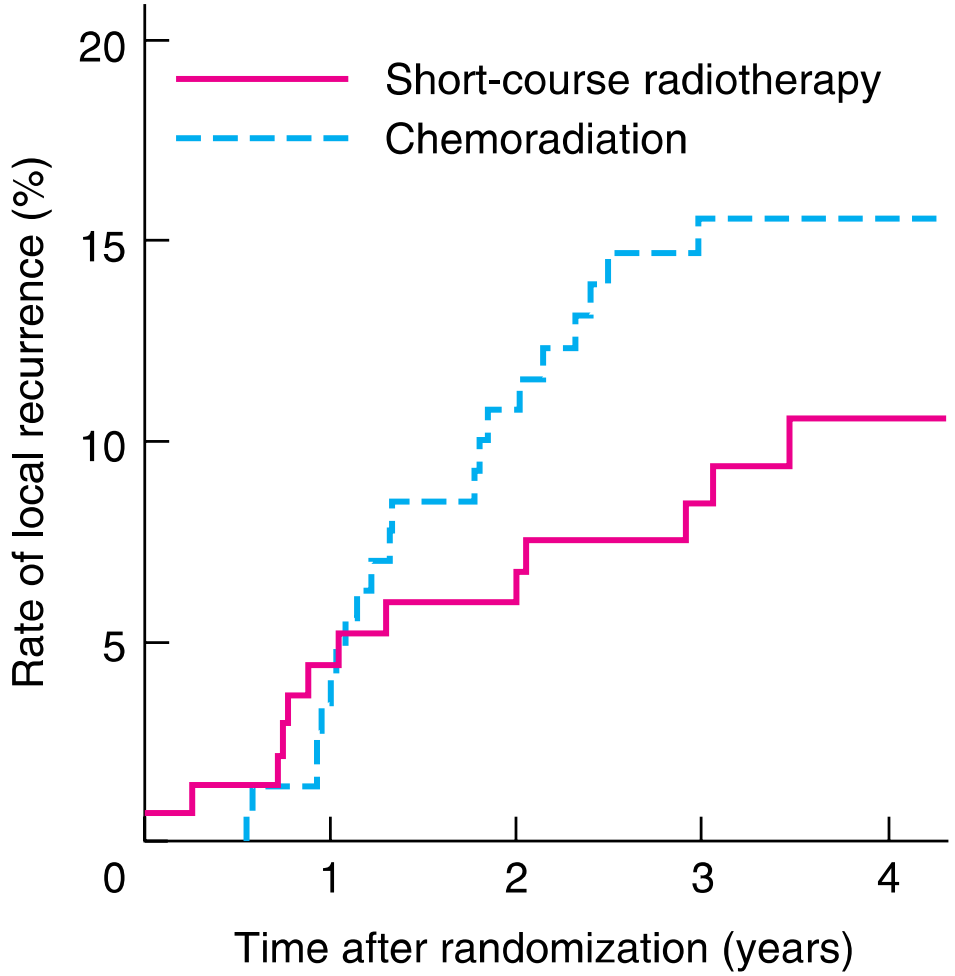
Bujko K et al Polish Colorectal Study group: *Br J Surg* 2006;93:1215

	cPR N(+)	**cPR**	**cPR T1/2**	**cPR T3/4**	**OS**	**DFS_4**
Short course	47.6	0.7	39.5	59.9	67.2	58.4
std	31.6	16.1	45.6	37.7	66.2	55.6

Long term results of randomized trial of preop short course vs conventional

Bujko K et al Polish Colorectal Study group: *Br J Surg* 2006;93:1215

	Actuarial LR $(\%)_4$	**Severe late complications**
Short course	10.6	10.1
Stnd	15.6	7.1



No. at risk

Short-course radiotherapy	146	125	118	100	46
Chemoradiation	149	136	116	98	53

Bujko et al *Br J Surg* 2006

- Crude late toxicity 28.3 v 27, short vs stnd
- Crude late severe toxicity was 10 vs 7 %, short vs standard
- Short follow-up
- Await australian trial and stockholm III trial has 5 fractions with immediate vs delayed surgery

Table 2 Intention-to-treat analysis of severe late toxic effects in 279 patients*

	Short-course radiotherapy ($n = 138$)	Chemoradiation ($n = 141$)
Small/large intestine†	7 (5·1)	2 (1·4)
Urinary bladder	2 (1·4)	1 (0·7)
Skin (non-healing perineal wound)	0	4 (2·8)
Urether	1 (0·7)	1 (0·7)
Nerves: motor function	3 (2·2)	2 (1·4)
Nerves: sensory function	1 (0·7)	1 (0·7)
Nerves: pain	0	1 (0·7)
Postoperative hernia requiring surgery	1 (0·7)	1 (0·7)
Fracture of femoral neck	1 (0·7)	0
Total complications	16 in 14 patients	13 in 10 patients

Bujko et al *Br J Surg* 2006

Association b/w path response in metastatic nodes after preop therapy and risk of DM – Polish study

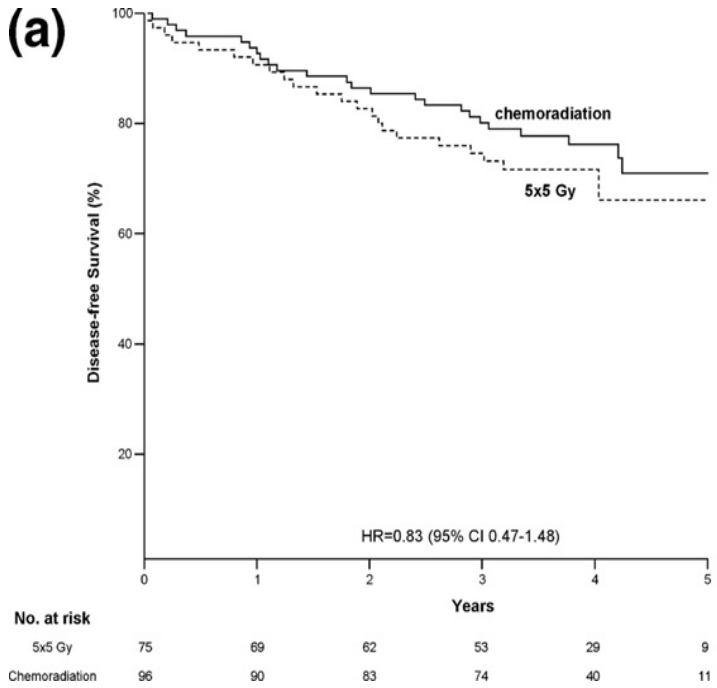
Bujko K et al *IJROBP* 2007;67:369

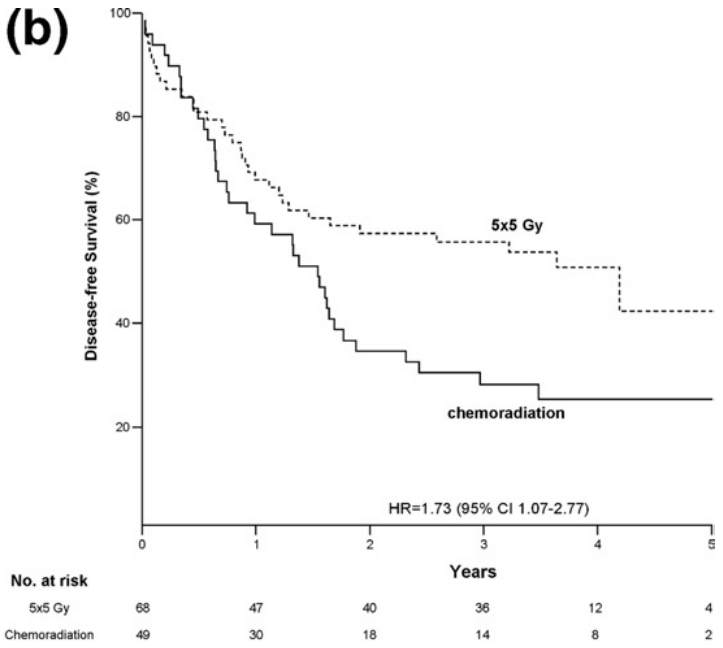
- N=316 randomized b/w 5Gy X 5 followed by 6 months chemo vs 1.8 Gy X 28 followed by 4 months chemotherapy. Surgery 1 week after short course and 4-6 weeks post standard
- RT four or three filed prone 1 cm above sacral promontory
- DFS, LC and DM similar in both arms
- ypN only independent prognostic factor for DFS
- ypN0 DFS similar
- ypN(+) DFS worse in standard arm 51% vs 25%
  - Same group LR 14% vs 27%
- More favorable path prognostic factors observed in chemoRT group

but no difference in long term outcomes

ypN0

ypN(+)





Bujko et al IJROBP 2007

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)
							%	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

How is Gyn the same? different?

- Likely not preop as in rectal
  - high risk StageIb cervical cancer, endometrial post op?
- Contains more tissue than prostate
  - true pelvis rather than to confluence of arteries
  - But….no IMRT used in these studies
- Same bowel concerns as pancreas and rectal…..
- Life span – many longer than pancreas but equivalent to rectal and prostate

Brachytherapy versus radical hysterectomy – non-randomized matched phase II study

Cetina et al, World Journal of Surgical Oncology 2009

- 80 pts – 40 in each arm
- Standard arm – external beam with cisplatin followed by 1-2 brachytherapy procedures for a total dose of 85 Gy
- For the surgery arm – type III radical hysterectomy with bilateral pelvic lymph node dissection and para-aortic lymph node sampling within 7 weeks of radiation therapy
  - Post-op vaginal brachytherapy was give to patients with one or more high-risk factors for recurrence

Brachytherapy versus radical hysterectomy – non-randomized matched phase II study

Cetina et al, World Journal of Surgical Oncology 2009

Treatment	Surgery	Brachytherapy
Number	40	40
Stage		
IB2	9 (22%)	9 (22%)
IIA	4 (10%)	4 (10%)
IIB	27 (68%)	27 (68%)
Histology		
Squamous	28 (70%)	28 (70%)
Adenocarcinoma	8 (20%)	8 (20%)
Adenosquamous	4 (10%)	4 (10%)

Brachytherapy versus radical hysterectomy – non-randomized matched phase II study

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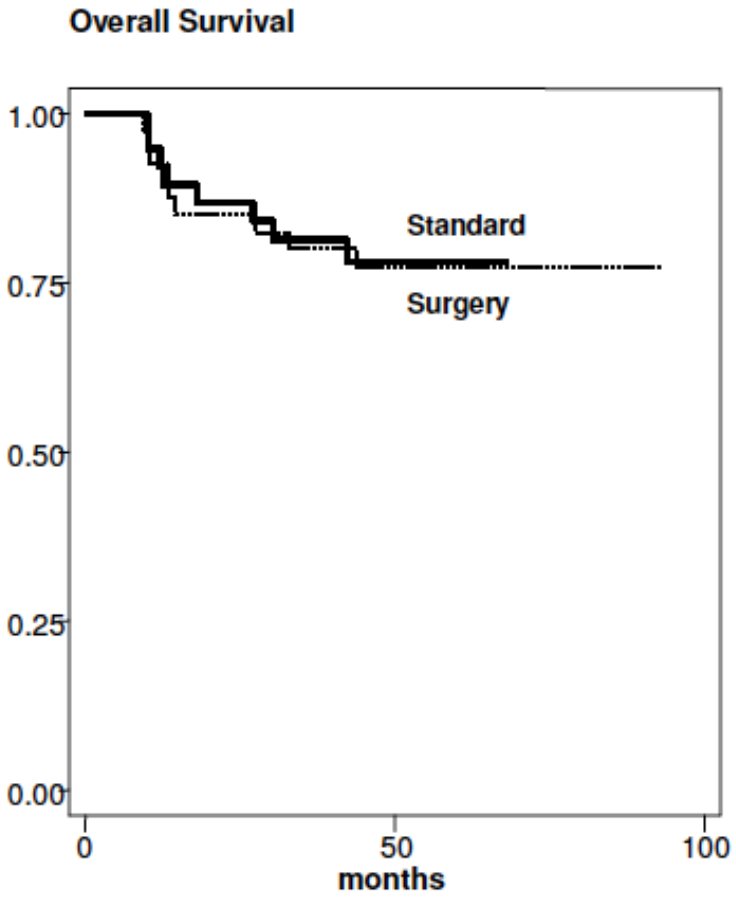
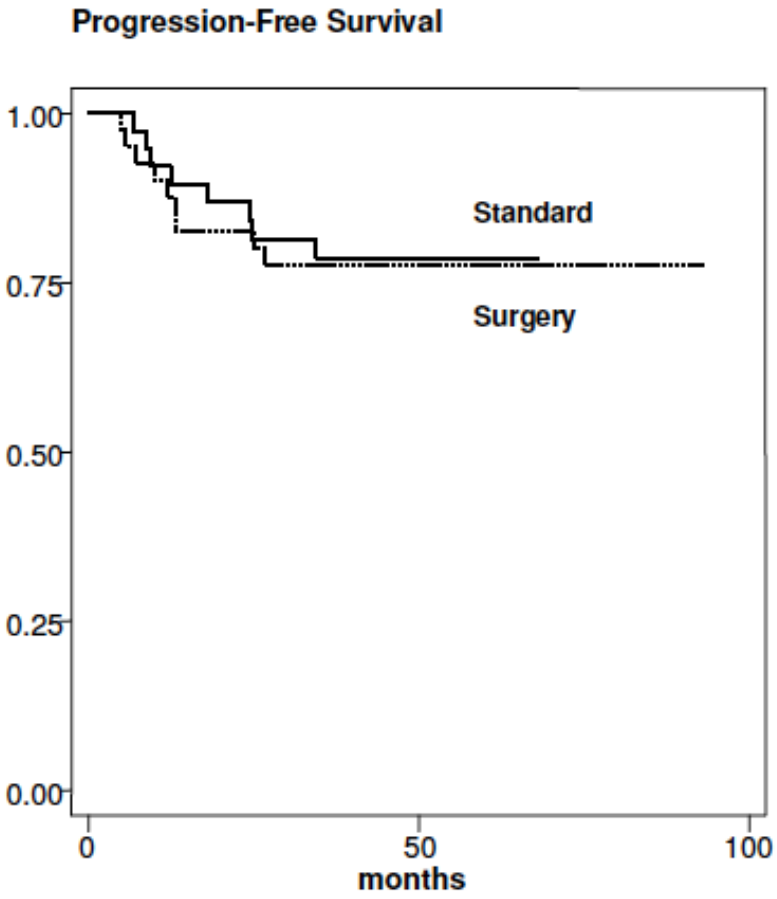




Brachytherapy versus radical hysterectomy – non-randomized matched phase II study

Cetina et al, World Journal of Surgical Oncology 2009

Treatment	Surgery				Brachytherapy				
Toxicity/Grade	1	2	3	4	1	2	3	4	
Hydronephrosis	3	3	0	0	0	0	0	0	P < 0.016
Proctitis	1	3	0	0	1	10	1	1	P < 0.008
Cystitis	0	1	2	0	0	0	2	1	P = 0.785

Phase III study – Randomize Surgery vs. Brachytherapy

Cetina et al, Annals of Oncology, 2013

- FIGO stage IB2-IIB
- No evidence of cancer in para-aortic lymph nodes via CT scan
- Randomized before chemoradiation
- Chemotherapy – cisplatin 40/m^2 and gemcitabine 125 mg/m^2 weekly for 6 weeks
- External beam for all pts. – 50.4 Gy/28 fx

Phase III study – Randomize Surgery vs. Brachytherapy

Cetina et al, Annals of Oncology, 2013

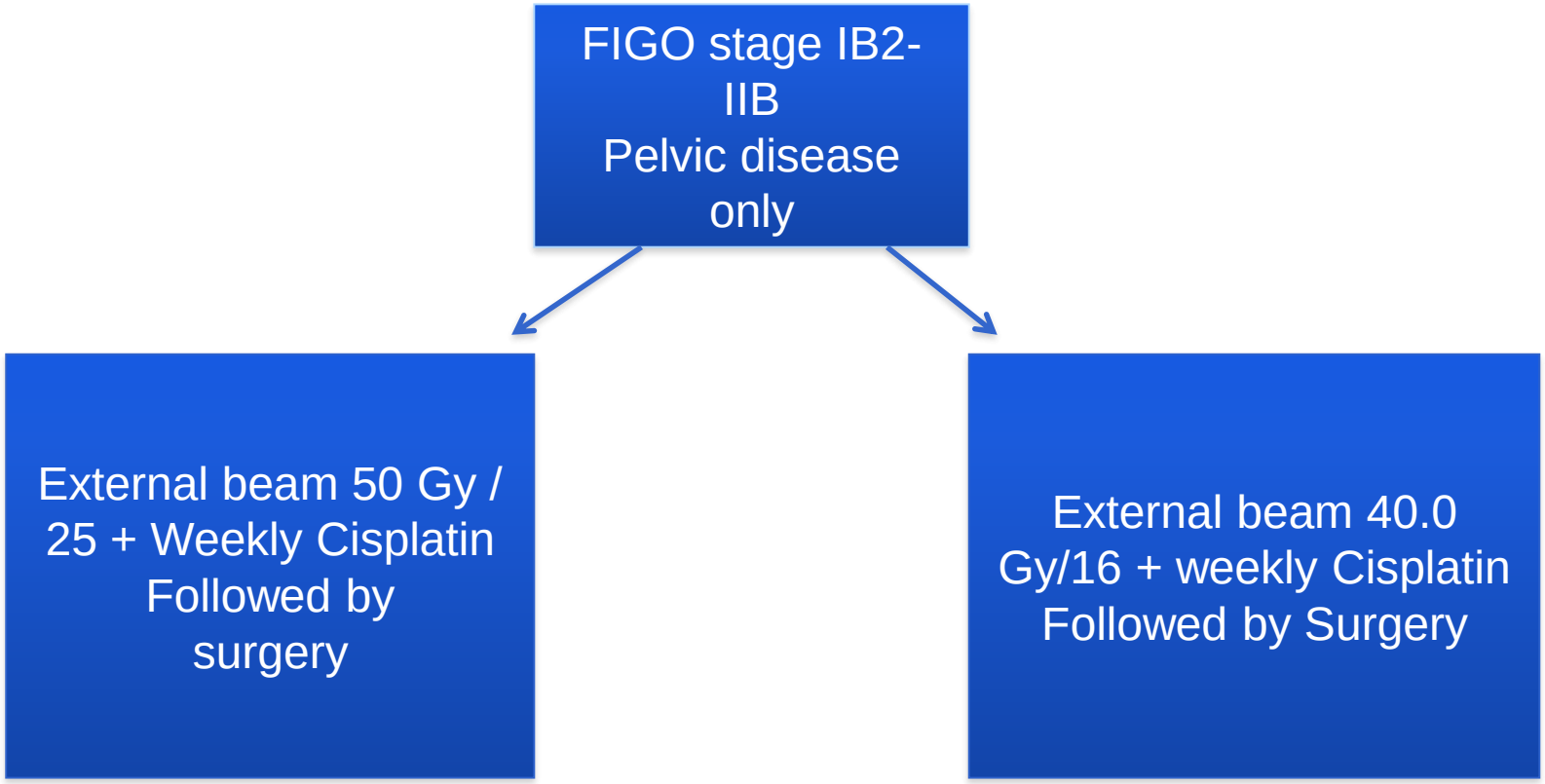
Procedure/results	Received intervention	Intent – to - treat
RH completed	86 (100%)	86 (77.4%)
Pathologic CR	62 (72%)	62 (56%)
Pathologic PR	24 (28%)	24 (21.6%)
Residual tumor 0.6-2 cm	16 (18.6%)	16 (14.4%)
Residual tumor 2-4	6 (7%)	6 (5.4%)
Residual tumor > 4 cm	2 (2.3%)	2 (1.8%)
Surgical margins in parametria		
Positive	2 (2.3%)	2 (1.8%)
Negative	84 (97.6%)	84 (75.6%)
Pelvic lymph nodes		
Positive	9 (10.4%)	9 (8.1%)
Negative	77 (89.5)	77 (69.3)

Phase III study – Randomize Surgery vs. Brachytherapy

Cetina et al, Annals of Oncology, 2013

- Conclusions:
  - RH after chemoRT did not improve survival outcomes compared to RT plus brachytherapy
  - RH after chemoRT is feasible and safe in hands of experience surgeons
  - The study strongly suggests that patients treated with effective chemoRT + RH instead of standard chemo RT + brachytherapy does not compromise survival – especially in settings where brachytherapy resources are limited

Definitive Trial: Phase II - No brachytherapy



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

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 only in the standard arm
- Endpoints:
  - Primary: PRO –EORTC 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 20 enrolled patients
- If increase toxicity seen – then terminate trial

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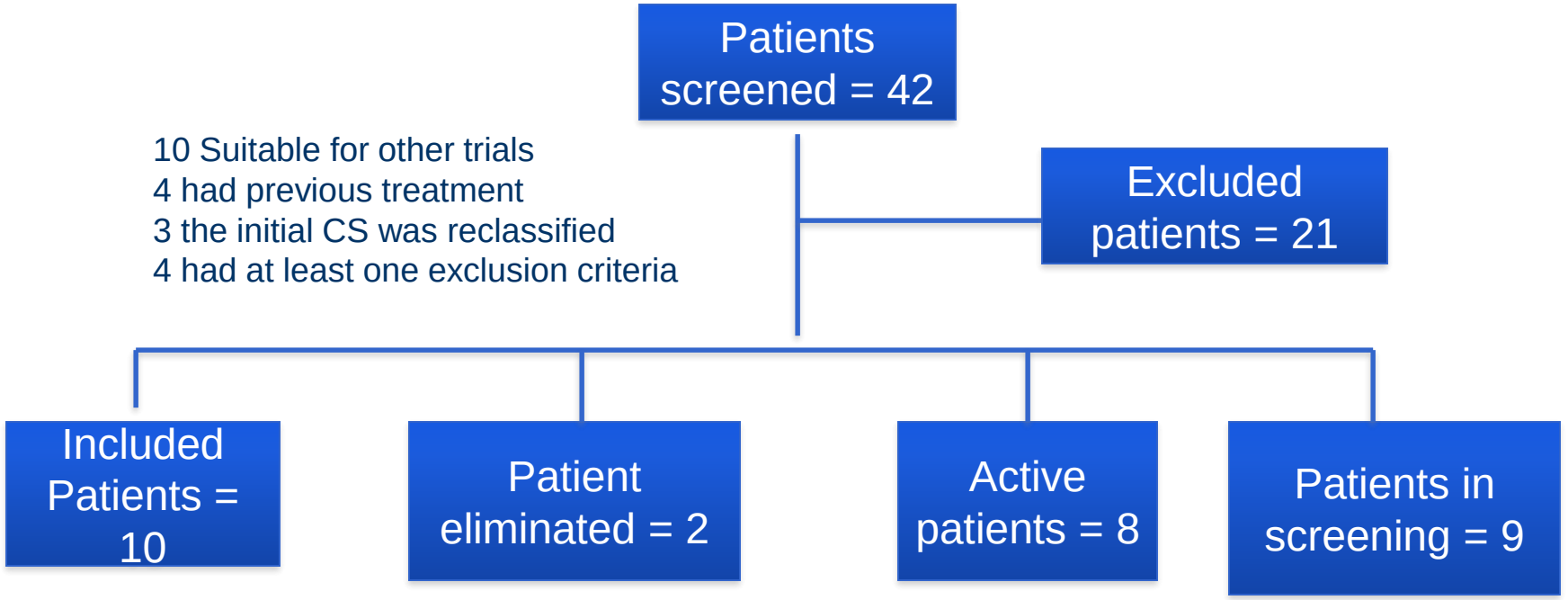
Hypofraction Trial in Mexico

Start of recruitment 11/20/2017



Cervix Cancer Education Symposium, January 2019

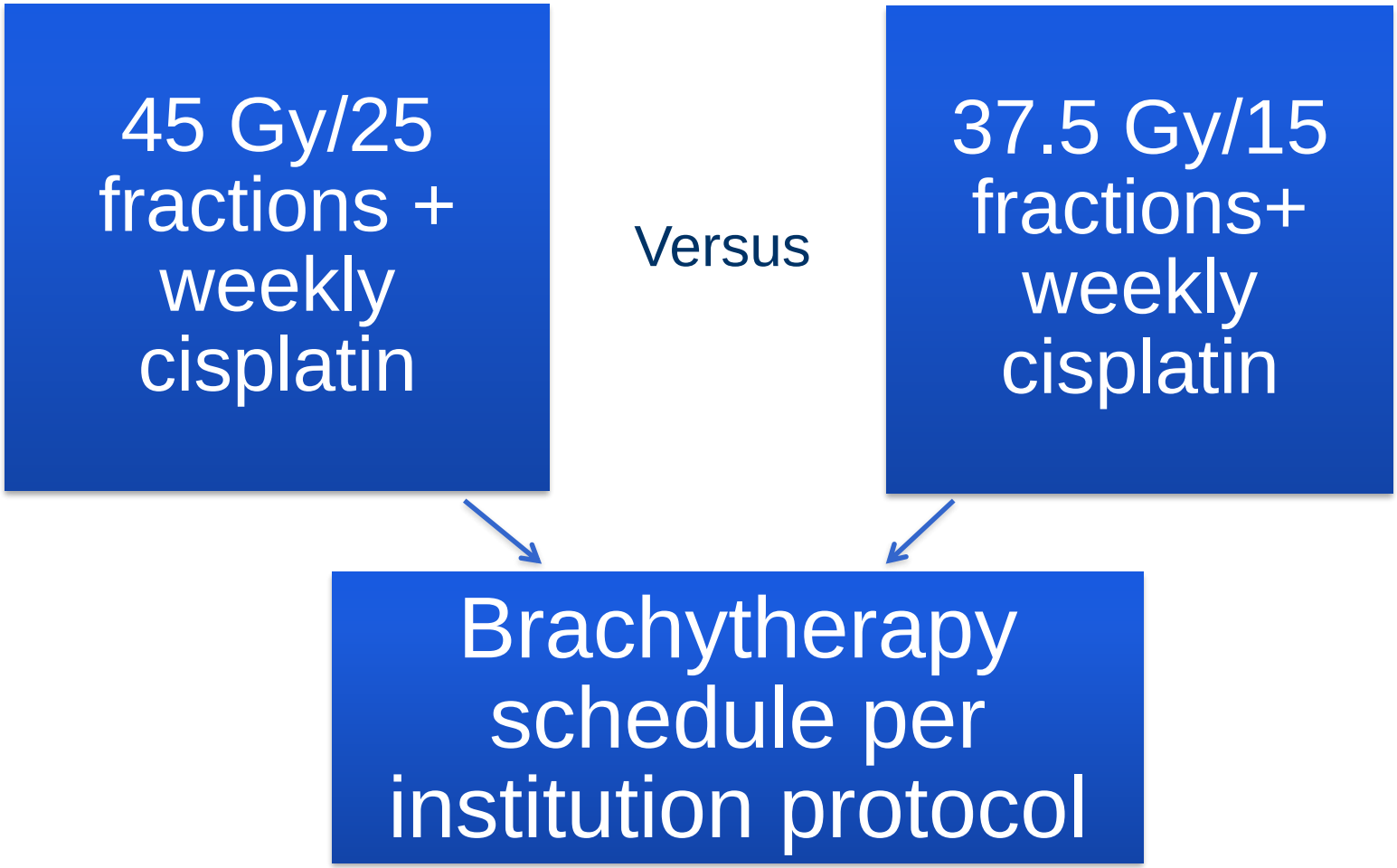
Hypofractionation Trial – Mexico Data

Age	Mean (min-max)	45 (24-69)
Clinical Stage	IB2	5
	IIA2	2
	IIB	2
Histology	Squamous Cell carcinoma	9
Grade	2	6
	3	3
LVSI	NO	7
	Yes	2
Treatment	Standard	4
	Hypofraction	5

Hypofractionation Mexico

	Pain	Dermatitis	Cystitis	Colitis	Trans-rectal Bleeding
0		0			0
1	1 (11%)	0	1 (11%)	2 (22%)	0
2		0		1 (11%)	0
3		0			0
4		0			0
5		0			0

Definitive CRT: Phase II Randomize



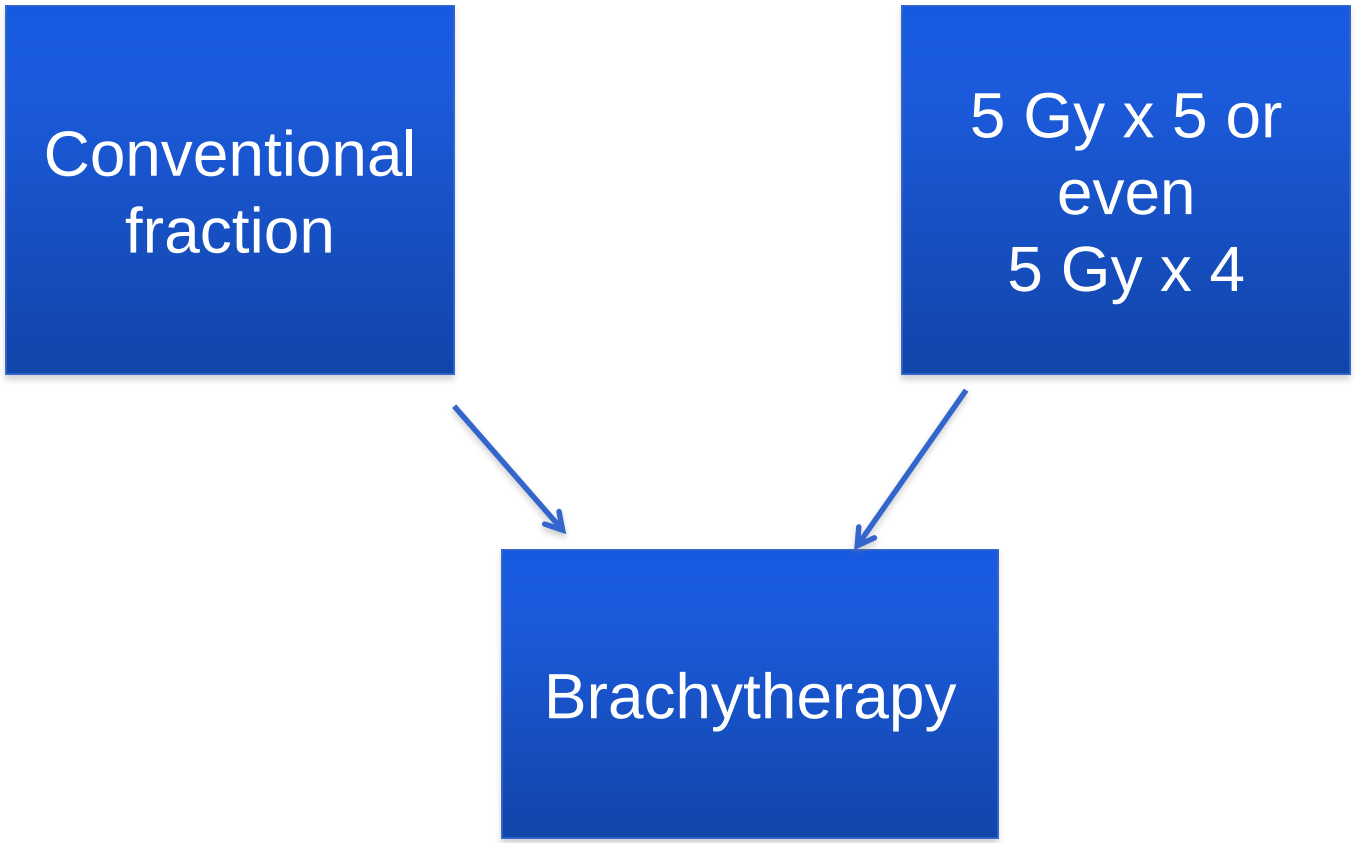
ENDPOINT: PRO

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

However – can we make it even shorter?????

Thought provoking Trial



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Thank You