

Protocolos de tratamento (RTOGs) estudos envolvendo novos protocolos CHHip trial - Fast Forward

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A Beneficência Portuguesa de São Paulo

Declaração de conflito de interesse

- Sem conflito de interesse

“Se o Radioterapeuta fosse esperar por bases científicas para tratar o primeiro paciente, a Radioterapia não teria começado”

Fowler

Fracionamento



Esterelidade sem reação de pele

Experiência do passado ...

“Doses grandes em poucos dias têm a desvantagem de não promover controle da lesão e desenvolver sequelas tardias”.

James D. Cox, Cancer 55:2105-11; 1985

“Frações maiores que 2 Gy/ dia produz sequelas tardias indesejáveis e a despeito do conforto para o paciente (menos tempo de tratamento) e a maior rotatividade do aparelho, HIPOFRACIONAMENTO NÃO DEVE SER INDICADO!

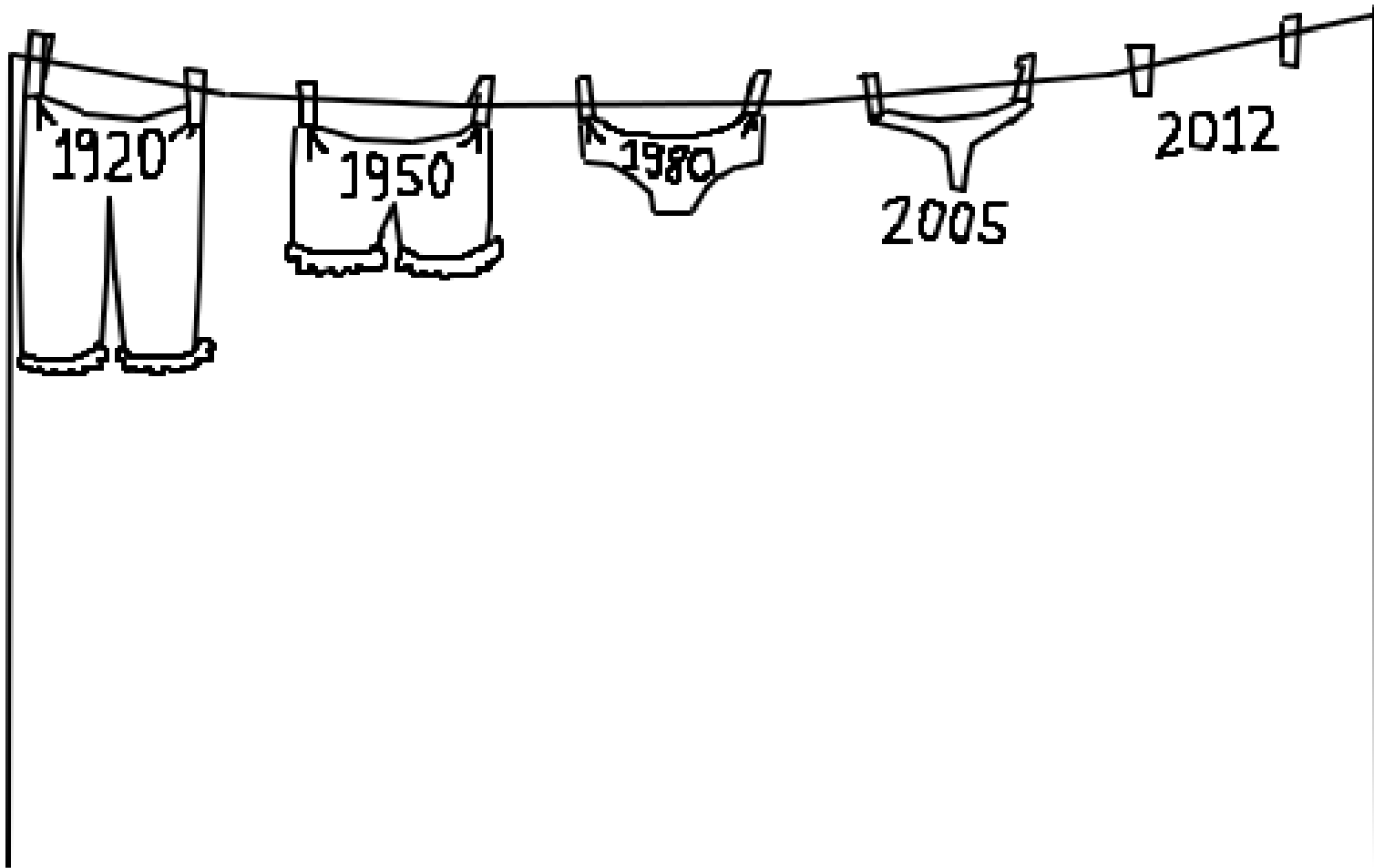
Gilbert H. Fletcher, Radiother Oncol 20: 10-15; 1991

Década de 70



*Noruega – gasto de aproximadamente US\$ 700.000 – toxicidade de 130 mulheres com Câncer de mama tratadas na década de 70

Evolução...

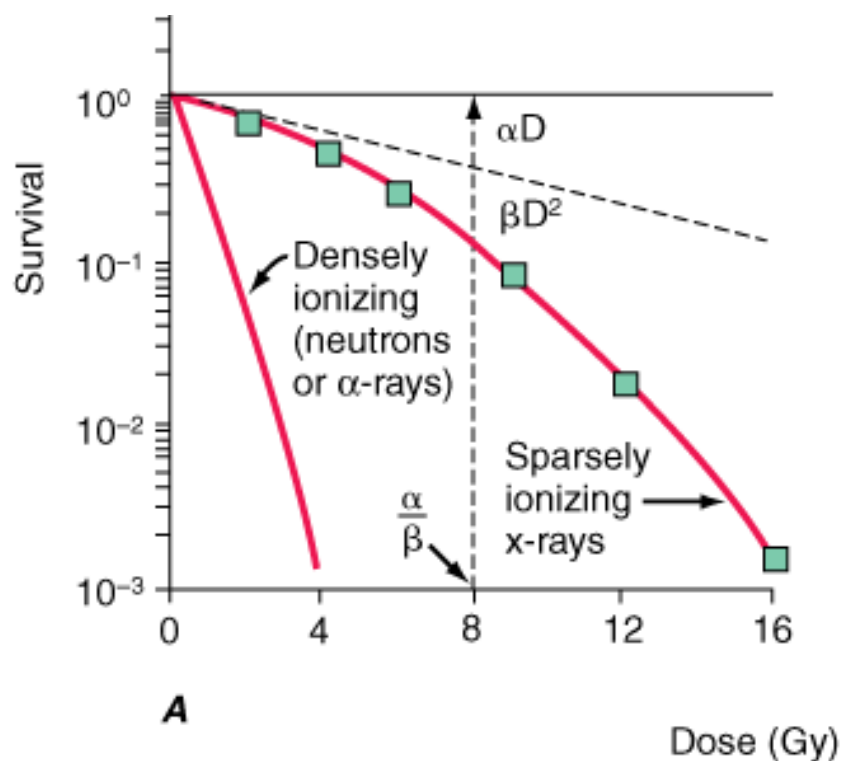


Dose x Fracionamento

Modelo Linear Quadrático

α = morte em evento único (componente linear)

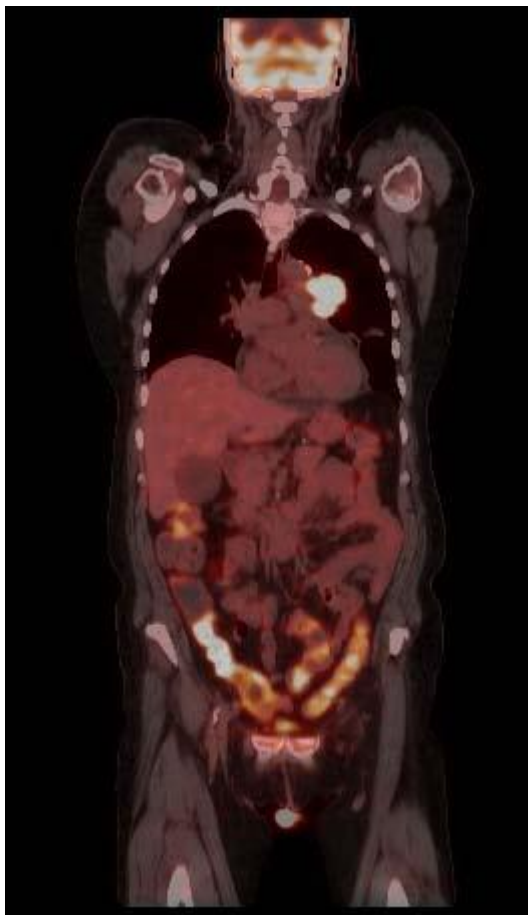
β = morte em eventos múltiplos (componente quadrático)



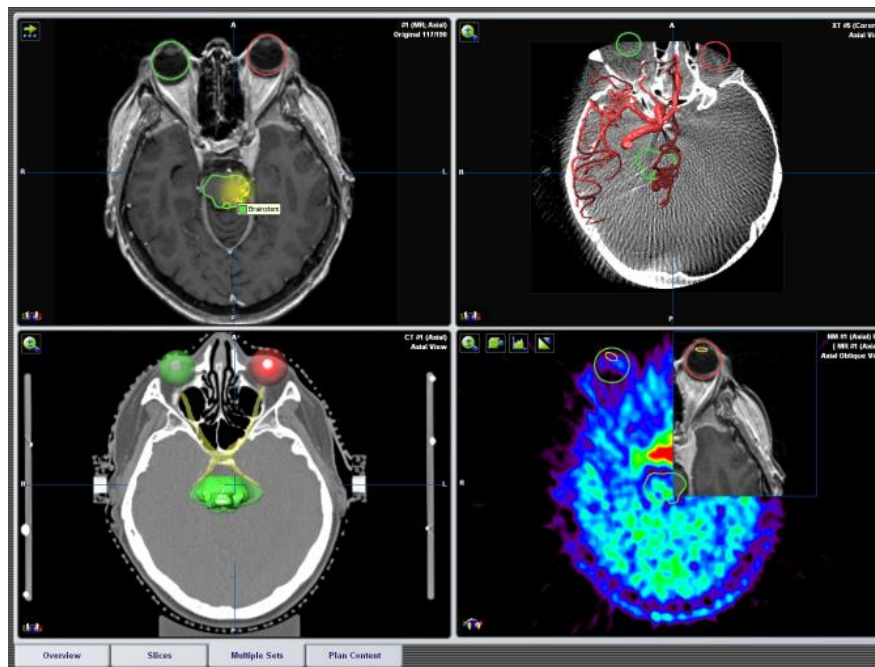
Efeitos precoces: α / β grande, pequena mudança devido ao fracionamento
 $\alpha / \beta = 10$

Efeitos tardios: α / β pequeno, grande mudança devido ao fracionamento
 $\alpha / \beta = 3$

Desenvolvimento tecnológico

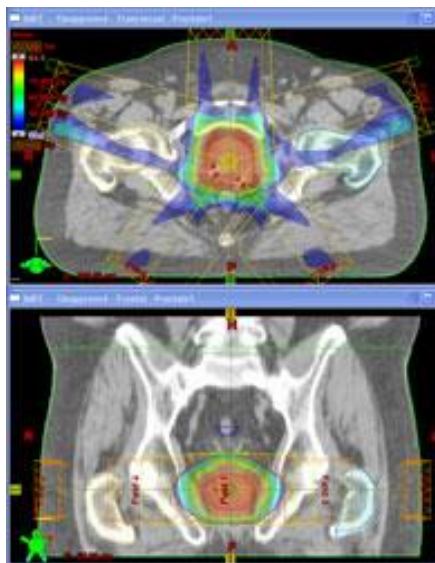


PET/CT

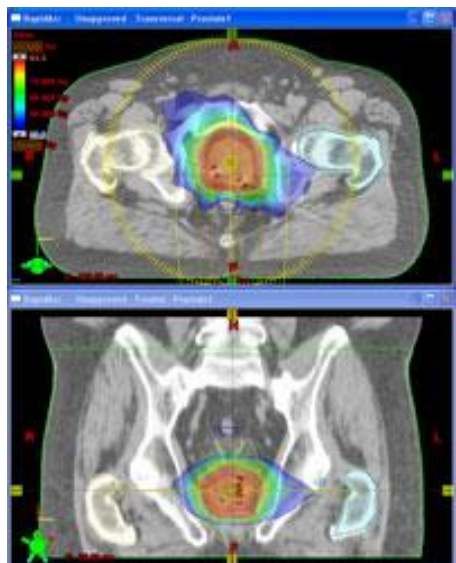


Ressonância magnética
Fusão de imagens

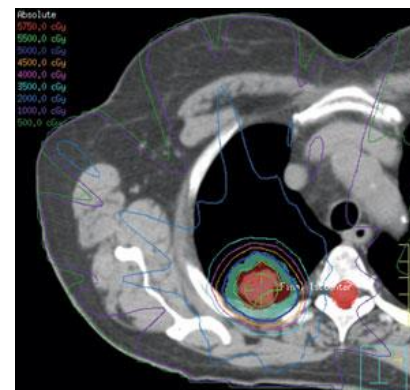
Desenvolvimento tecnológico



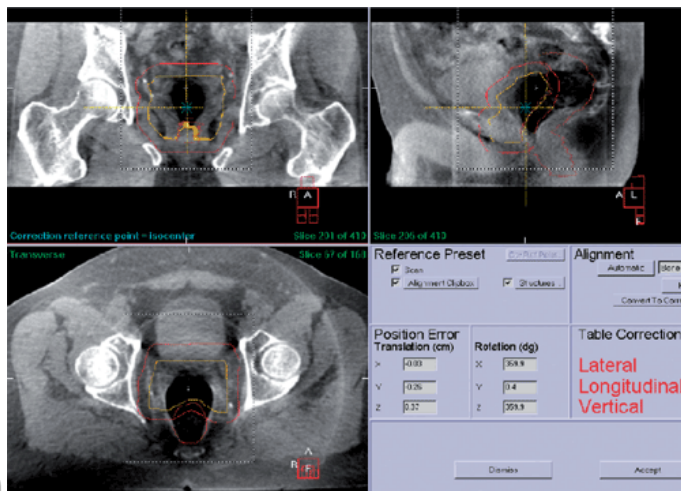
IMRT



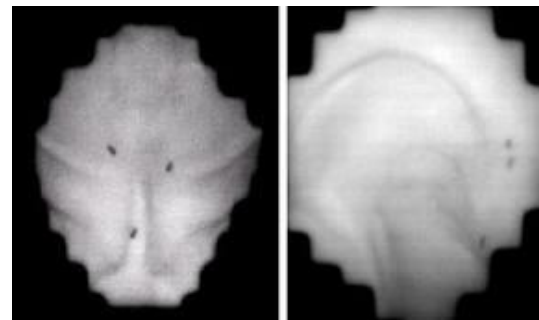
Rapid Arc



SBRT



IGRT



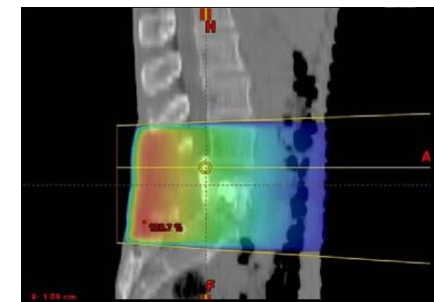
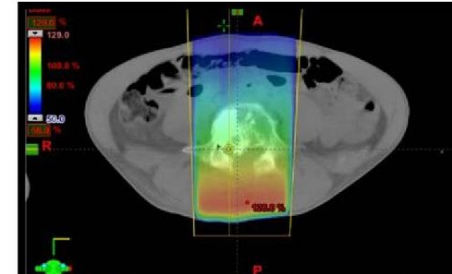
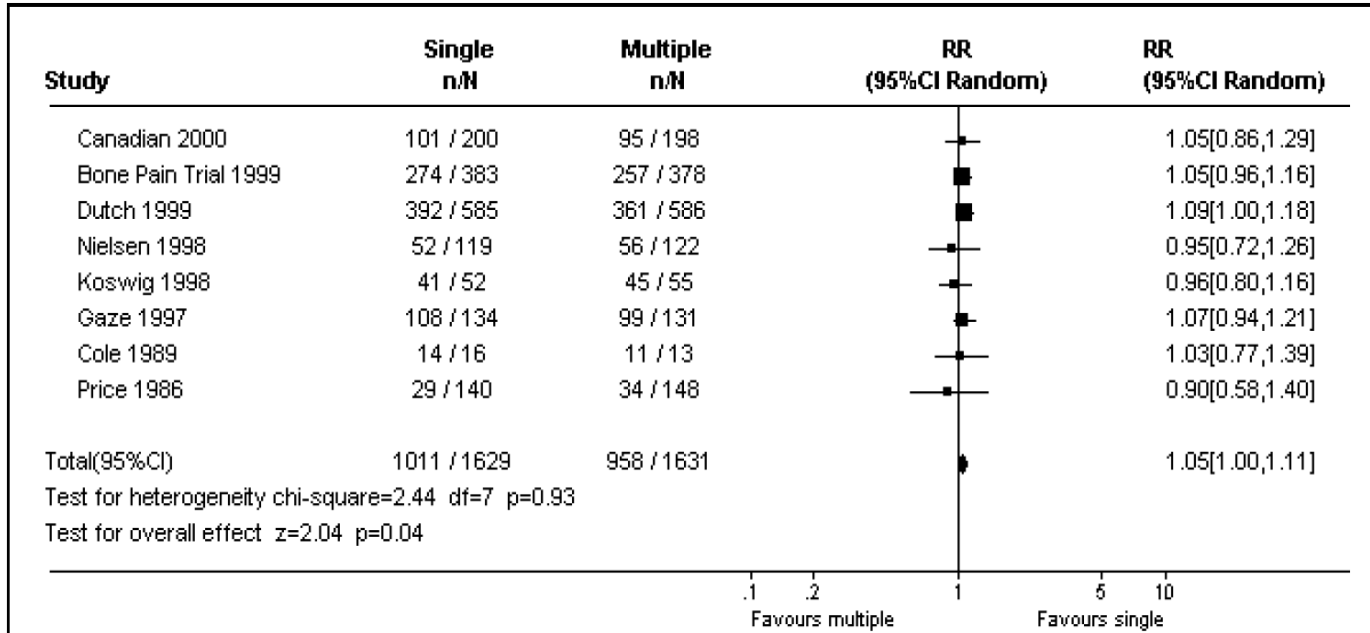
Definição

- Dose convencional – 1.8 a 2.0 Gy/dia
- **Doses por dia maiores** que a convencional em um **tempo menor** de tratamento
- Doses acima de 2.0 Gy/ dia
 - Moderado 2.4 a 4 Gy/dia – 15 a 30 frações
 - Extremo 6,5 a 10 Gy/dia – 4 a 7 frações
 - Radiocirurgia/Radioterapia estereotática

Hipofracionamento

Tratamento paliativo

Metástases Ósseas - Dor

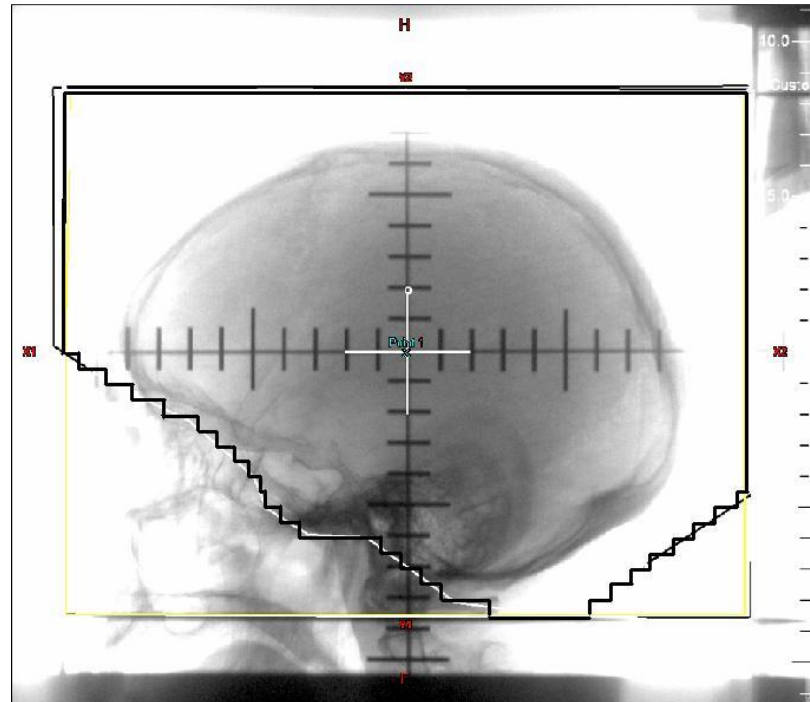


20 x 200 cGy
10 x 300 cGy

5 x 400 cGy
1 x 800 cGy

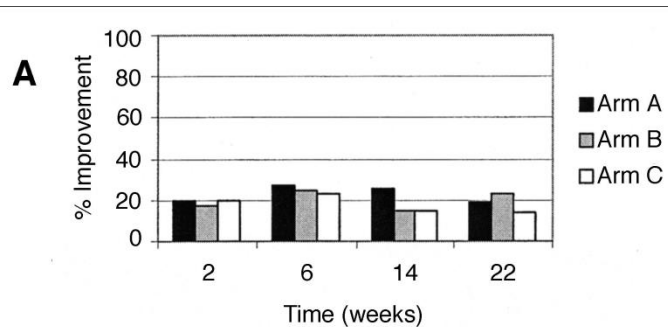
Metástases Cerebrais

- 20 x 200 cGy
- 15 x 250 cGy
- 10 x 300 cGy
- 5 x 400 cGy



Sintomas Respiratórios

Tosse

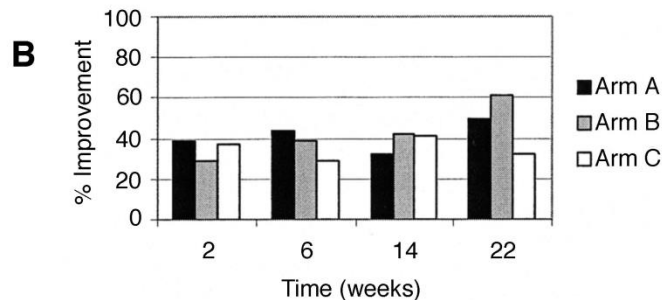


A - 2 x 8.5 Gy

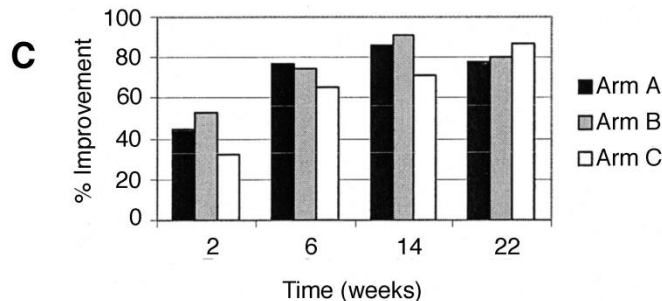
B - 15 x 2.8 Gy

C - 25 x 2.0 Gy

Dispneia



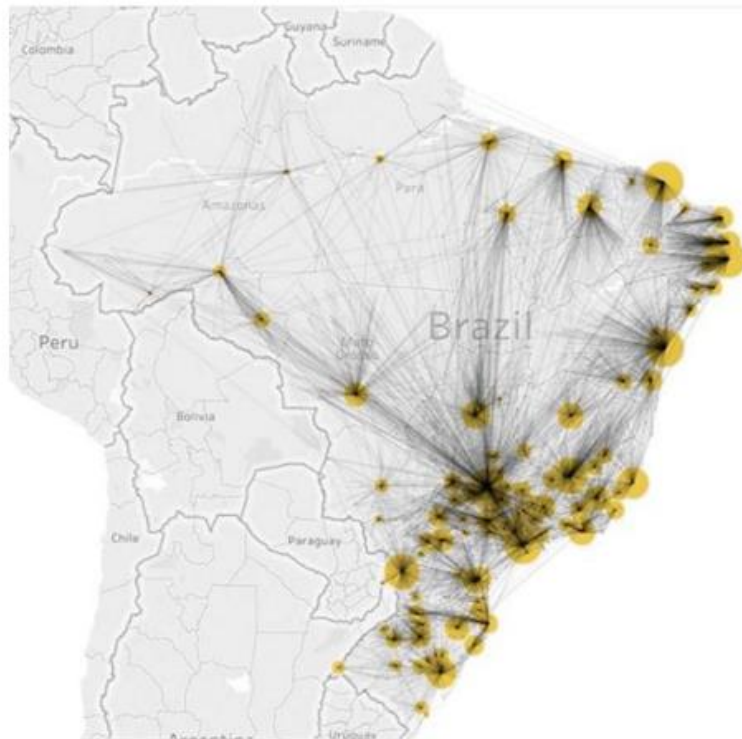
Sangramento



Sem diferença em toxicidade
e
sobrevivência entre os grupos

Hipofracionamento - Brasil

A distância média percorrida para **realizar tratamento** é de 72 km.



Legenda: O tamanho dos círculos representa a quantidade de procedimentos realizados por pacientes de outras cidades.

UF	Média de km percorridos para realizar o procedimento
AC	387,8
AL	47,9
AM	60,5
AP	1487,3
BA	121,7
CE	75,5
DF	610,6
ES	48,0
GO	104,3
MA	180,1
MG	64,8
MS	142,8
MT	333,9
PA	139,8
PB	82,2
PE	104,4
PI	239,9
PR	54,3
RJ	27,0
RN	61,0
RO	254,0
RR	1605,5
RS	48,7
SC	40,2
SE	89,0
SP	33,7
TO	524,3
Brasil	72,3

Fonte: Sociedade Brasileira de Radioterapia, 2018.

Hipofracionamento em Mama

INTERESSE...

- 20-30% das mulheres não recebem RT após cirurgia conservadora
 - Inconveniência do deslocamento diário
 - Custos
 - Ausência do trabalho ou do lar
 - Acesso aos serviços de RT
- Razão α / β baixa - benefício no hipofracionamento



Whelan T., Semin Radiat Oncol 18:257-264, 2008

Hipofracionamento em Mama

Estudo	N	Período	Esquema	Publicação
Canadense	1234	1993 -1996	42.5Gy/16f	2010
RMH/GOC	1410	1986-1998	42.9Gy/13f 39Gy/13f	2006
START A	2236	1998-2002	41.6Gy/13f 39Gy/13f	2008
START B	2215	1999-2001	40Gy/15f	2008
UK fast trial	915	2004-2007	28,5Gy/5f 30Gy/5f	2011

UK FAST TRIAL

Desenho do Estudo

- Idade ≥ 50 anos

- Estádios T1-T2N0

- 3 Braços

- Sem quimioterapia

- Recrutamento de
2004 a 2007

25 x 2 Gy

5 x 6 Gy semanal

5 x 5.7 Gy semanal

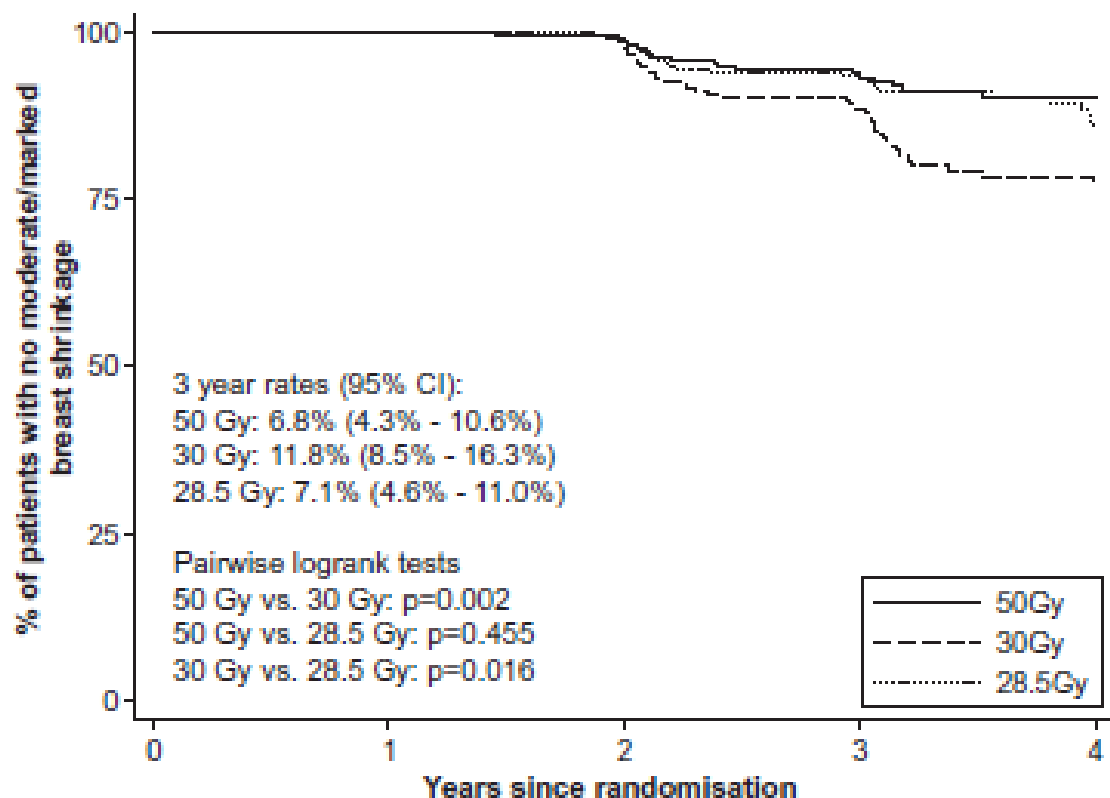
A.M. Brunt, ASTRO 2018 - FAST Phase III RCT of Radiotherapy Hypofractionation for Treatment of Early Breast Cancer: 10-Year Results

UK FAST TRIAL

Pior Grau de Complicação na Mama	50 Gy/25 fr	30 Gy/5 fr	28.5 Gy/5 fr
Durante Tratamento RTOG	N = 302	N = 308	N = 305
0	8 (7%)	28 (25%)	42 (39%)
1	51 (46%)	67 (60%)	53 (50%)
2	39 (35%)	13 (11%)	9 (8.5%)
3	12 (10%)	3 (2.7%)	2 (1.9%)
4	0	0	0
EM 2 ANOS	N =239	N = 234	N = 242
Nenhuma	189 (79%)	160 (64%)	184 (76%)
Pequena	46 (19%)	65 (26%)	49 (20%)
Moderada/Maior	4 (1.7%)	9 (3.7%)	9 (37%)

UK FAST TRIAL

Breast hypofractionation trial



Number at risk (events)

	0	1	2	3	4
50 Gy	302	299	273 (4)	185 (14)	72 (4)
30 Gy	308	301	281 (7)	183 (25)	63 (16)
28.5 Gy	305	298	279 (4)	191 (15)	64 (8)

A.M. Brunt, et al Radiotherapy and Oncology 2011

UK FAST TRIAL

Atualização 2018

- Idade ≥ 50 anos

- Estádios T1-T2N0

- 3 Braços

- Sem quimioterapia

- Recrutamento de
2004 a 2007

25 x 2 Gy

5 x 6 Gy semanal

5 x 5.7 Gy semanal

A.M. Brunt, ASTRO 2018 - FAST Phase III RCT of Radiotherapy Hypofractionation for Treatment of Early Breast Cancer: 10-Year Results

UK FAST TRIAL

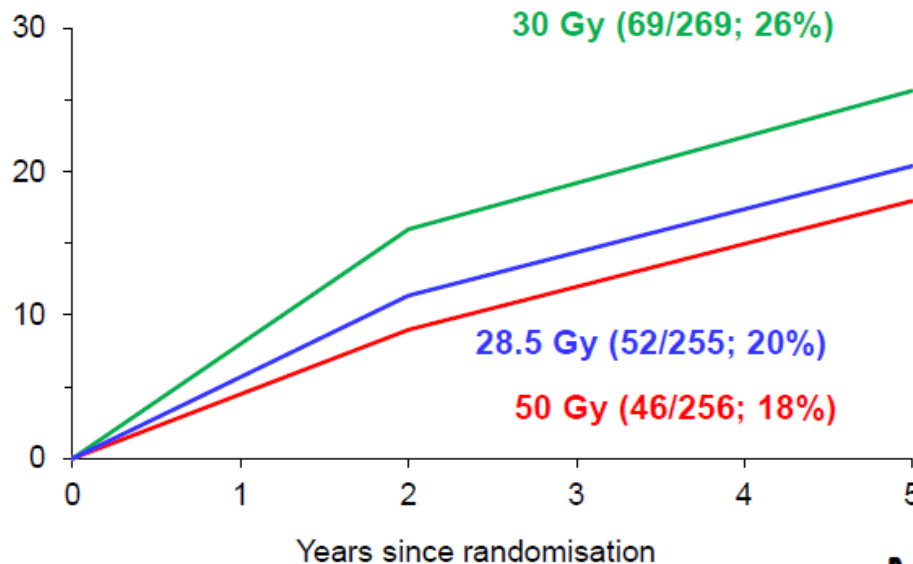
Grau de Complicação na Mama	50 Gy/25 fr	30 Gy/5 fr	28.5 Gy/5 fr
EM 5 ANOS	N = 254	N = 267	N = 253
Nenhuma	160 (63%)	152 (56.9%)	155 (61.3%)
Pequena	75 (29.5%)	67 (25%)	73 (28.8%)
Moderada	15 (5.9%)	40 (15%)	24 (9.5%)
Maior	4 (1.6%)	8 (3%)	1 (0.4%)
EM 10 ANOS	N = 132	N = 130	N = 130
Nenhuma	90 (68.2%)	66 (50.8%)	72 (55%)
Pequena	30 (22%)	40 (30.8%)	39 (30%)
Moderada	11 (8.3%)	18 (13.8%)	17 (13.1%)
Maior	1 (0.8%)	6 (4.6%)	2 (1.5%)

A.M. Brunt, ASTRO 2018 - FAST Phase III RCT of Radiotherapy Hypofractionation for Treatment of Early Breast Cancer: 10-Year Results

UK FAST TRIAL

Photographic assessment of overall change in breast appearance by 5 years

% with mild / severe change in breast appearance



Difference (95%CI)

**30Gy vs
50Gy**

**+7.4% (0.3, 16.7)
p=0.03**

**28.5Gy vs
50Gy**

**+2.4% (-3.8, 10.8)
p=0.47**

Marked changes: 2%, 4%, 2%

  #ASTRO18

2018 ANNUAL MEETING | HENRY B. GONZALEZ CONVENTION CENTER | SAN ANTONIO

A.M. Brunt, ASTRO 2018 - FAST Phase III RCT of Radiotherapy Hypofractionation for Treatment of Early Breast Cancer: 10-Year Results



UK FAST TRIAL

Relapse and survival at median 10 years' follow-up

	50Gy/25# N=302	30Gy/5# N=308	28.5Gy/5# N=305	Total N=915
Local relapse	3	4	4	11
Regional relapse	2	0	3	5
Distant relapse	17	15	15	47
Death (breast cancer)	30 (7)	33 (8)	33 (10)	96 (25)

Estimate of 10-year local relapse rate: 1.3% (95%CI 0.7, 2.3%)

  #ASTRO18

2018 ANNUAL MEETING | HENRY B. GONZALEZ CONVENTION CENTER | SAN ANTONIO

A.M. Brunt, ASTRO 2018 - FAST Phase III RCT of Radiotherapy Hypofractionation for Treatment of Early Breast Cancer: 10-Year Results



UK FAST-FORWARD TRIAL

Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial

- Cirurgia conservadora ou Mastectomia
- 3 Braços
- Com ou sem quimioterapia
- Recrutamento de 2011 a 2013

15 x 2.67 Gy

5 x 5.4 Gy diário

5 x 5.2 Gy diário

UK FAST-FOWARD TRIAL

3.1.2.2 Field-based planning

When outlining a CTV volume on each axial slice it can be very difficult to accurately delineate breast tissue on X-ray CT images, and this can result in an overestimate of the whole breast volume, especially in obese patients. An alternative strategy is to generate a field-based structure which is not a true PTV, but is helpful for reporting purposes. A provisional tangential field pair is selected to cover the breast tissue and minimise dose to the normal tissues, by scrolling up and down the CT dataset. The whole breast field based PTV is then generated according to the following criteria, as illustrated on the images below:

- 5 mm from the skin surface
- 5 mm from the lung/chest wall interface
- 5 mm from the posterior beam edge (or the MLC if it is used on the main beams)
- 10 mm from the superior and inferior beam edges

The margins of the field-based PTV from the superior and inferior field borders are valid under the assumption that the isocentre of the plan has been placed in the central region of the target. For a mono-isocentric technique or if divergence has been removed from the superior edge using floor twist please contact the QA team for guidance.

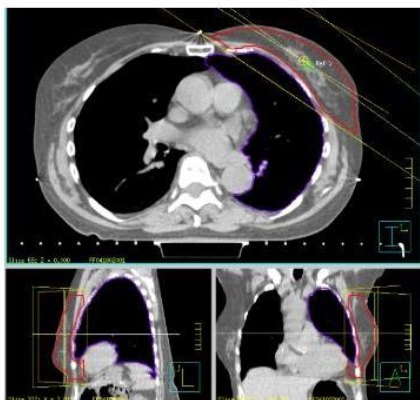


Fig. 5: Field-based whole breast PTV in axial, sagittal, and coronal planes

The Chest Wall CTV encompasses the skin flaps and includes the soft tissues down to the deep fascia, excluding the underlying muscle and rib cage. A 10 mm margin is added to create the Chest Wall PTV. This PTV is then cropped 5 mm inside the skin or along the skin (depending on the centre's practice of bolus use) and 5 mm from the lung surface for dose reporting purposes. This structure is denoted as PTV_{CW} DVH.

The same field based PTV principle listed above can also be applied to chest wall patients in the trial as shown in Fig. 6. In case of a very thin chest wall when the field-based PTV_{CW} generated according to the procedure outlined above does not represent the irradiated volume adequately, contact the QA team for advice.

If it is the centre's policy to use bolus for part of the treatment fractions, the bolus and no bolus plans should be evaluated and submitted separately, and two dose reporting structures should be created: one cropped 5 mm inside the skin for the no bolus plan, and one including the skin for the bolus plan. Target dose constraints should be met for both structures individually.

UK FAST-FORWARD TRIAL

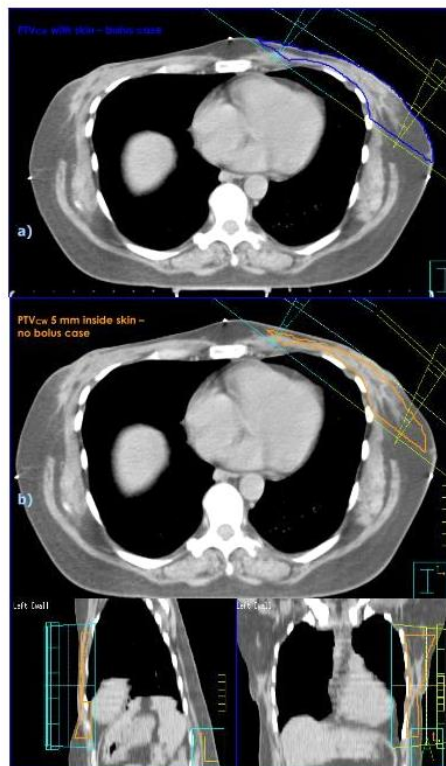


Fig. 6: Field based chest wall PTV with (a) and without bolus (b)

It is often necessary to use the MLC to shield organs at risk in the treatment beams and this is recommended, provided that the tumour bed is away from the shielded area. In cases like this, when the MLC is used on the main tangential beams, the field-based reporting structure should be contoured 5 mm inside the MLC instead of 5 mm inside the field border. The example on Fig. 7 shows a left side patient with MLC shielding for the heart; the same can be done to shield parts of the lung or the liver in right side plans.

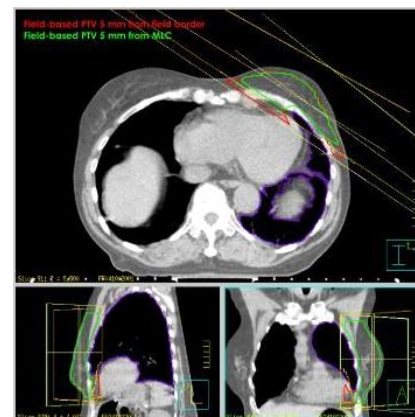


Fig. 7: Field-based PTV in case of MLC shielding for the heart.

The achieved target and OAR dose constraints should in this case be reported for the modified field-based PTV structure.

Once created according to the criteria outlined above, the field-based PTV must not be modified any further. It will sometimes include tissues that are not breast in the

UK FAST-FOWARD TRIAL

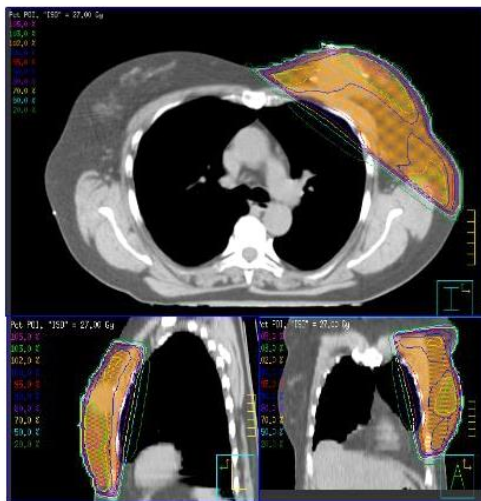


Fig. 15: Dose distribution in whole breast PTV: axial, sagittal and coronal view

On Fig. 16-b) below a projection of the dose clouds in the beam's eye view shows that using simple 3D compensation can minimise hotspots across the breast volume. The image on a) illustrates that using wedged tangents optimised on the central axis with no compensation can produce very large areas of 107% (shown in lavender dose cloud) away from the central axis.

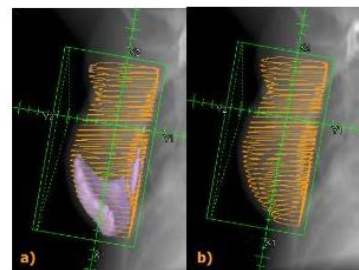


Fig. 16: 3D compensation technique

4.4.2 Electrons

If a centre wishes to treat chest wall patients with electrons, this should be discussed with the QA team.

4.5 Tumour Bed Boost

4.5.1 Photons

Mini-tangential fields can be used for the tumour bed boost, covering the tumour bed PTV with an appropriate penumbra margin. The whole breast field borders are decreased so as to include the tumour bed PTV only. A mini-tangential beam arrangement for the tumour bed boost is presented on Fig. 17.

UK FAST-FORWARD TRIAL

Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial

95 % do PTV recebendo 95% da dose prescrita
<5% do PTV recebendo >105% da dose prescrita
<2% do PTV recebendo > 107% da dose prescrita
 $D_{\text{máx}} < 110\%$ da dose prescrita

A.M. Brunt et al, Radiotherapy and Oncology 2016



UK FAST-FOWARD TRIAL

**Pior Grau de
Complicação na
Mama**

40 Gy/15 fr

27 Gy/5 fr

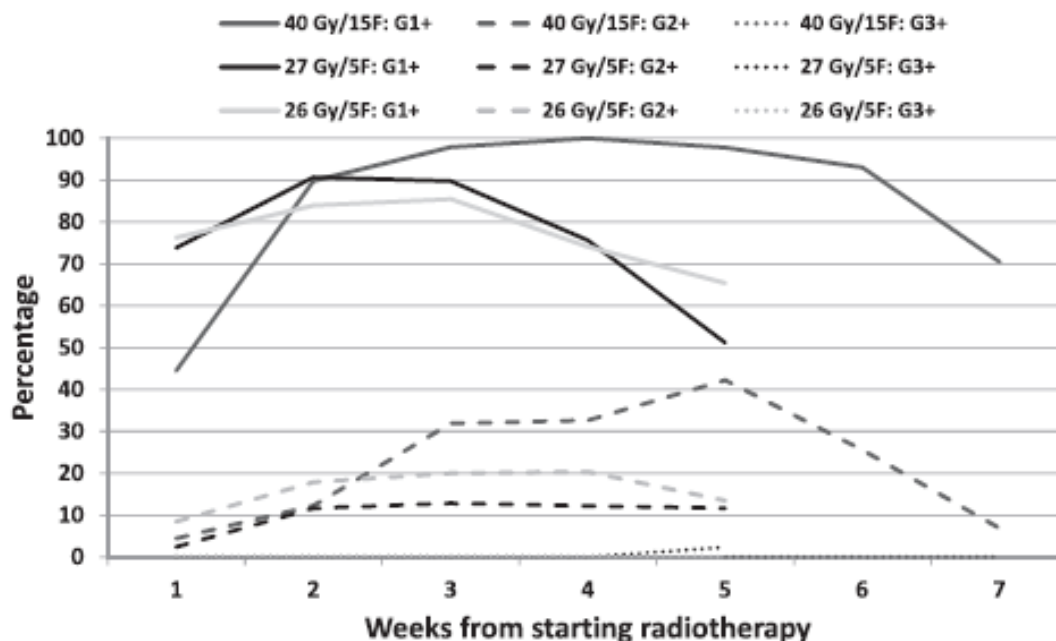
26 Gy/5 fr

Durante ou Após Tratamento RTOG	N = 44	N = 51	N = 52
0	0	2 (4%)	3 (6%)
1	14 (32%)	24 (47%)	32 (62%)
2	24 (55%)	20 (39%)	14 (27%)
3	6 (14%)	5 (10%)	3 (6%)
4	0	0	0

A.M. Brunt et al, Radiotherapy and Oncology 2016

UK FAST-FORWARD TRIAL

Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial



Grade 3 toxicity reported at 4 weeks post-RT in 27 Gy/5F patient resolved to grade 1 one week later

Fig. 1. Acute toxicity substudy 2 – Prevalence of grade 1+, grade 2+ and grade 3+ CTCAE toxicity.

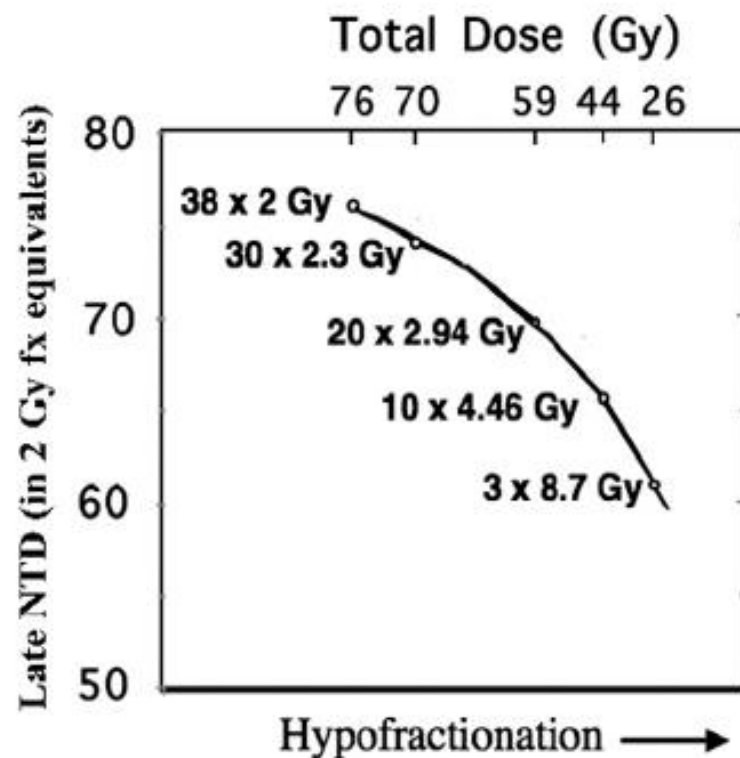
A.M. Brunt et al, Radiotherapy and Oncology 2016

Hipofracionamento

Definitivo

Hipofracionamento em Próstata

Estudos demonstram que a razão α/β da próstata é baixa, em torno de 1 a 3 Gy.



Hipofracionamento em próstata

Author	# of pts	Fractionation Schedule (dose/fx size/ # of fxs)	RT Technique	NTD _{2Gy} ($\alpha\beta=1.5$ Gy) Tumor	NTD _{2Gy} ($\alpha\beta=3$ Gy) Late tox	Median FU (mo)	% bRFS	≥ Grade 2 Late Toxicity (%)	
								GI	GU
Kupelian <i>et al.</i> Cleveland Clinic	770	70 Gy/2.5 Gy/28 fx	IMRT	80.0 Gy	77.0 Gy	45	83%	4.5	5.3
Ritter <i>et al.</i> Wisconsin	100	64.7Gy/2.94 Gy/22 fx	IMRT/TOMO	82.6 Gy	77.0 Gy	60	92%	10.7	~15
	100	58.1 Gy/3.63 Gy/16 fx		85.1 Gy	77.0 Gy	48	94%		
	100	51.6 Gy/4.3 Gy/12 fx		85.5 Gy	75.0 Gy	36	98%		
Martin <i>et al.</i> PMH	92	60 Gy/3 Gy/20 fx	IMRT	77.2 Gy	72.0 Gy	36	85%	4	3
Leborgne <i>et al.</i> Uruguay	52	60 Gy/3 Gy /20 fx	3D-CRT	77.1 Gy	72.0 Gy	49	89%	5.5	5.6
	37	63 Gy/3.15 Gy/20 fx		83.7 Gy	77.2 Gy	49			
Tsuji <i>et al.</i> CHIBA	201	66 GyE/3.3 GyE/20 fx	3D-CRT Carbon ions	90.5 Gy	83.1 Gy	30	97%	2	6
Soete <i>et al.</i> Italy & Belgium	102	56 Gy/3.5 Gy/16 fx	3D-CRT	80.0 Gy	77.0 Gy	45	85%	4.5	5.3
Zilli <i>et al.</i> Geneva	82	56 Gy/4 Gy /15 fx	IMRT	88.0 Gy	78.4 Gy	48	82%	3.9	5.8

CHHiP Trial

Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer:
5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial

- Multicêntrico Randomizado
Fase 3, não inferioridade

- 3 Braços

3216 pacientes

- T1b-T3aN0

- PSA < 30 ng/ml

- Risco linfonodal < 30%

- T3 + Gleason 8+ excluídos

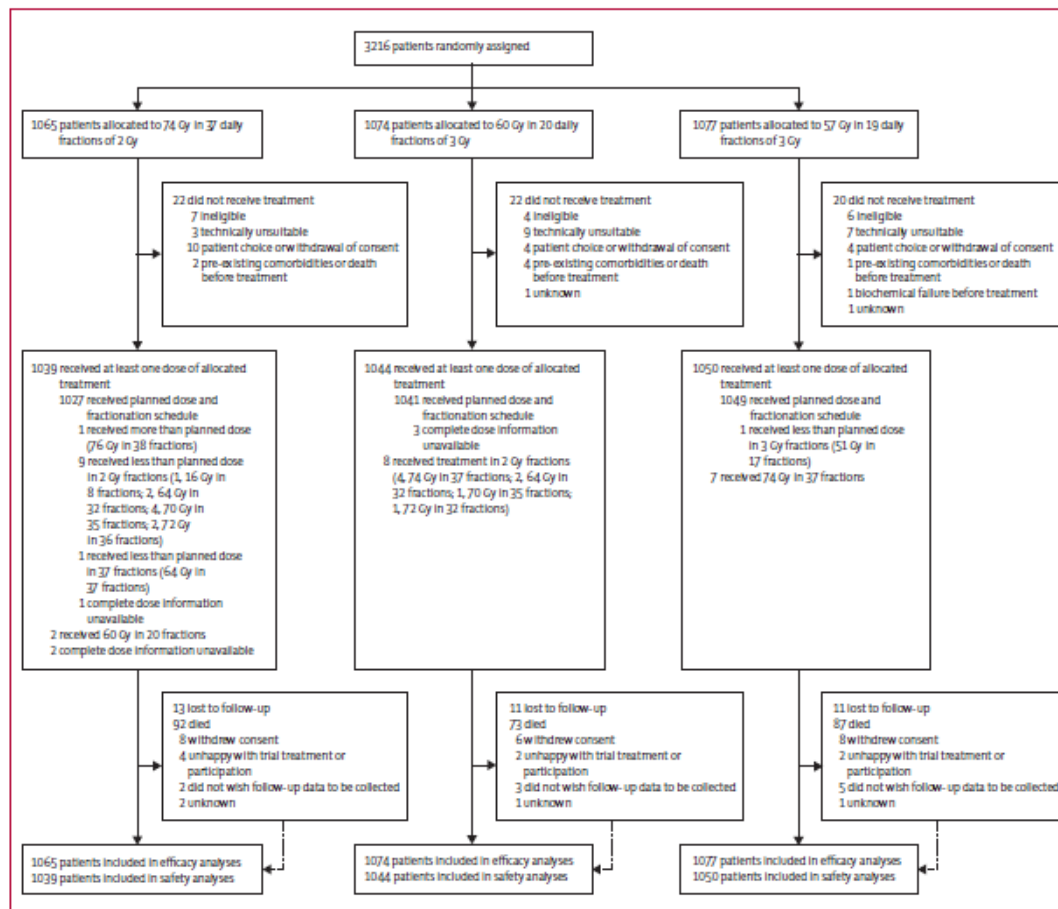
37 x 2 Gy

20 x 3 Gy

19 x 3 Gy

CHHiP Trial

Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial



Dearnaley, D et al. Lancet 2016

Radiotherapy Quality Assurance for the CHHiP Trial: Conventional Versus Hypofractionated High-Dose Intensity-Modulated Radiotherapy in Prostate Cancer

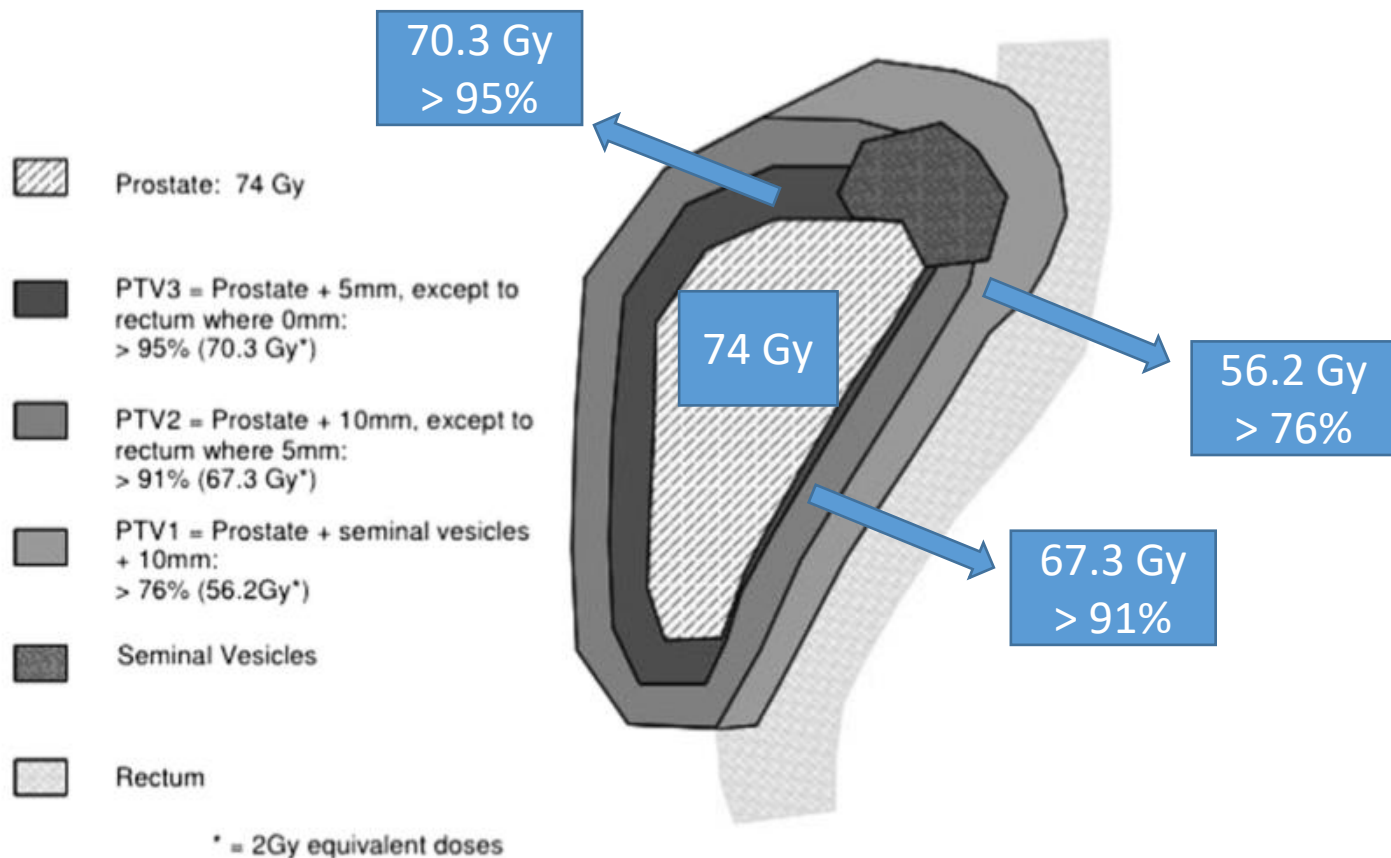


Fig 1. Planning target volume (PTV) margins and doses for the CHHiP trial. In patients with a low risk [4] of seminal vesicle involvement, the base of the seminal vesicles (proximal 2 cm) was included; those with a moderate or high risk of involvement had all of the seminal vesicles included.

Radiotherapy Quality Assurance for the CHHiP Trial: Conventional Versus Hypofractionated High-Dose Intensity-Modulated Radiotherapy in Prostate Cancer

- 41 centros
- Implementação Técnica
 - Forward planning
 - Inverse planning

TC com cortes 0.5 cm

Recomendado IGRT

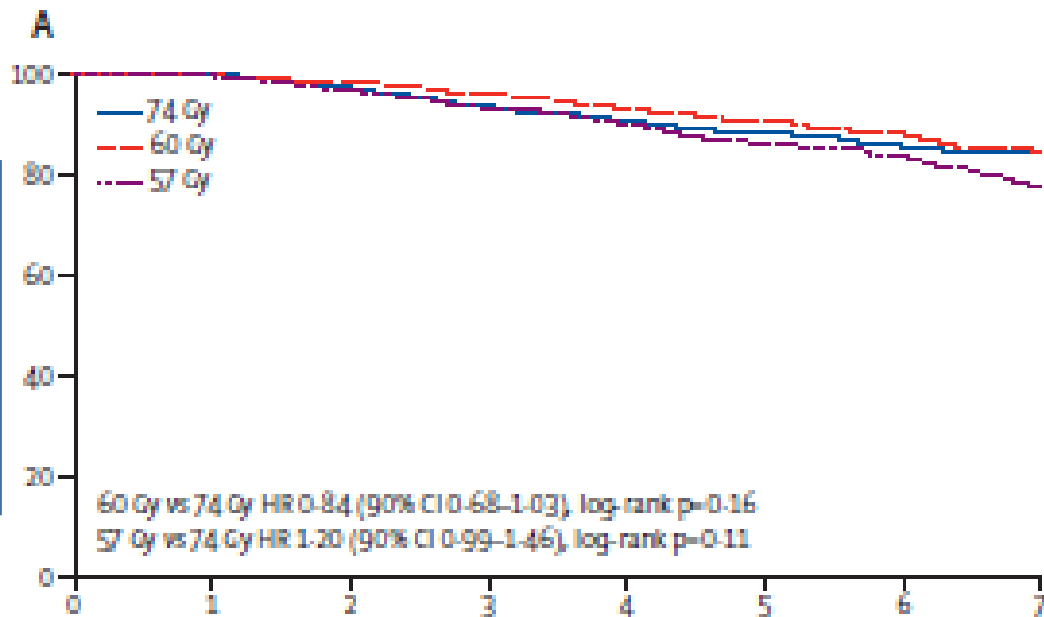
Radiotherapy Quality Assurance for the CHHiP Trial: Conventional Versus Hypofractionated High-Dose Intensity-Modulated Radiotherapy in Prostate Cancer

Table A1: Normal tissue dose constraints for the CHHiP trial.

Organ	Prescribed Dose (Gy)			Dose (%)	Maximum volume	
	74 Gy/37 fractions	60 Gy/20 fractions	57 Gy/19 fractions		Optimal	Mandatory
Rectum	30	24.3	23.1	41%	80%	—
	40	32.4	30.8	54%	70%	—
	50	40.5	38.5	68%	—	60%
	60	48.6	46.2	81%	—	50%
	65	52.7	50.1	88%	—	30%
	70	56.8	53.9	95%	—	15%
	74	60	57	100%	—	3%
Bladder	50	40.5	38.5	68%		50%
	60	48.6	46.2	81%		25%
	74	60	57	100%		5%
Bowel	50	40.5	38.5	68%		17cc
Penile bulb	50	40.5	38.5	68%	50%	
	60	48.6	46.2	81%	10%	
Femoral heads	50	40.5	38.5	68%	—	50%

CHHip Trial

Sobrevida
Livre
de
Falha
Bioquímica



Number at risk
(events)

74 Gy	1065 (4)	1037 (24)	991 (39)	926 (24)	795 (20)	495 (11)	284 (3)	167 (11*)
60 Gy	1074 (4)	1042 (15)	1011 (23)	965 (28)	816 (18)	533 (10)	280 (10)	176 (10*)
57 Gy	1077 (5)	1044 (30)	1004 (35)	944 (31)	798 (31)	492 (9)	262 (13)	151 (9*)

Number censored

74 Gy	0	24	22	26	107	280	200	114
60 Gy	0	28	16	23	121	265	243	94
57 Gy	0	28	10	25	115	275	221	98

Dearnaley, D et al. Lancet 2016

CHHip Trial

Sobrevida
Livre
de
Falha
Bioquímica

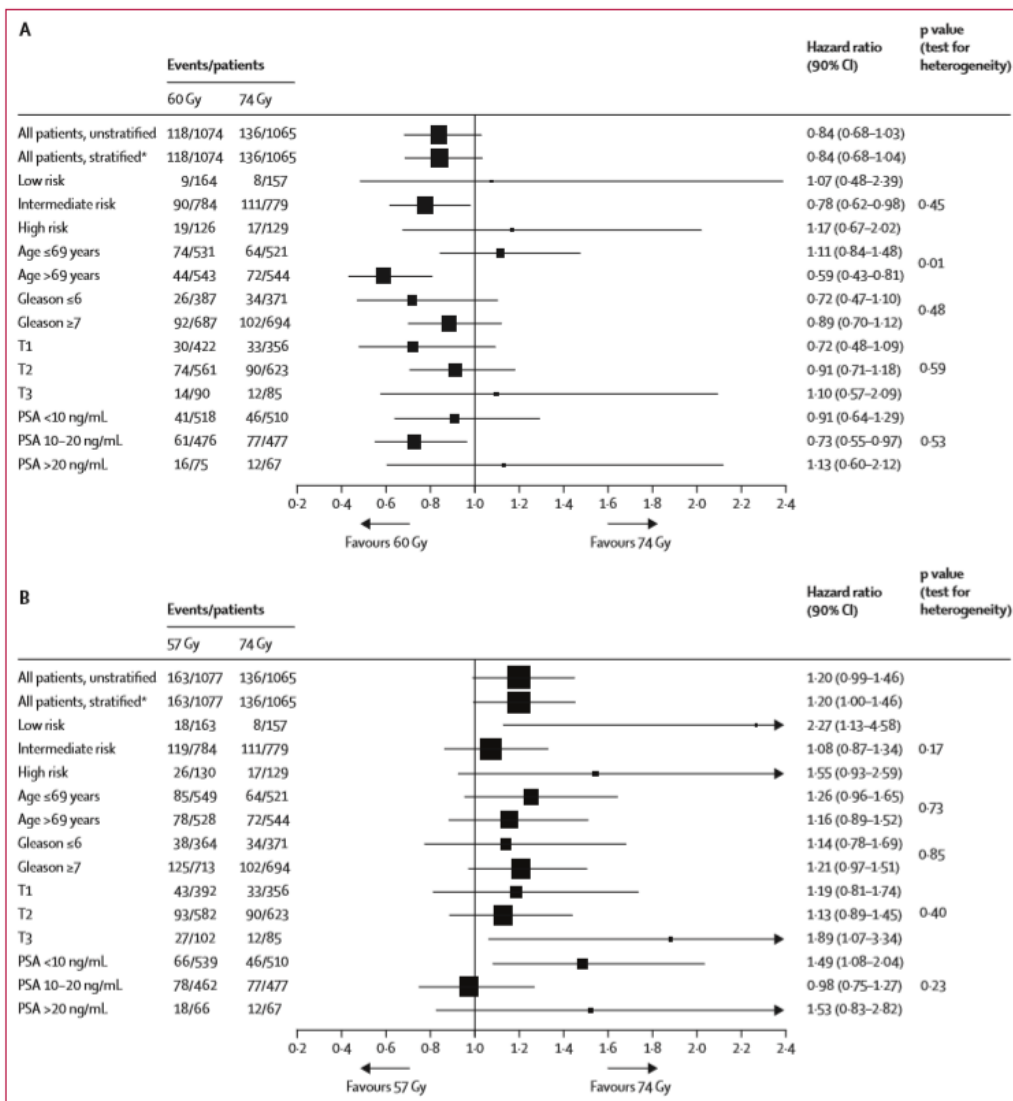
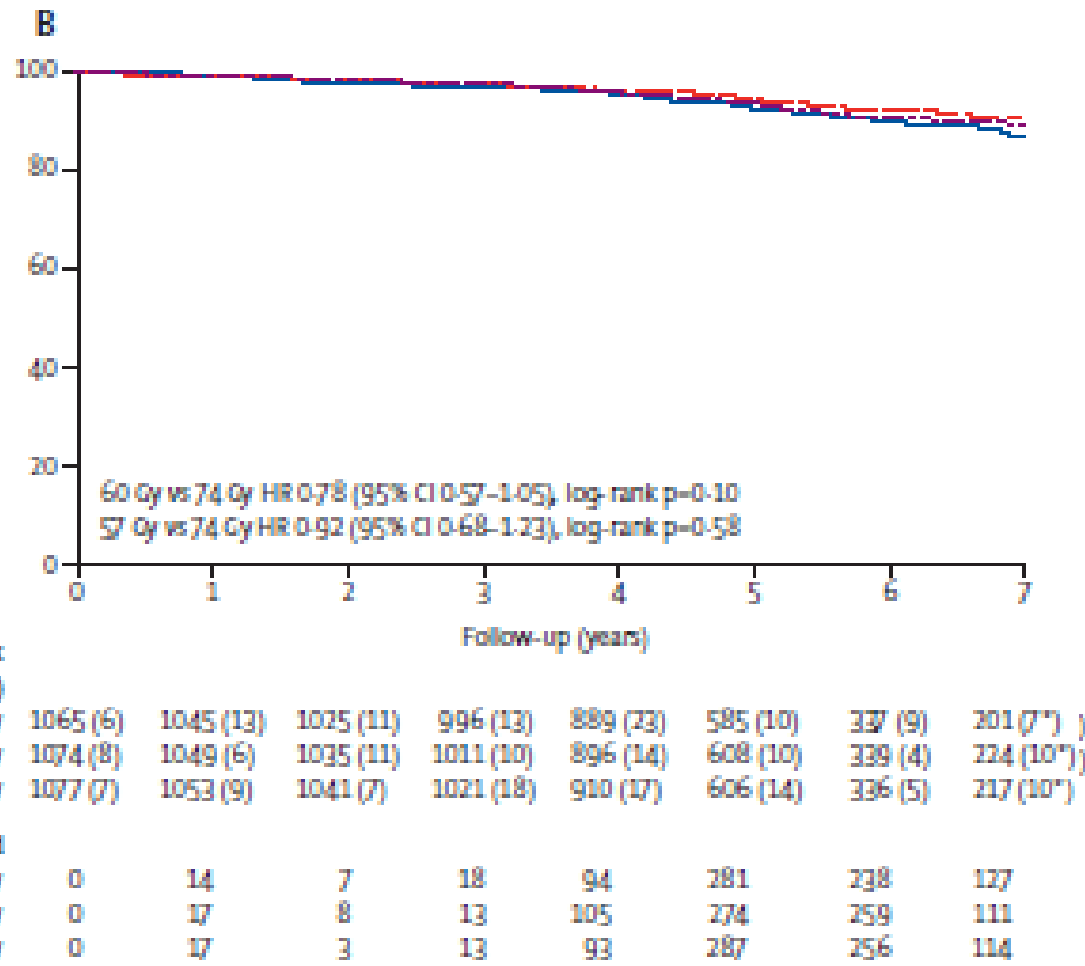


Figure 3: Univariable subgroup analyses of biochemical or clinical failure comparing 60 Gy (A) and 57 Gy (B) with conventional radiotherapy
*Stratified by risk group; all other analyses are unstratified.

Dearnaley, D et al. Lancet 2016

CHHip Trial

Sobrevida
Global



CHHip Trial

Toxicidade
Aguda

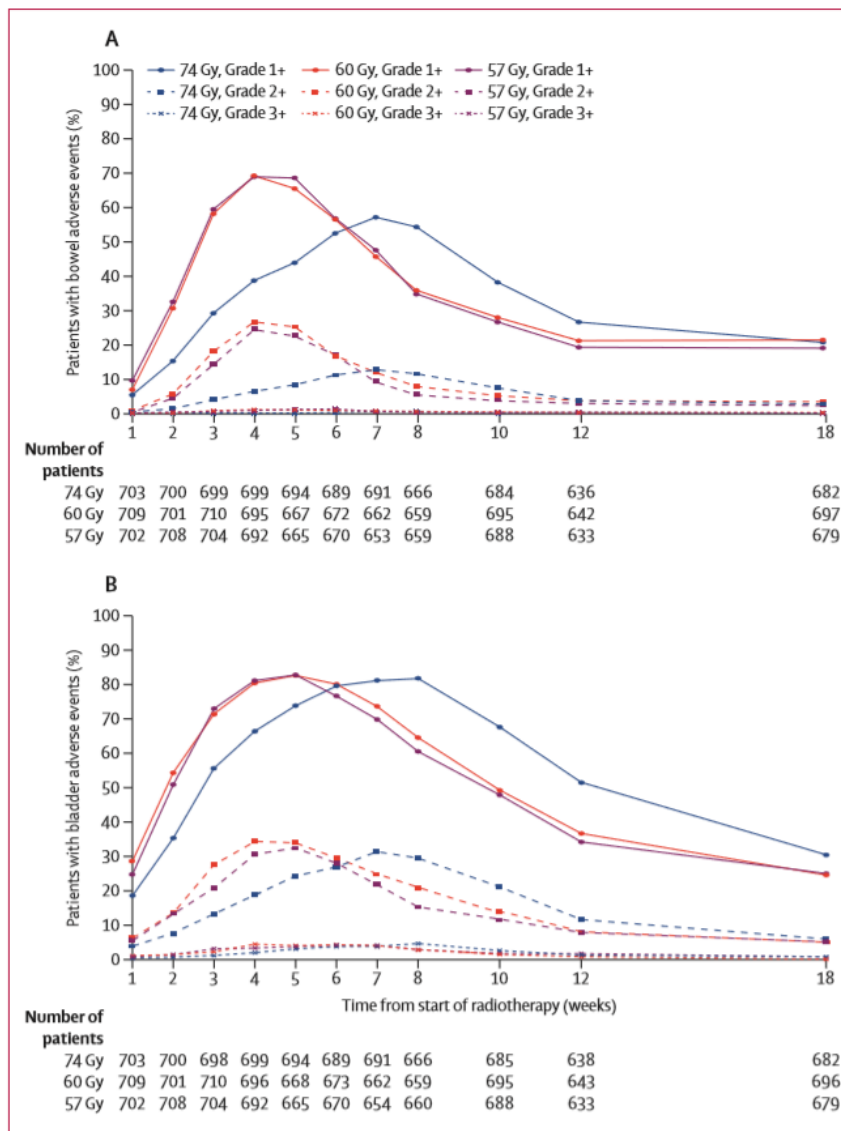


Figure 4: Acute RTOG toxicity by timepoint and randomised treatment group

Dearnaley, D et al. Lancet 2016

CHHip Trial

Toxicidade Tardia

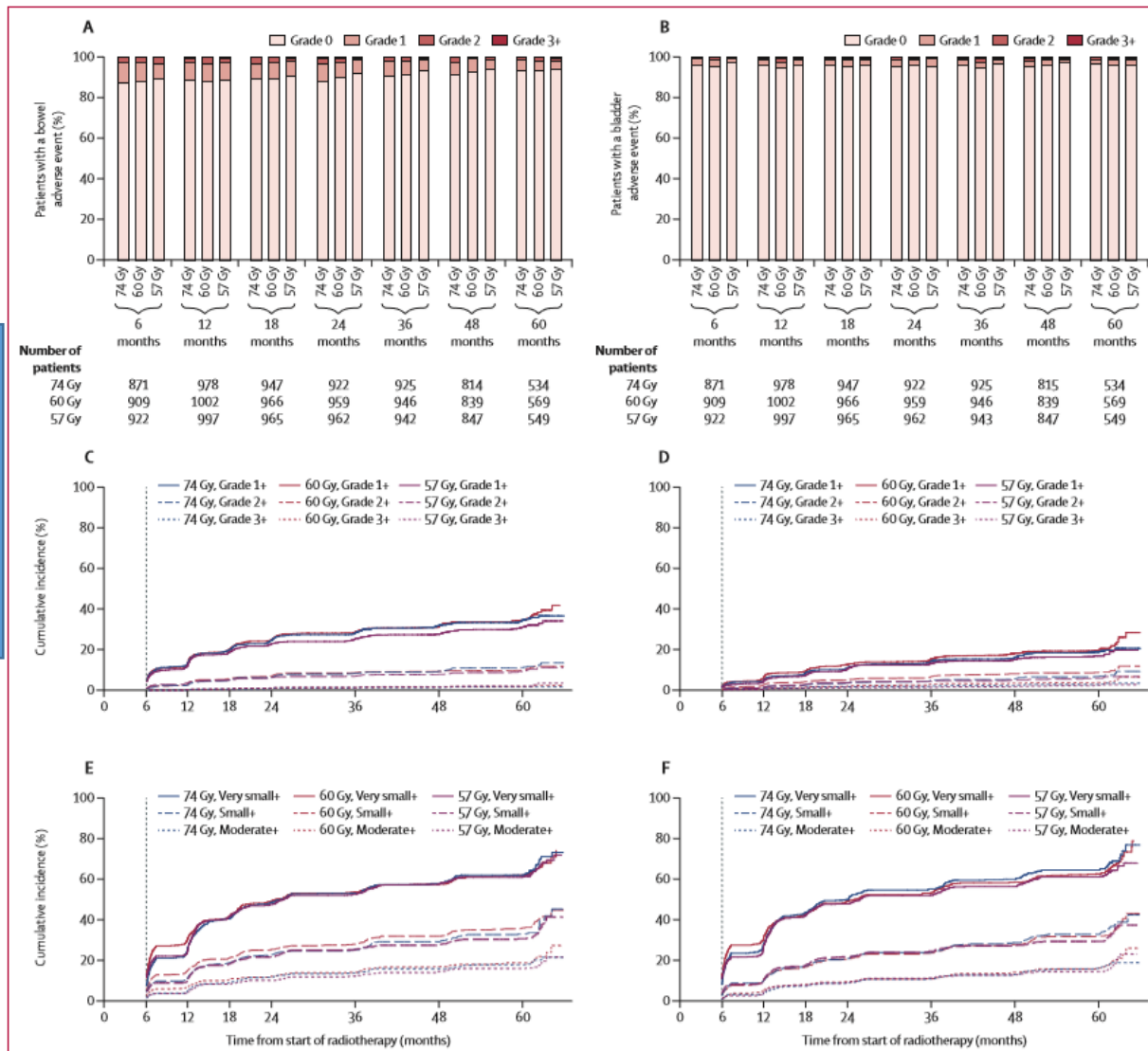


Figure 5: Late bowel and bladder toxicity by timepoint, assessment, and randomised treatment group

Dearnaley, D et al. Lancet 2016

Vantagens do hipofracionamento

- Diminui custos
- Maior conveniência
 - Diminui viagem dos pacientes, alojamento
 - Maior adesão e aceitação do tratamento
- Maior efeito em lesões radioresistentes
 - Melanoma
 - Sarcomas
 - Hipernefomas
- Maior efeito em tecidos com o α / β baixo com baixa toxicidade
 - Próstata
 - Mama

Obrigado

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