“5 frazioni: il nuovo paradigma di trattamento?»

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Negrar-Verona, Italy

DISCLOSURES & CONFLICTS OF INTERESTS

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HYPOFRACTIONATION:

(DURING COVID…)THE WINDS HAVE CHANGED

JAMA Network | Open

Invited Commentary | Oncology

A Modeling Approach to Radiation Therapy in the Era of COVID-19

Jimmy T. Efird, PhD, MSc; Tarun Podder, PhD; Tithi Biswas, MD

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

ELSEVIER

COVID-19 Rapid Letter

Hypofractionation in COVID-19 radiotherapy: A mix of evidence based medicine and of opportunities ☆

M. Portaluri [a,*], M.C. Barba [b], D. Musio [b], F. Tramacere [a], F. Pati [a], S. Bambace [c]

[a] Dept Radiation Oncology, "A.Perrino Hospital", Brindisi; [b] Dept Radiation Oncology, "Vito Fazzi" Hospital, Lecce; and [c] Dept Radiation Oncology, "Mons. Dimiccoli Hospital", Barletta, Italy

International Journal of Radiation Oncology biology • physics

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FRACTIONATION AND CHANGES IN PATIENT CARE

Breast, Prostate, and Rectal Cancer: Should 5-5-5 Be a New Standard of Care?

Diane C. Ling, MD, John A. Vargo, MD, and Sushil Beriwal, MD, MBA

Department of Radiation Oncology, UPMC Hillman Cancer Center, Magee Women's Hospital, Pittsburgh, Pennslyvania

Efird J et al, Jama Open 2021
Portaluri M et, al Radiat Oncol 2020
Ling D et al, IJROBP 2020

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WHAT ABOUT …..

5# EXTREME HYPOFRACTIONATION IN CLINICAL PRACTICE?

HYPOFRACTIONATION IN 5#:

THE WINDS HAVE CHANGED

Braunstein [4]	NY-USA	Breast	PBI: 30 Gy/5f every other day (preferred) or daily (acceptable) or 40 Gy/10 daily WBRT: 26 Gy/5 daily +/- 5.2 Gy × 1 boost or 40 Gy/15 daily or 42.4 Gy/16 daily PM-RT: 42.56 Gy/16f BREAST AND RNI: 42.56 Gy/16f with SIB on tumor bed 48 Gy/16f or 40 Gy/15f with SIB on tumor bed 48 Gy/15f
Coles [5]	International	Breast	WBRT, node negative: 28–30 Gy/5f (weekly) or 26 Gy/5f (daily) (FAST and FAST Forward trials, respectively) WBRT, node positive: 40.05 Gy/15f PBI: 28.5–6 Gy/5f (over 1–2 weeks)
Romesser [8]	NY-USA	Rectum	Locally advanced (also low-located, close CRM): 25 Gy/5f (SCRT) delay surgery
Marijnen [9]	International	Rectum	ESMO rectal cancer guidelines Intermediate group (if good TME cannot be assured): 25 Gy/5f (SCRT) Locally advanced rectal cancer: 25 Gy/5f (SCRT delay surgery) Advanced group: pre-operative CRT or 25 Gy/5f (SCRT followed by neo-adjuvant chemotherapy)
Zaorsky [11]	USA-UK	Prostate	IR/HR localized: 5 to 7f (SBRT) (v. 2020 NCCN guidelines) or 60–62 Gy/20f post-prostatectomy: 52.5 Gy/20f oligometastatic: 1 or 3 fractions (SBRT) low volume M1: 3–5 fractions (SBRT) or 36 Gy/6f (STAMPEDE)

Portaluri M et al 2020

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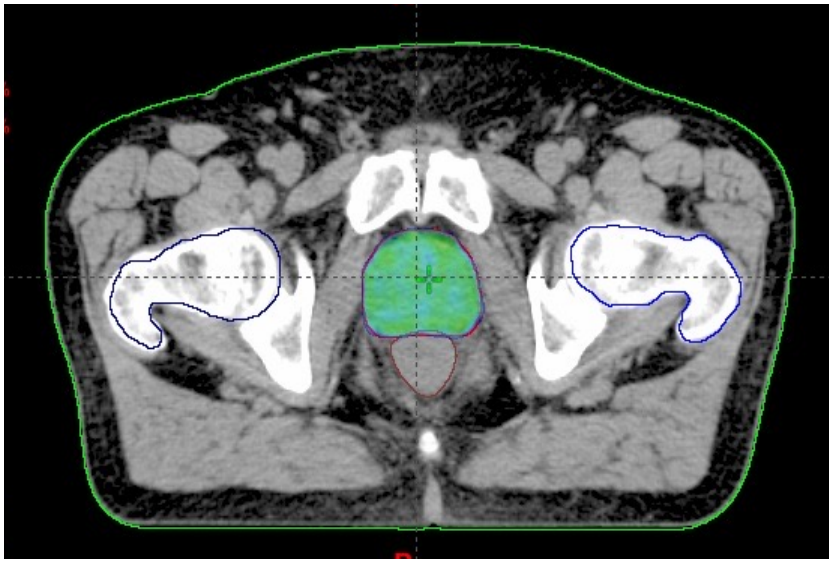
HYPOFRACTIONATION IN 5#:

PROSTATE CANCER



Portaluri M et al 2020

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PROSTATE EXTREME HYPOFRACTIONATION IN 5#:
BASES OF THE RATIONALE


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Critical Reviews in Oncology/Hematology xxx (2012) xxx–xxx

CRITICAL REVIEWS IN Oncology Hematology Incorporating Geriatric Oncology

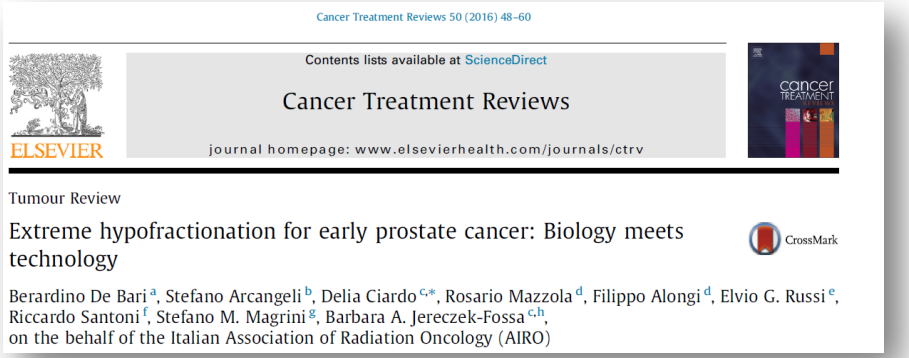
www.elsevier.com/locate/critrevonc

Will SBRT replace conventional radiotherapy in patients with low-intermediate risk prostate cancer? A review

Stefano Arcangeli*, Marta Scorsetti, Filippo Alongi

Radiotherapy and Radiosurgery department, Istituto Clinico Humanitas, Humanitas Cancer Center, Rozzano, Milano, Italy

Accepted 23 November 2011


Cancer Treatment Reviews 50 (2016) 48–60

Contents lists available at ScienceDirect

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journal homepage: www.elsevierhealth.com/journals/ctrv

ELSEVIER

Tumour Review

Extreme hypofractionation for early prostate cancer: Biology meets technology

CrossMark

Berardino De Bari[a], Stefano Arcangeli[b], Delia Ciardo[c,*], Rosario Mazzola[d], Filippo Alongi[d], Elvio G. Russi[e], Riccardo Santoni[f], Stefano M. Magrini[g], Barbara A. Jereczek-Fossa[c,h], on the behalf of the Italian Association of Radiation Oncology (AIRO)

1. ***RADIOBIOLOGY: Low α/β*** ratio could justify the significant reduction of fractions to increase the therapeutic window

2. **TECHNOLOGY**: A potential ***technology advancement*** stems from using upgraded **IGRT, IMRT** or integrating both and ***modern SBRT,*** providing sharper dose fall-offs and better dose conformity.

3. ***COST/EFFECTIVENSS:*** ***Convenience*** for patients and departments, and for the health system (<costs).

4. ***EVIDENCE***: the clinical validity of short term schedules is proven by a body of prospective (non-randomized trials) even if frequently with relatively short follow up.

Arcangeli et al, Critical rev Oncol/hematol 2012
De Bari et al, Cancer Treatment review 2016

PROSTATE EXTREME HYPOFRACTIONATION IN 5# :
EFFICACY

SBRT studies (with at least 40 patients).

Citation	Risk group	# Patients	Study type	Median follow-up (months)	Dose/ fractions	ADT	Disease control	GI toxicity (≥G2)	GU toxicity (≥G2)
Meier	Intermediate	129	Prospective	30	40 Gy/5 fx	N/A	**99%**	2%	10%
Aluwini	Low Intermediate	162	Prospective	28	38 Gy/4 fx	N/A	**98%**	3%	15%
Fuller	Low Intermediate	260	Prospective	20	38 Gy/4 fx	N/A	**98%**	0%	2%
Freeman	Low	41	Prospective	60	35–36.25 Gy/5 fx	N/A	**N/A**	2.5%	9.5%
Madsen	Low	40	Prospective	41	33.5 Gy/5 fx	N/A	**90%**	13%	23%
McBride	Low	45	Prospective	44.5	36.25–37.5 Gy/ 5 fx	N/A	**100%**	27%	19%
Oliai	Low Intermediate High	70	Retrospective	31	35–37 Gy/5 fx	33%	**100%–low 95%–int. 77.1%–high**	12%	23%
Hannan	Low Intermediate	91	Prospective	74 (45 Gy) 72 (47.5 Gy) 66 (50 Gy)	45–50 Gy/5 fx	16.5%	**100%–3 years 98.6%–5 years**	6.7%–45 Gy 26.7%–47.5 Gy 23%–50 Gy	33.3%–45 Gy 6.7%–47.5 Gy 23%–50 Gy

Biochemical control @ 3-5 years
Low-intermediate risk~92-100%

Beckta et et al, Urologic Oncology 2019

PROSTATE EXTREME HYPOFRACTIONATION IN 5#:
LATE TOXICITY

SBRT studies (with at least 40 patients).

Citation	Risk group	# Patients	Study type	Median follow-up (months)	Dose/ fractions	ADT	Disease control	GI toxicity (≥G2)	GU toxicity (≥G2)
Meier	Intermediate	129	Prospective	30	40 Gy/5 fx	N/A	**99%**	2%	10%
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Hannan	Low Intermediate	91	Prospective	74 (45 Gy) 72 (47.5 Gy) 66 (50 Gy)	45–50 Gy/5 fx	16.5%	**100%–3 years 98.6%–5 years**	6.7%–45 Gy 26.7%–47.5 Gy 23%–50 Gy	33.3%–45 Gy 6.7%–47.5 Gy 23%–50 Gy

TOX≥3:
LATE <5%

Beckta et et al, Urologic Oncology 2019

PROSTATE EXTREME HYPOFRACTIONATION IN 5#:
ACUTE TOXICITY

Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial

Douglas H Brand, Alison C Tree*, Peter Ostler, Hans van der Voet, Andrew Loblaw, William Chu, Daniel Ford, Shaun Tolan, Suneil Jain, Alexander Martin, John Staffurth, Philip Camilleri, Kiran Kancherla, John Frew, Andrew Chan, Ian S Dayes, Daniel Henderson, Stephanie Brown, Clare Cruickshank, Stephanie Burnett, Aileen Duffton, Clare Griffin, Victoria Hinder, Kirsty Morrison, Olivia Naismith, Emma Hall, Nicholas van As, on behalf of the PACE Trial Investigators*

	Conventionally fractionated or moderately hypofractionated radiotherapy (n=432)				Stereotactic body radiotherapy (n=415)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Gastrointestinal	264 (61%)	49 (11%)	4 (1%)	0	219 (53%)	42 (10%)	1 (<1%)	0
Genitourinary	254 (59%)	111 (26%)	6 (1%)	1 (<1%)	236 (57%)	86 (21%)	8 (2%)	2 (<1%)

Data are n (%). No death due to adverse events were reported.

Table 2: Radiation Therapy Oncology Group adverse events

SBRT = CONVENTIONAL/MODERATED HYPO
ACUTE TOX ≥3:
1-2%

Brand et et al, Lancet Oncol 2019

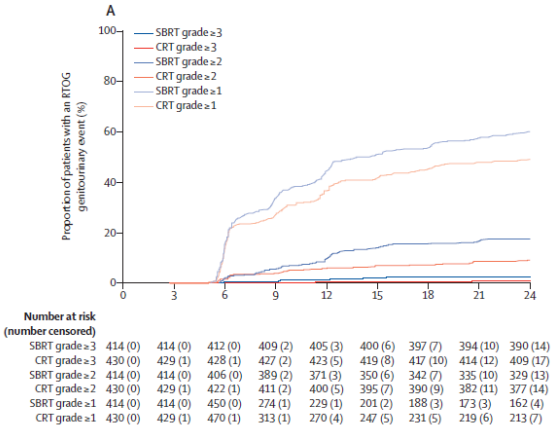
PROSTATE EXTREME HYPOFRACTIONATION IN 5#:
LATE TOXICITY

Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial

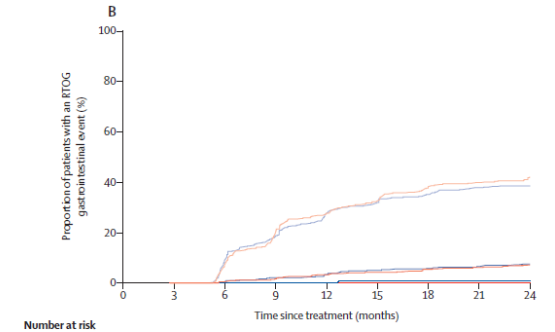
Alison C Tree, Peter Ostler, Hans van der Voet, William Chu, Andrew Loblaw, Daniel Ford, Shaun Tolan, Suneil Jain, Alexander Martin, John Staffurth, John Armstrong, Philip Camilleri, Kiran Kancherla, John Frew, Andrew Chan, Ian S Dayes, Aileen Duffton, Douglas H Brand, Daniel Henderson, Kirsty Morrison, Stephanie Brown, Julia Pugh, Stephanie Burnett, Muneeb Mahmud, Victoria Hinder, Olivia Naismith, Emma Hall, Nicholas van As*, on behalf of the PACE Trial Investigators*

Interpretation In the PACE-B trial, 2-year RTOG toxicity rates were similar for five fraction SBRT and conventional schedules of radiotherapy. Prostate SBRT was found to be safe and associated with low rates of side-effects. Biochemical outcomes are awaited.

- ✓ ***RTOG GU Grade ≥ 2 was 2%CRT and 3% SBRT; RTOG GI Grade ≥ 2 was 3%CRT and 2% SBRT;***
- ✓ LATE TOXICITY with ultra-hypofractionation to 2 years is low and similar to longer schedules.
- ✓ However, a flare of toxicity is seen at around 1 year after SBRT and overall rates of genitourinary toxicity remain higher at 2 years after SBRT than standard prostate radiotherapy



Number at risk (number censored)									
SBRT grade ≥3	414 (0)	414 (0)	412 (0)	409 (2)	405 (3)	400 (6)	397 (7)	394 (10)	390 (14)
CRT grade ≥3	430 (0)	429 (1)	428 (1)	427 (2)	423 (5)	419 (8)	417 (10)	414 (12)	409 (17)
SBRT grade ≥2	414 (0)	414 (0)	406 (0)	389 (2)	371 (3)	350 (6)	342 (7)	335 (10)	329 (13)
CRT grade ≥2	430 (0)	429 (1)	422 (1)	411 (2)	400 (5)	395 (7)	390 (9)	382 (11)	377 (14)
SBRT grade ≥1	414 (0)	414 (0)	450 (0)	274 (1)	229 (1)	201 (2)	188 (3)	173 (3)	162 (4)
CRT grade ≥1	430 (0)	429 (1)	470 (1)	313 (1)	270 (4)	247 (5)	231 (5)	219 (6)	213 (7)



Number at risk (number censored)									
SBRT grade ≥3	414 (0)	414 (0)	413 (0)	411 (2)	410 (3)	405 (6)	403 (7)	400 (10)	396 (14)
CRT grade ≥3	430 (0)	429 (1)	429 (1)	428 (2)	425 (5)	422 (8)	420 (10)	416 (13)	411 (18)
SBRT grade ≥2	414 (0)	414 (0)	412 (0)	403 (2)	398 (2)	388 (5)	384 (6)	378 (9)	370 (13)
CRT grade ≥2	430 (0)	429 (1)	427 (1)	421 (2)	411 (5)	404 (8)	397 (10)	391 (13)	382 (18)
SBRT grade ≥1	414 (0)	414 (0)	376 (0)	335 (2)	298 (2)	278 (4)	264 (5)	253 (5)	247 (8)
CRT grade ≥1	430 (0)	429 (1)	396 (1)	341 (2)	307 (4)	284 (7)	261 (8)	250 (10)	237 (14)

Tree et al, Lancet Oncol 2022

EXTREME HYPOFRACTIONATION & PROSTATE CANCER IN 5#:

EVIDENCE BASED GUIDELINES

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline 2018

Scott C. Morgan, Karen Hoffman, D. Andrew Loblaw, Mark K. Buyyounouski, Caroline Patton, Daniel Barocas, Soren Bentzen, Michael Chang, Jason Efstathiou, Patrick Greany, Per Halvorsen, Bridget F. Koontz, Colleen Lawton, C. Marc Leyrer, Daniel Lin, Michael Ray, and Howard Sandler

Statement KQ3A: In men with low-risk prostate cancer who decline active surveillance and choose active treatment with EBRT, ultrahypofractionation may be offered as an alternative to conventional fractionation.

- **Recommendation strength:** Conditional
- **Quality of evidence:** Moderate
- **Consensus:** 88%

Statement KQ3B: In men with intermediate-risk prostate cancer receiving EBRT, ultrahypofractionation may be offered as an alternative to conventional fractionation. The task force strongly encourages that these patients be treated as part of a clinical trial or multi-institutional registry.

- **Strength of recommendation:** Conditional
- **Quality of evidence:** Low
- **Consensus:** 94%

Statement KQ3C: In men with high-risk prostate cancer receiving EBRT, the task force does not suggest offering ultrahypofractionation outside of a clinical trial or multi-institutional registry due to insufficient comparative evidence.

- **Strength of recommendation:** Conditional
- **Quality of evidence:** Low
- **Consensus:** 94%

Morgan et al JCO 2018

5# EXTREME HYPOFRACTIONATION & PROSTATE CANCER:

EVIDENCE BASED GUIDELINES

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Prostate Cancer

NCCN Guic
Table

PRINCIPLES OF RADIATION THERAPY

Table 1: Below are examples of regimens that have shown acceptable efficacy and toxicity. The optimal regimen for an individual patient warrants evaluation of comorbid conditions symptoms and toxicity of therapy. Additional fractionation schemes may be used as long as sound oncologic principles and appropriate estimate of BED are considered.
See PROS-3, PROS-4, PROS-5, PROS-6, PROS-7, PROS-8, PROS-12, and PROS-I for other recommendations, including recommendations for neoadjuvant/concomitant/adjuvant AD

Regimen	Preferred Dose/Fractionation	NCCN Risk Group (✓ indicates an appropriate regimen option if RT is given)					
		Very Low and Low	Favorable Intermediate	Unfavorable Intermediate	High and Very High	Regional N1	Low Volume M1[a]
EBRT							
Moderate Hypofractionation (Preferred)	3 Gy x 20 fx 2.7 Gy x 26 fx 2.5 Gy x 28 fx	✓	✓	✓	✓	✓	
	2.75 Gy x 20 fx						✓
Conventional Fractionation	1.8–2 Gy x 37–45 fx	✓	✓	✓	✓	✓	
	2.2 Gy x 35 fx + micro-boost to MRI-dominant lesion to up to 95 Gy (fractions up to 2.7 Gy)		✓	✓	✓		
SBRT	9.5 Gy x 4 fx	✓	✓	✓	✓		
Ultra-Hypofractionation	7.25–8 Gy x 5 fx 6.1 Gy x 7 fx	✓	✓	✓	✓		
	6 Gy x 6 fx						✓

PROSTATE EXTREME HYPOFRACTIONATION IN 5#:
PREDICTORS OF TOXICITY: DOSE ESCALATION

WARNING FOR RECTAL TOXICITY MOVING FROM 7-8 Gy/fr 10 Gy/fr.

Clinical Investigation: Genitourinary Cancer

Predictors of Rectal Tolerance Observed in a Dose-Escalated Phase 1-2 Trial of Stereotactic Body Radiation Therapy for Prostate Cancer

D. W. Nathan Kim, MD, PhD,* L. Chinsoo Cho, MD,† Christopher Straka, BS,* Alana Christie, MS,‡ Yair Lotan, MD,§ David Pistenmaa, MD,* Brian D. Kavanagh, MD,‖ Akash Nanda, MD, PhD,¶ Patrick Kueplian, MD,# Jeffrey Brindle, MD,** Susan Cooley, RN,* Alida Perkins, ANP,* David Raben, MD,‖ Xian-Jin Xie, PhD,‡ and Robert D. Timmerman, MD*

*Departments of *Radiation Oncology and §Urology, †Harold C. Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, Texas; †Department of Radiation Oncology, University of Minnesota, Minneapolis, Minnesota; ‖Department of Radiation Oncology, University of Colorado, Denver, Colorado; ¶Department of Radiation Oncology, University of Florida Health Cancer Center at Orlando Health, Orlando, Florida; #Department of Radiation Oncology, University of California, Los Angeles, Los Angeles, California; and **Prairie Lakes Hospital, Watertown, South Dakota*

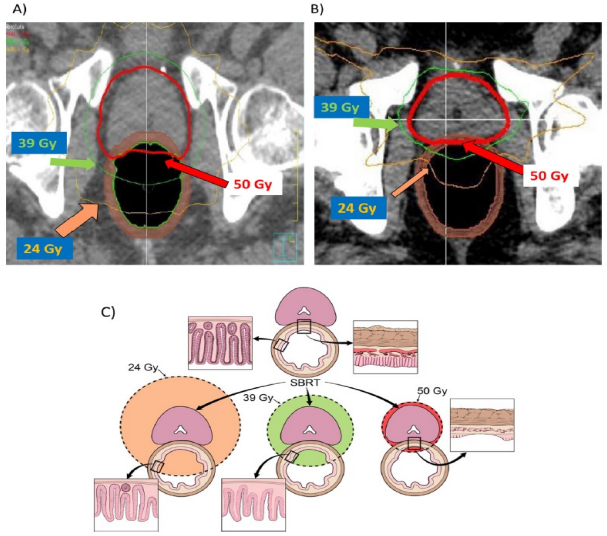


Fig. 2. Representative treatment plans of patients treated to 50 Gy in 5 fractions, with (A) grade 2 acute and grade 3 delayed rectal toxicity, and (B) grade 1 acute/delayed rectal toxicity only. (C) Representation of biologic consequence of rectal wall irradiated to 24 Gy, 39 Gy, and 50 Gy.

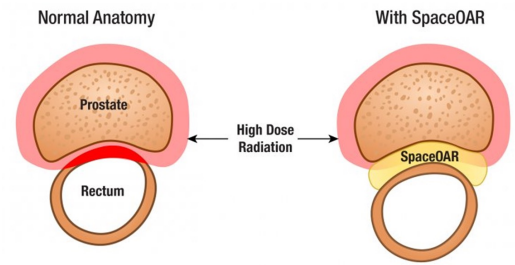
✓91 patients enrolled in a dose-escalation (45, 47.5, and 50 Gy in 5 fractions) phase 1-2 clinical study

✓At the highest dose level (50 Gy in 5), 6.6% of patients treated (6 of 91) developed high-grade rectal toxicity, 5 of whom required colostomy.
✓Grade 3+ delayed rectal toxicity was strongly correlated with volume of rectal wall receiving 50 Gy

⇧⇧DOSE
⇧⇧TOX≥3!!!

Kim et al Red J 2014

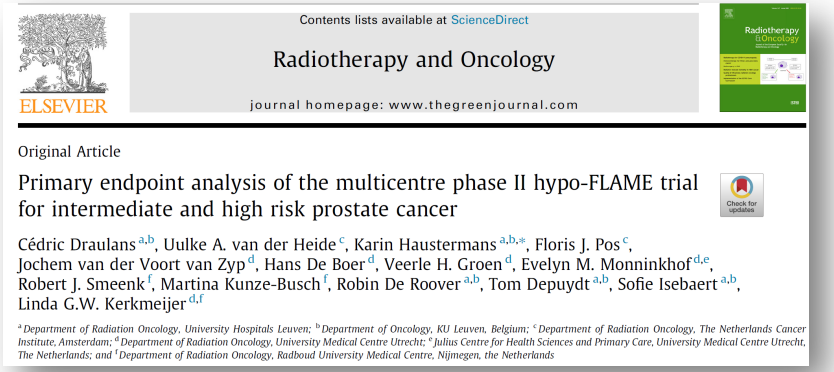
PROSTATE EXTREME HYPOFRACTIONATION IN 5#:
SPACEOAR SABRE TRIAL



Design	Prospective, multicenter randomized control trial of the SpaceOAR Vue System in subjects with prostate cancer undergoing Stereotactic Body Radiotherapy (SBRT)
Randomization	2:1 Randomization Treatment to Control Treatment Group: SpaceOAR Vue System Control Group: No SpaceOAR Vue System
SBRT	40 Gy in 5 x 8 Gy fractions to the Planning Target Volume (PTV)
Planned Number of Sites and Subjects	Up to 500 subjects at up to 45 sites globally
Follow-Up Schedule	Follow Up: 3, 6, 12, 18, 24, 36, 48 and 60 months post-SBRT initiation 6-, 18-, 36-, 48- and 60- months visits can be conducted remotely
Objective	To demonstrate the effectiveness of the SpaceOAR Vue System in reducing late gastrointestinal (GI) toxicity in subjects undergoing Stereotactic Body Radiotherapy (SBRT) to treat prostate cancer.

PROSTATE EXTREME HYPOFRACTIONATION IN 5#:
HYPO-FLAME

Our Rating



Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

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Original Article

Primary endpoint analysis of the multicentre phase II hypo-FLAME trial for intermediate and high risk prostate cancer

Cédric Draulans [a,b], Uulke A. van der Heide [c], Karin Haustermans [a,b,*], Floris J. Pos [c], Jochem van der Voort van Zyp [d], Hans De Boer [d], Veerle H. Groen [d], Evelyn M. Monninkhof [d,e], Robert J. Smeenk [f], Martina Kunze-Busch [f], Robin De Roover [a,b], Tom Depuydt [a,b], Sofie Isebaert [a,b], Linda G.W. Kerkmeijer [d,f]

[a] Department of Radiation Oncology, University Hospitals Leuven; [b] Department of Oncology, KU Leuven, Belgium; [c] Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam; [d] Department of Radiation Oncology, University Medical Centre Utrecht; [e] Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, The Netherlands; and [f] Department of Radiation Oncology, Radboud University Medical Centre, Nijmegen, the Netherlands

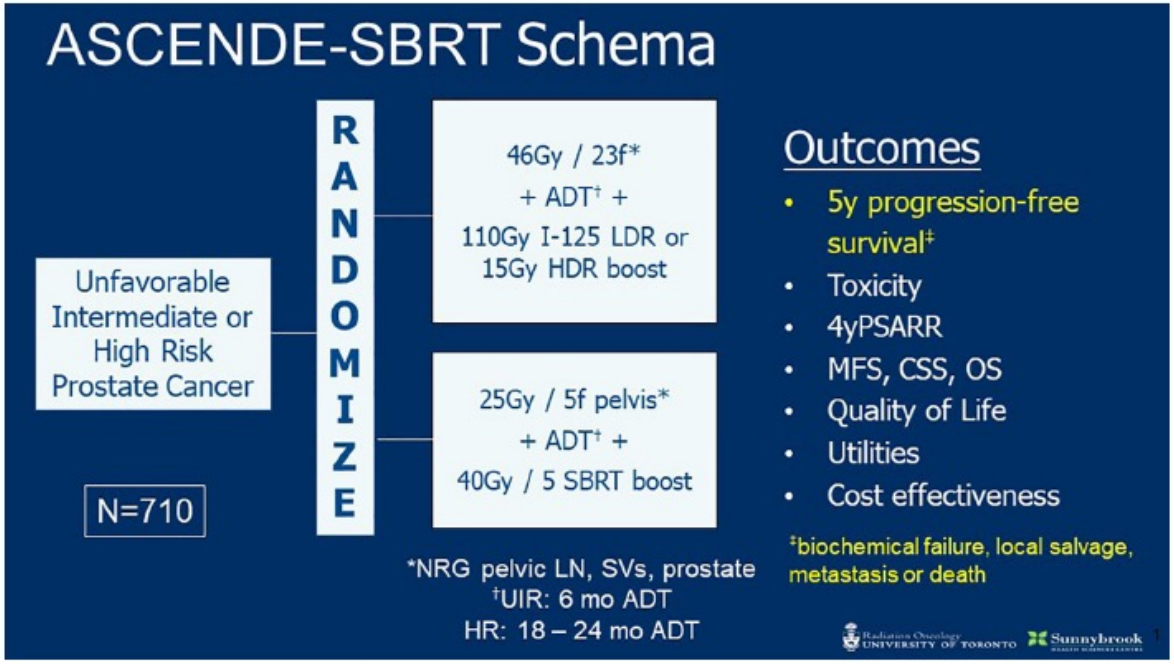
✓100 patients were treated with extreme hypofractionated doses of 35 Gy in 5 weekly fractions to the whole prostate gland with an integrated boost up to 50 Gy to the multiparametric (mp) MRI-defined tumour(s).
✓ Treatment-related toxicity was measured using the CTCAE v4.0.

✓At 6 months while the clinical benefit of focal dose escalation is still under investigation in the phase III FLAME trial, the current phase II hypo-FLAME trial showed that a focal SBRT boost to the macroscopic tumour(s) is associated with acceptable acute GU and GI toxicity in addition to whole gland prostate SBRT

Draulans et al, Green J 2020

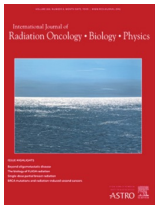
PROSTATE EXTREME HYPOFRACTIONATION IN 5#:
FUTURE DIRECTIONS: HIGH RISK???

Technology driven SBRT to prostate and pelvis in 5 session is now being tested at the phase III level, with international RCTs like the ASCENDE-SBRT study launching soon.



Correa et al, Frontiers in Oncology 2022

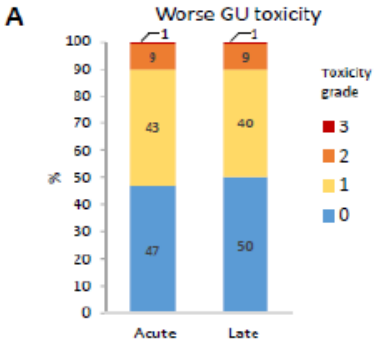
PROSTATE EXTREME HYPOFRACTIONATION IN 5#:
FUTURE DIRECTIONS: POST-OP SETTING???

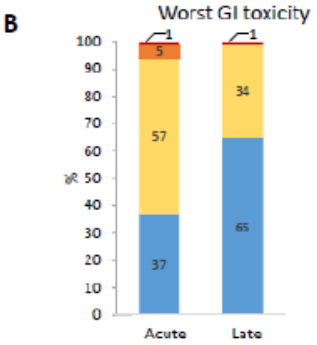


Quality-of-Life Outcomes and Toxicity Profile Among Patients with Localized Prostate Cancer After Radical Prostatectomy Treated With Stereotactic Body Radiation: The SCIMITAR Multi-Center Phase 2 Trial

- Phase 2, single arm trial enrolling patients with postoperative prostate-specific antigen (PSA)>0.03 ng/mL or adverse pathologic features
- 100 patients (CTgRT, n=69; MRgRT, n=31) and 6 months of mFUP
- Median prostate bed dose was 32 (30-34) Gy.
- Acute and late grade 2 GU toxicities were both 9%, while acute and late grade 2 GI toxicities were 5% and 0%.
- Three patients had grade 3 toxicity (n=1 GU and n=2 GI).

Conclusions: Post-prostatectomy SBRT was well tolerated at short-term follow-up. MRgRT may decrease GI toxicity.





Ma et al, IJROBP 2022

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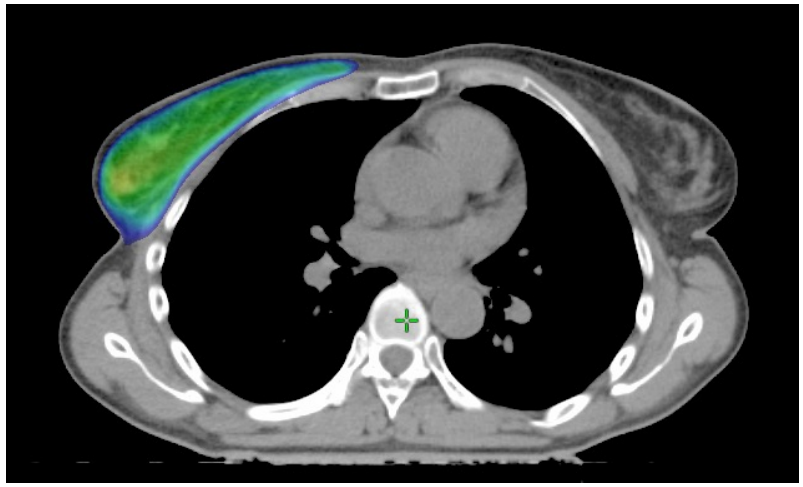
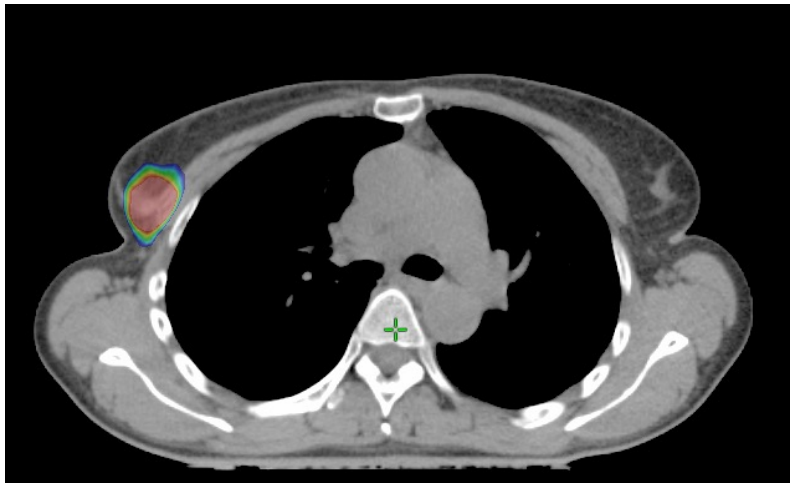
HYPOFRACTIONATION IN 5#:

BREAST CANCER





UNIVERSITAS STUDIORUM BRIXIAE

BREAST & HYPOFRACTIONATION: EVIDENCE

Standard vs IPO RT

4 randomized trials, > 7000 women : START-A trial , START-B trial, RMH/GOC trial, ONTARIO trial.
#13-16 are safe and effective.

Lancet Oncol 2008;9:331–341.
Lancet 2008;371:1098–1107.
Lancet Oncol 2006;7:467–471.
N Engl J Med 2010;362:513–520

Table 1 Four prospective phase 3 randomized trials of hypofractionated WBI versus conventional fractionation in early-stage breast cancer

Trial	Years conducted	*n*	Fractionation Gy/*n* of fractions	Local recurrence,%	Good/excellent cosmesis,%	Time point
RMH/GOC	1986–1998	470	50/25	12.1	71	10 years
[7, 8]		466	42.9/13	9.6	74	
		474	39/13	14.8	58	
START A	1998–2002	749	50/25	3.6	60[a]	5 Years
[9]		750	41.6/13	3.5	58[a]	
		737	39/13	5.2	66[a]	
START B	1999–2001	1105	50/25	3.3	61[a]	5 Years
[10•]		1110	40/15	2.2	66[a]	
OCOG	1993–1996	612	50/25	6.7	71	10 Years
[11•]		622	42.5/16	6.2	70	

BREAST & EXTREME HYPOFRACTIONATION IN 5#:
EVIDENCE OF WBI

5 sessions: 1 fraction per week

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

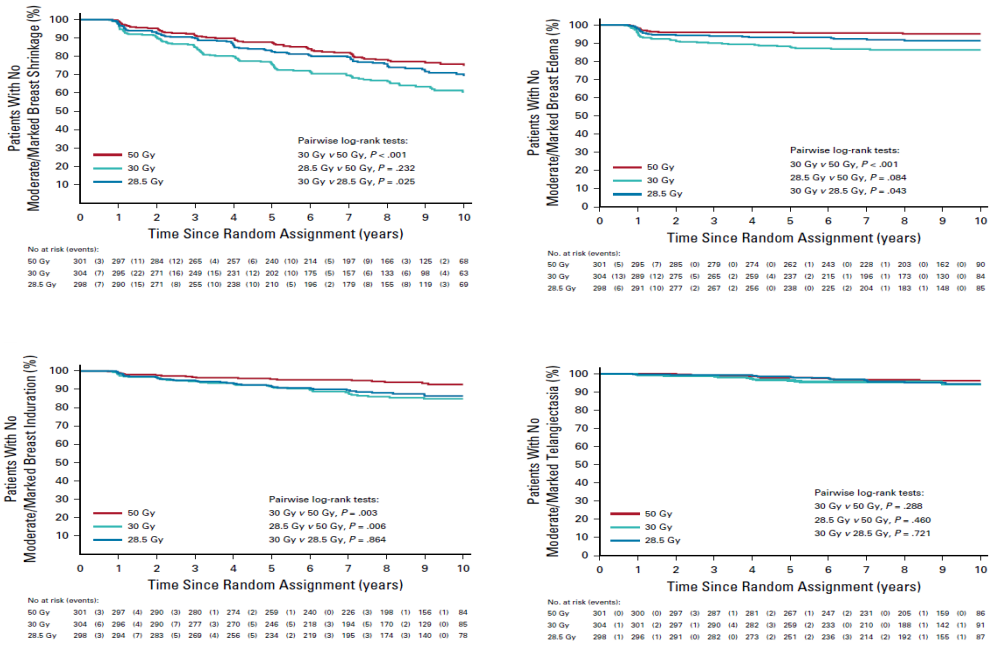
Ten-Year Results of FAST: A Randomized Controlled Trial of 5-Fraction Whole-Breast Radiotherapy for Early Breast Cancer

Adrian Murray Brunt, FRCR[1]; Joanne S. Haviland, MSc[2]; Mark Sydenham, BSc Hons[2]; Rajiv K. Agrawal, FRCR[3]; Hafiz Algurafi, FRCR[4]; Abdulla Alhasso, FRCR[5]; Peter Barrett-Lee, FRCR[6]; Peter Bliss, FRCR[7]; David Bloomfield, FRCR[8]; Joanna Bowen, FRCR[9]; Ellen Donovan, PhD[10]; Andy Goodman, FRCR[11]; Adrian Hamett, FRCR[12]; Martin Hogg, FRCR[13]; Sri Kumar, FRCR[14]; Helen Passant, FRCR[6]; Mary Quigley, FRCR[15]; Liz Sherwin, FRCR[16]; Alan Stewart, FRCR[17]; Isabel Syndikus, FRCR[18]; Jean Tremlett, MSc[8]; Yat Tsang, PhD[19]; Karen Venables, PhD[19]; Duncan Wheatley, FRCR[20]; Judith M. Bliss, MSc[2]; and John R. Yarnold, FRCR[21]

METHODS Women ≥ 50 years of age with low-risk invasive breast carcinoma (pT1-2 pN0) were randomly assigned to 50 Gy/25 fr (5 weeks) or 30 or 28.5 Gy in 5 once-weekly fr of 6.0 or 5.7 Gy. The primary end point was change in photographic breast appearance at 2 and 5 years; secondary end points were physician assessments of NTE and local tumor control. Odds ratios (ORs) from longitudinal analyses compared regimens.

RESULTS A total of 915 women were recruited from 18 UK centers (2004-2007). Five-year photographs were available for 615/862 (71%) eligible patients. ORs for change in photographic breast appearance were 1.64 (95% CI, 1.08 to 2.49; $P = .019$) for 30 Gy and 1.10 (95% CI, 0.70 to 1.71; $P = .686$) for 28.5 Gy versus 50 Gy. α/β estimate for photographic end point was 2.7 Gy (95% CI, 1.5 to 3.9 Gy), giving a 5-fr schedule of 28 Gy (95% CI, 26 to 30 Gy) estimated to be isoeffective with 50 Gy/25 fr. ORs for any moderate/marked physician-assessed breast NTE (shrinkage, induration, telangiectasia, edema) were 2.12 (95% CI, 1.55 to 2.89; $P < .001$) for 30 Gy and 1.22 (95% CI, 0.87 to 1.72; $P = .248$) for 28.5 Gy versus 50 Gy. With 9.9 years median follow-up, 11 ipsilateral breast cancer events (50 Gy: 3; 30 Gy: 4; 28.5 Gy: 4) and 96 deaths (50 Gy: 30; 30 Gy: 33; 28.5 Gy: 33) have occurred.

CONCLUSION At 10 years, there was no significant difference in NTE rates after 28.5 Gy/5 fr compared with 50 Gy/25 fr, but NTE were higher after 30 Gy/5 fr. Results confirm the published 3-year findings that a once-weekly 5-fr schedule of whole-breast radiotherapy can be identified that appears to be radiobiologically comparable for NTE to a conventionally fractionated regimen.



For *whole breast irradiation*, 10-year f-up from the UK FAST trial with >900 patients showed *no difference in cancer control or toxicity* for 28.5 Gy in **5 <u>weekly</u> fractions** compared with conventional fractionation

Brunt AM et al, JCO 2020

BREAST & EXTREME HYPOFRACTIONATION IN 5#:
EVIDENCE OF WBI

TABLE Survival Analysis of Ipsilateral Disease in the Breast Overall and by Fractionation Schedule

Fractionation Schedule	Ipsilateral Breast Event[a]/Total (%)	KM Estimate (95% CI) of Cumulative Incidence (%)		Hazard Ratio (95% CI)
		5 Years	10 Years	
All patients	11/915 (1.2)	0.7 (0.3 to 1.6)	1.3 (0.7 to 2.3)	—
50 Gy	3/302 (1.0)	0.7 (0.2 to 2.8)	0.7 (0.2 to 2.8)	1
30 Gy	4/308 (1.3)	1.0 (0.3 to 3.2)	1.4 (0.5 to 3.8)	1.36 (0.30 to 6.06)
28.5 Gy	4/305 (1.3)	0.4 (0.05 to 2.6)	1.7 (0.6 to 4.4)	1.35 (0.30 to 6.05)

Although not powered for tumor control, the FAST trial suggests that for patients at low risk of relapse and for whom daily visits over 3 or 5 weeks are not possible because of frailty or comorbidities, 28 Gy in 5 fractions as a once-weekly schedule might be an appropriate alternative to no treatment.

Brunt AM et al, JCO 2020

BREAST & EXTREME HYPOFRACTIONATION IN 5#:
EVIDENCE OF WBI

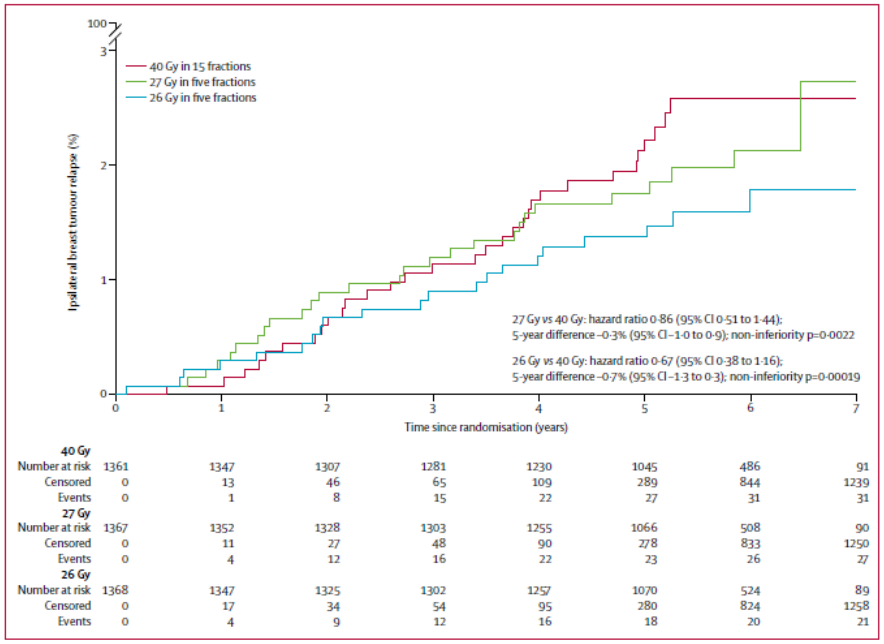
5 sessions over 1 week

Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial

Adrian Murray Brunt, Joanne S Haviland*, Duncan A Wheatley, Mark A Sydenham, Abdulla Alhasso, David J Bloomfield, Charlie Chan, Mark Churn, Susan Cleator, Charlotte E Coles, Andrew Goodman, Adrian Harnett, Penelope Hopwood, Anna M Kirby, Cliona C Kirwan, Carolyn Morris, Zohal Nabi, Elinor Sawyer, Navita Somaiah, Liba Stones, Isabel Syndikus, Judith M Bliss†, John R Yarnold†, on behalf of the FAST-Forward Trial Management Group*

Methods FAST-Forward is a multicentre, phase 3, randomised, non-inferiority trial done at 97 hospitals (47 radiotherapy centres and 50 referring hospitals) in the UK. Patients aged at least 18 years with invasive carcinoma of the breast (pT1–3, pN0–1, M0) after breast conservation surgery or mastectomy were eligible. We randomly allocated patients to either 40 Gy in 15 fractions (over 3 weeks), 27 Gy in five fractions (over 1 week), or 26 Gy in five fractions (over 1 week) to the whole breast or chest wall. Allocation was not masked because of the nature of the intervention. The primary endpoint was ipsilateral breast tumour relapse; assuming a 2% 5-year incidence for 40 Gy, non-inferiority was predefined as ≤1·6% excess for five-fraction schedules (critical hazard ratio [HR] of 1·81). Normal tissue effects were assessed by clinicians, patients, and from photographs. This trial is registered at isrctn.com, ISRCTN19906132.

Findings Between Nov 24, 2011, and June 19, 2014, we recruited and obtained consent from 4096 patients from 97 UK centres, of whom 1361 were assigned to the 40 Gy schedule, 1367 to the 27 Gy schedule, and 1368 to the 26 Gy schedule. At a median follow-up of 71·5 months (IQR 71·3 to 71·7), the primary endpoint event occurred in 79 patients (31 in the 40 Gy group, 27 in the 27 Gy group, and 21 in the 26 Gy group); HRs versus 40 Gy in 15 fractions were 0·86 (95% CI 0·51 to 1·44) for 27 Gy in five fractions and 0·67 (0·38 to 1·16) for 26 Gy in five fractions. 5-year incidence of ipsilateral breast tumour relapse after 40 Gy was 2·1% (1·4 to 3·1); estimated absolute differences versus 40 Gy in 15 fractions were −0·3% (−1·0 to 0·9) for 27 Gy in five fractions (probability of incorrectly accepting an inferior five-fraction schedule: p=0·0022 *vs* 40 Gy in 15 fractions) and −0·7% (−1·3 to 0·3) for 26 Gy in five fractions (p=0·00019 *vs* 40 Gy in 15 fractions). At 5 years, any moderate or marked clinician-assessed normal tissue effects in the breast or chest wall was reported for 98 of 986 (9·9%) 40 Gy patients, 155 (15·4%) of 1005 27 Gy patients, and 121 of 1020 (11·9%) 26 Gy patients. Across all clinician assessments from 1–5 years, odds ratios versus 40 Gy in 15 fractions were 1·55 (95% CI 1·32 to 1·83, p<0·0001) for 27 Gy in five fractions and 1·12 (0·94 to 1·34, p=0·20) for 26 Gy in five fractions. Patient and photographic assessments showed higher normal tissue effect risk for 27 Gy versus 40 Gy but not for 26 Gy versus 40 Gy.



40 Gy								
Number at risk	1361	1347	1307	1281	1230	1045	486	91
Censored	0	13	46	65	109	289	844	1239
Events	0	1	8	15	22	27	31	31
27 Gy								
Number at risk	1367	1352	1328	1303	1255	1066	508	90
Censored	0	11	27	48	90	278	833	1250
Events	0	4	12	16	22	23	26	27
26 Gy								
Number at risk	1368	1347	1325	1302	1257	1070	524	89
Censored	0	17	34	54	95	280	824	1258
Events	0	4	9	12	16	18	20	21

Figure 2: Cumulative risk of ipsilateral breast tumour relapse by fractionation schedule

Interpretation 26 Gy in five fractions over 1 week is non-inferior to the standard of 40 Gy in 15 fractions over 3 weeks for local tumour control, and is as safe in terms of normal tissue effects up to 5 years for patients prescribed adjuvant local radiotherapy after primary surgery for early-stage breast cancer.

The consistency of FAST-Forward results supports the adoption of **26 Gy in five daily fractions as a new standard** as adjuvant RT

Brunt AM et al, Lancet 2020

BREAST & EXTREME HYPOFRACTIONATION IN 5#:
EVIDENCE OF PBI

Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast Cancer: Long-Term Results of the Randomized Phase III APBI-IMRT-Florence Trial

5 non-consecutive once-daily fractions

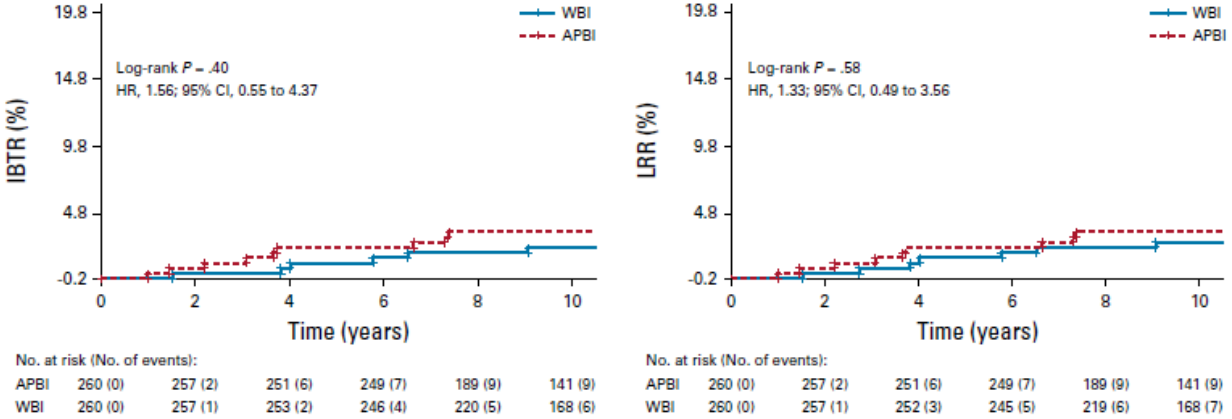
Icro Meattini, MD[1,2]; Livia Marrazzo, MS[2]; Calogero Saieva, MD[3]; Isacco Desideri, MD[1,2]; Vieri Scotti, MD[2]; Gabriele Simontacchi, MD[2]; Pierluigi Bonomo, MD[2]; Daniela Greto, MD[2]; Monica Mangoni, MD, PhD[1,2]; Silvia Scoccianti, MD[2]; Sara Lucidi, MD[1]; Lisa Paoletti, MD[4]; Massimiliano Fambrini, MD[1,2]; Marco Bernini, MD, PhD[2]; Luis Sanchez, MD[2]; Lorenzo Orzalesi, MD[1,2]; Jacopo Nori, MD[2]; Simonetta Bianchi, MD[1,2]; Stefania Pallotta, MS[1,2]; and Lorenzo Livi, MD[1,2]

PURPOSE To report the long-term results of external-beam accelerated partial-breast irradiation (APBI) intensity-modulated radiation therapy (IMRT) Florence phase III trial comparing whole-breast irradiation (WBI) to APBI in early-stage breast cancer.

PATIENTS AND METHODS The primary end point was to determine the 5-year difference in ipsilateral breast tumor recurrence (IBTR) between 30 Gy in 5 once-daily fractions (APBI arm) and 50 Gy in 25 fractions with a tumor bed boost (WBI arm) after breast-conserving surgery.

RESULTS Five hundred twenty patients, more than 90% of whom had characteristics associated with low recurrence risk, were randomly assigned (WBI, n = 260; APBI, n = 260) between 2005 and 2013. Median follow-up was 10.7 years. The 10-year cumulative incidence of IBTR was 2.5% (n = 6) in the WBI and 3.7% (n = 9) in the APBI arm (hazard ratio [HR], 1.56; 95% CI, 0.55 to 4.37; $P = .40$). Overall survival at 10 years was 91.9% in both arms (HR, 0.95; 95% CI, 0.50 to 1.79; $P = .86$). Breast cancer–specific survival at 10 years was 96.7% in the WBI and 97.8% in the APBI arm (HR, 0.65; 95% CI, 0.21 to 1.99; $P = .45$). The APBI arm showed significantly less acute toxicity ($P = .0001$) and late toxicity ($P = .0001$) and improved cosmetic outcome as evaluated by both physician ($P = .0001$) and patient ($P = .0001$).

CONCLUSION The 10-year cumulative IBTR incidence in early breast cancer treated with external APBI using IMRT technique in 5 once-daily fractions is low and not different from that after WBI. Acute and late treatment-related toxicity and cosmesis outcomes were significantly in favor of APBI.



Relevance

APBI approach using an intensity-modulated radiation therapy technique in 5 once-daily fractions should be considered an attractive option when an external APBI approach is chosen to treat a patient with low-risk early BC.

Meattini I et al, JCO 2020

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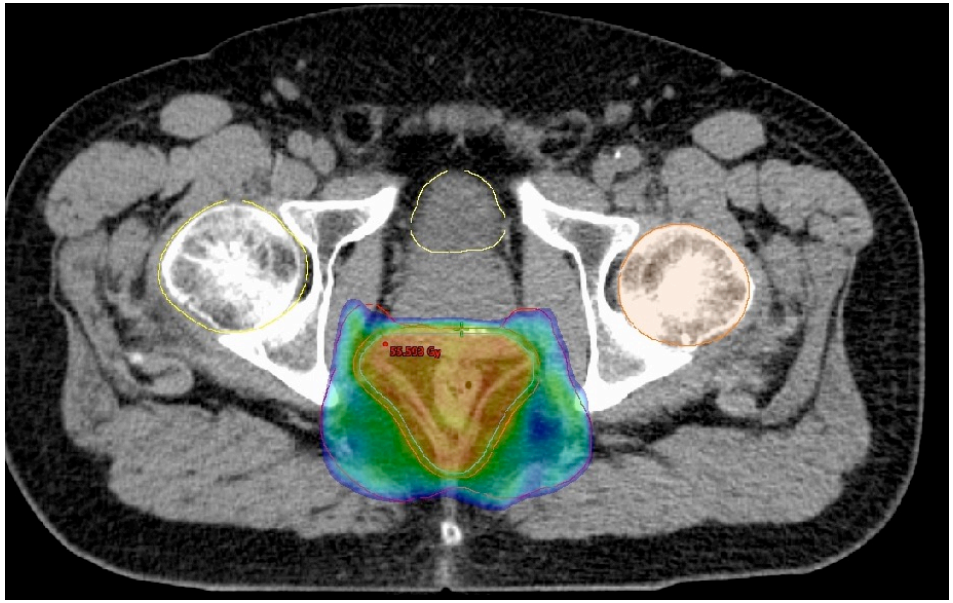
HYPOFRACTIONATION IN 5#:

RECTAL CANCER



5 DAYS

RECTUM & EXTREME HYPOFRACTIONATION IN 5#:
GUIDELINES

Radiation Therapy for Rectal Cancer: Executive Summary of an ASTRO Clinical Practice Guideline

Table 3 Recommendations for neoadjuvant regimens

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with rectal cancer receiving neoadjuvant chemoradiation, conventional fractionation from 5000-5040 cGy in 25-28 fractions with concurrent chemotherapy is recommended.	Strong	High 9,21,22
2. For patients with rectal cancer receiving neoadjuvant short-course RT, 2500 cGy in 5 fractions without concurrent chemotherapy is recommended.	Strong	High 7,11
3. For patients with rectal cancer undergoing neoadjuvant chemoradiation, only concurrent 5-fluorouracil or capecitabine is recommended with RT for radiosensitization.	Strong	High 21-28
4. For patients with rectal cancer undergoing neoadjuvant therapy, chemotherapy alone (FOLFOX or CAPOX) is conditionally recommended only in the context of a clinical trial or multi-institutional registry.	Conditional	Low 29

Wo J, et al., PRO 2021

RECTUM & EXTREME HYPOFRACTIONATION IN 5#: EVIDENCE

Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial

Willem van Gijn, Corrie A M Marijnen, Iris D Nagtegaal, Elma Meershoek-Klein Kranenbarg, Hein Putter, Theo Wiggers, Harm J T Rutten, Lars Påhlman, Bengt Glimelius, Cornelis J H van de Velde, for the Dutch Colorectal Cancer Group

1861 rectal cancer patients randomized to:

- Neoadjuvant RT (**25 Gy/5 fr**)

followed by TME (maximum 10 days from RT start)

- TME alone

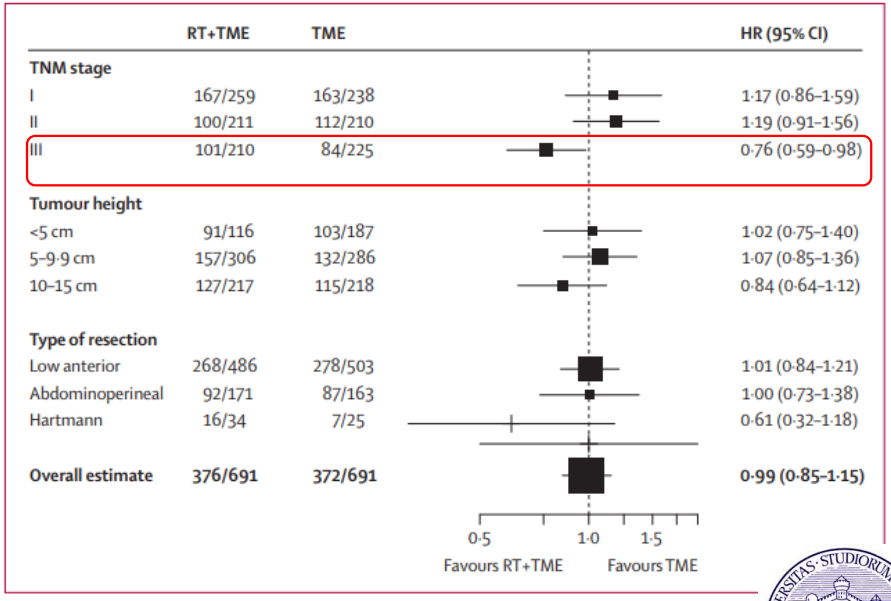
Median follow-up: 11.6 years

RESULTS:

10-y local recurrence rate: 5% vs 11%

10-y cancer-specific death: 17% vs 22%

No differences in distant recurrence and OS



Van Gijn et al Lancet 2011

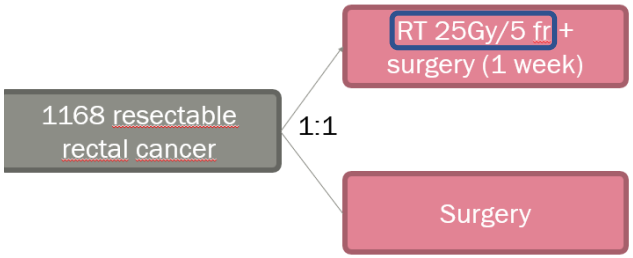
RECTUM & EXTREME HYPOFRACTIONATION IN 5#:
INTRODUCTION

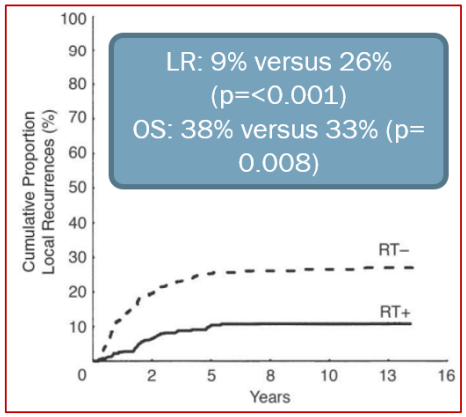
Swedish Rectal Cancer Trial: Long Lasting Benefits From Radiotherapy on Survival and Local Recurrence Rate

Joakim Folkesson, Helgi Birgisson, Lars Pahlman, Bjorn Cedermark, Bengt Glimelius, and Ulf Gunnarsson

JCO, 2005

- Median follow-up 13 years



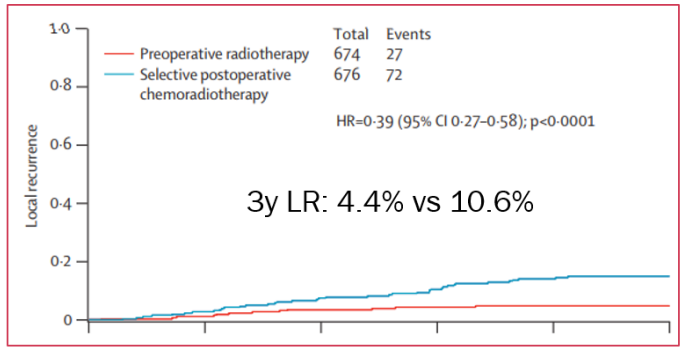


Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial

*David Sebag-Montefiore, Richard J Stephens, Robert Steele, John Monson, Robert Grieve, Subhash Khanna, Phil Quirke, Jean Couture, Catherine de Metz, Arthur Sun Myint, Eric Bessell, Gareth Griffiths, Lindsay C Thompson, Mahesh Parmar, on behalf of all the trial collaborators**

Lancet, 2009

- 1350 randomized to pre- or postoperative RT:
- 25 Gy/5 fr + surgery
- Surgery + 45 Gy/25 fr + 5FU (only to CRM+)



No differences in OS

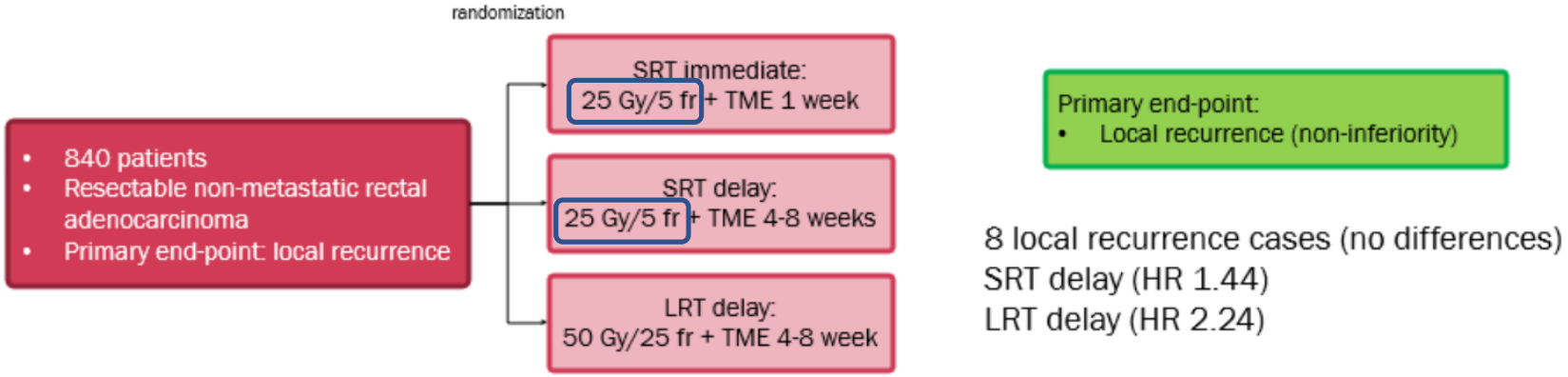
Folkesson et al JCO 2005
Montefiore et et al Lancet 2009

RECTUM & EXTREME HYPOFRACTIONATION IN 5#:
INTRODUCTION

Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial

Lancet, 2017

Johan Erlandsson, Torbjörn Holm, David Pettersson, Åke Berglund, Björn Cedermark, Calin Radu, Hemming Johansson, Mikael Machado, Fredrik Hjern, Olof Hallböök, Ingvar Syk, Bengt Glimelius, Anna Martling



Primary end-point:
- Local recurrence (non-inferiority)

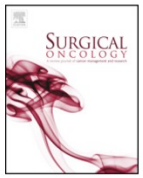
8 local recurrence cases (no differences)
SRT delay (HR 1.44)
LRT delay (HR 2.24)

The risk of postoperative complications significantly lower after SRT-delay than SRT-immediate (41% versus 53%; OR 0·61 [95% CI 0·45–0·83] p=0·001)

Erlandsoon et al, Lancet 2017

RECTUM & EXTREME HYPOFRACTIONATION IN 5#: EVIDENCE

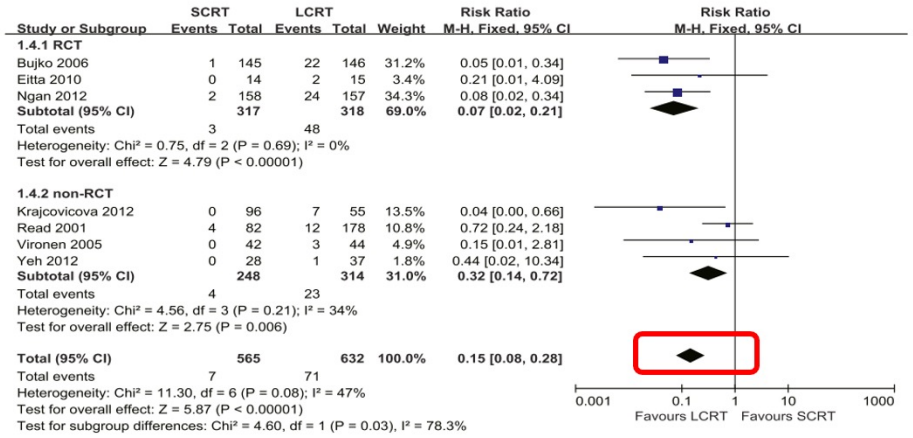
Short-course preoperative radiotherapy with immediate surgery versus long-course chemoradiation with delayed surgery in the treatment of rectal cancer: A systematic review and meta-analysis



2014

Zhi-Rui Zhou [a, b], Shi-Xin Liu [c, *], Tian-Song Zhang [d], Ling-Xiao Chen [e], Jun Xia [f], Zhi-De Hu [g], Bo Li [h]

- 12 clinical trials
- No differences in sphincther preservation, R0, local recurrence, distant metastases, DFS, OS
- Better pCR rate and downstaging with long-course radiochemotherapy



Zhou et al, Surg Oncol 2014

RECTUM & EXTREME HYPOFRACTIONATION IN 5#:
PRACTICAL CONSIDERATIONS

- ✓ Recent studies have included 5-fraction short-course RT as part of total neoadjuvant therapy and shown comparable pathologic complete response rates to long course, with no increase in surgical complications

- ✓ Since 2020 National Comprehensive Cancer Network clinical practice guidelines supported long-course chemoradiation as the preferred option for T3 and node-positive T1-2 patients, stating that 5-fraction short-course radiation “can also be considered for patients with stage T3 rectal cancer.”

- ✓ Memorial Sloan Kettering Cancer Center has gone a step further to mandate 5-fraction RT for all localized rectal cancers until the pandemic passes

Ling D et al, IJROBP 2020
NCCN 2022

HYPOFRACTIONATION IN 5#:

CONCLUSIONS

✓The COVID-19 pandemic has imposed sweeping and potentially long-lasting changes on the world.

✓The evidence behind hypofractionated regimens recommended in various COVID-19 guidelines includes large, randomized prospective trials with thousands of patients published before the COVID-19 era.

✓These shorter courses are *patient-friendly*, associated with *with less financial toxicity*, *equally efficacious*, and *similar to or less morbid* than prolonged schedules.

✓Older concerns regarding hypofractionation were driven by 2-dimensional planning limitations, which are now mitigated by *conformal or inverse planning, use of hydrogel spacer, heart-sparing techniques such as deep inspiration breathhold, and daily image guidance*.

Ling D et al, IJROBP 2020

THANK YOU!!!!

WELCOME TO VERONA-NEGRAR, ITALY TO OUR REALITY !!!

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FILIPPO ALONGI