Decennale di
HIGHLIGHTS in
RADIOTERAPIA

Update degli Studi
Practice Changing 2024

Undicesima Edizione

In memoria di Renzo Corvò

IPOFRAZIONAMENTO NEL CARCINOMA MAMMARIO: TOO FAST?

Cynthia Aristei

ROMA
30-31 gennaio 2025
Starhotels Metropole

No Conflitti di Interesse

L’ IPOFRAZIONAMENTO
È FAST

INTRODUZIONE

Dopo chirurgia conservativa e mastectomia sono stati tradizionalmente somministrati 1.8-2 Gy/frazione x 5 giorni/settimana fino alla dose totale di 50.4-50 Gy ± boost su letto tumorale (10-20 Gy)

I risultati degli studi START e Canadese hanno rivoluzionato la modalità di somministrazione della dose, introducendo

IPOFRAZIONAMENTO

Studi Randomizzati di Fase III

Controllo tumorale non inferiore con l'ipofrazionamento rispetto al convenzionale

Trial	Hypofractionated Schedule
RMH/GOC *Lancet Oncol 2006*	3.3 Gy → 42.9 Gy 3 Gy → 39 Gy
START A *Lancet Oncol 2008*	3.2 Gy → 41.6 Gy 3 Gy → 39 Gy
START B *Lancet 2008*	2.67 Gy → 40 Gy
Canadian *JNCI 2002* *NEJM 2010*	2.66 Gy → 42.5 Gy

Rates of Local recurrence in the altered fractionation trials.

	Total dose (Gy)/fraction	5 yr local recurrence (%)	10 yr local recurrence (%)
RMH/GOC	50/25		12.1
	39/13		14.8
	42.9/13		9.6
START A	50/25	3.6	
	39/13	5.2	
	41.6/13	3.5	
START B	50/25	3.3	
	40/15	2.2	
Canadian	50/25	3.2	6.7
	42.5/16	2.8	6.2

Owen et al. Lancet Oncol 2006
Bentzen et al. Lancet 2008
Bentzen et al. Lancet Oncol 2008
Haviland et al., Lancet Oncol 2013
Whelan, JNCI 2002 e NEJM 2010

Studi Randomizzati di Fase III

Buona cosmesi e non peggiore tossicità tardiva con ipofrazionamento

Cosmesis and normal tissue effects of hypofractionated compared to standard breast radiation therapy.

Trial	Reference no.	Endpoint assessment (years)	Total dose (Gy)/fraction	Excellent/good cosmesis or no change (%)		Marked change (% or HR*)		Moderate/marked induration (% or HR*)		Skin toxicity (% or HR*)	
				5 yr	10 yr	5 yr	10 yr	5 yr	10 yr	5 yr	10 yr
RMH/GOC	19,31	5, 10	50/25	60.4	46.6	6.4	9.8	23.1	36.3	12.0	18.1
			42.9/13	54.3	42.0	11.2	15.6	35.6	51.1	13.0	18.0
			39/13	69.7	43.9	3.9	6.6	16.0	27.7	5.6	12.0
START A	29,34	5	50/25	59.0		1.0*		1.0*		1.0*	
			41.6/13	58.1		1.09*		1.09*		0.83*	
			39/13	65.9		0.69*		0.79*		0.63*	
START B	30,34	5	50/25	58.8		1.0*		1.0*		1.0*	
			40/15	64.5		0.83*		0.88*		0.76*	
Canadian	28,35	5, 10	50/25	79.2	71.3			6.1	10.4	3.3	7.7
			42.5/16	77.9	69.8			4.7	11.9	3.2	8.9

Hazard ratio (HR) = *.

Ipofrazionamento

NCCN® Practice Guidelines in Oncology – v.1.2010 **Invasive Breast Cancer**

Whole Breast Radiation:
Target delineation includes the majority of the breast tissue, and is best done by both clinical assessment and CT-based treatment planning. A uniform dose distribution is the objective, using compensators such as wedges, forward planning using segments, or intensity modulated radiation therapy (IMRT). The breast should receive a dose of 45-50 Gy in 1.8 - 2 Gy per fraction, or 42.5 Gy at 2.66 Gy per fraction. A boost to the tumor bed is recommended in patients at higher risk for local failure, (age < 50, positive axillary nodes, lymphovascular invasion, or close margins). This can be achieved with brachytherapy or electron beam or photon fields. Typical doses are 10-16 Gy at 2 Gy/fx. All dose schedules are given 5 days per week.

The Breast 19 (2010) 159–162

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The Breast

journal homepage: www.elsevier.com/brst

Original article

Fewer fractions of adjuvant external beam radiotherapy for early breast cancer are safe and effective and can now be the standard of care

Why the UK's NICE accepts fewer fractions as the standard of care for adjuvant radiotherapy in early breast cancer

Adrian Harnett*

Norfolk & Norwich University Hospital, Colney Lane, Norwich NR4 7UY, UK

should also feel confident with the 15-fraction regimen. Assuming an α/β value of 3.0 Gy for late adverse effects in the breast, 40 Gy in 15 fractions of 2.67 Gy is equivalent to 45.5 Gy in 2.0 Gy fractions, or to 47 Gy in 2.0 Gy fractions assuming a/b = 2.0 Gy for brachial plexus.[1] This 15-fraction schedule delivered over 3 weeks is now recommended by the National Institute for Clinical Excellence as standard of care for adjuvant radiotherapy for breast cancer patients in the United Kingdom (UK).[2]

Harnett et al, BMJ 2009

Ipofrazionamento non è stato accettato per dubbi relativi a:

1. Efficacia a lungo termine
2. Efficacia in tumori ad alto grado
3. Efficacia nei sottotipi sfavorevoli
4. Efficacia nelle pazienti giovani
5. Effetti collaterali, soprattutto dopo irradiazione dei linfonodi regionali e/o di mammelle voluminose

1. Efficacia a lungo termine

The NEW ENGLAND JOURNAL of MEDICINE

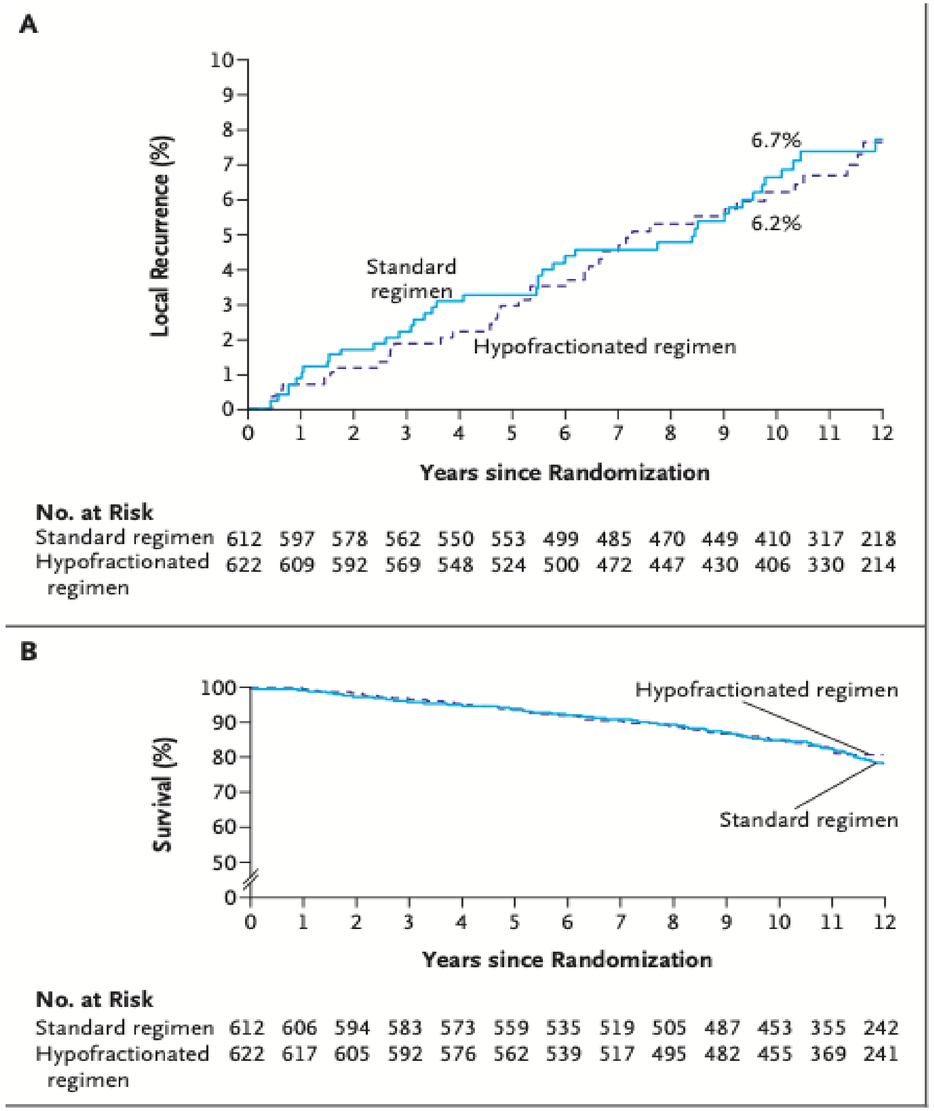
ORIGINAL ARTICLE

Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer

Timothy J. Whelan, B.M., B.Ch., Jean-Philippe Pignol, M.D., Mark N. Levine, M.D., Jim A. Julian, Ph.D., Robert MacKenzie, M.D., Sameer Parpia, M.Sc., Wendy Shelley, M.D., Laval Grimard, M.D., Julie Bowen, M.D., Himu Lukka, M.D., Francisco Perera, M.D., Anthony Fyles, M.D., Ken Schneider, M.D., Sunil Gulavita, M.D., and Carolyn Freeman, M.D.

CONCLUSIONS

Ten years after treatment, accelerated, hypofractionated whole-breast irradiation was not inferior to standard radiation treatment in women who had undergone breast-conserving surgery for invasive breast cancer with clear surgical margins and negative axillary nodes. (ClinicalTrials.gov number, NCT00156052.)

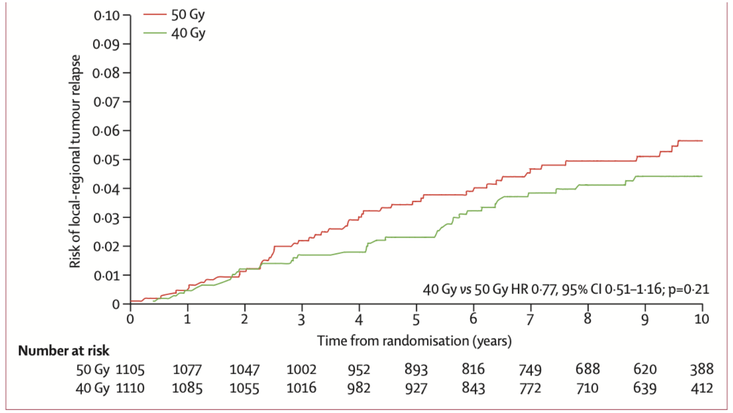


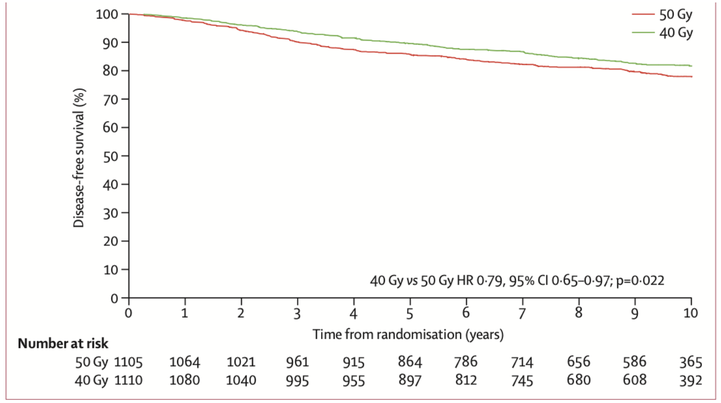
1. Efficacia a lungo termine

The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials

Joanne S Haviland, J Roger Owen, John A Dewar, Rajiv K Agrawal, Jane Barrett, Peter J Barrett-Lee, H Jane Dobbs, Penelope Hopwood, Pat A Lawton, Brian J Magee, Judith Mills, Sandra Simmons, Mark A Sydenham, Karen Venables, Judith M Bliss*, John R Yarnold*, on behalf of the START Trialists' Group

www.thelancet.com/oncology Published online September 19, 2013





Interpretation Long-term follow-up confirms that appropriately dosed hypofractionated radiotherapy is safe and effective for patients with early breast cancer. The results support the continued use of 40 Gy in 15 fractions, which has already been adopted by most UK centres as the standard of care for women requiring adjuvant radiotherapy for invasive early breast cancer.

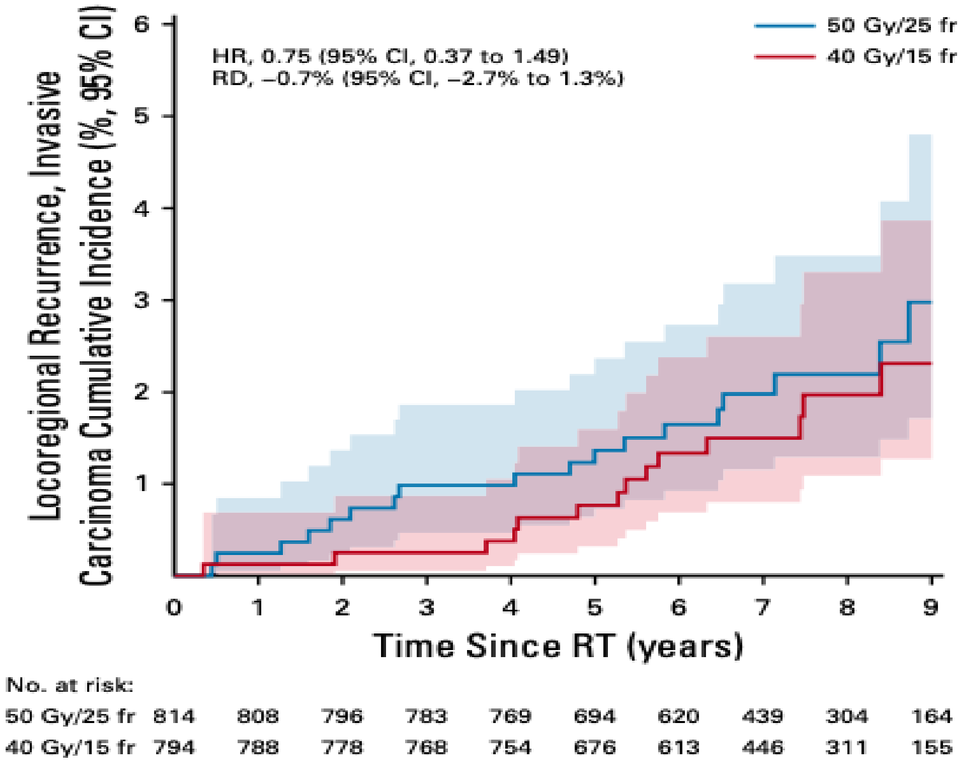
1. Efficacia a lungo termine

original reports

Hypofractionated Versus Standard Fractionated Radiotherapy in Patients With Early Breast Cancer or Ductal Carcinoma In Situ in a Randomized Phase III Trial: The DBCG HYPO Trial

Birgitte V. Offersen, MD, PhD[1,2]; Jan Alsner, PhD[1]; Hanne M. Nielsen, PhD[2]; Erik H. Jakobsen, MD[3]; Mette H. Nielsen, PhD[4]; Mechthild Krause, MD, PhD[5]; Lars Stenbygaard, MD[6]; Ingvil Mjaaland, MD[7]; Andreas Schreiber, MD, PhD[8]; Unn-Miriam Kasti, MD[9]; and Jens Overgaard, MD, DMSc[1]; on behalf of the Danish Breast Cancer Group Radiation Therapy Committee

JCO 2020; **Median follow-up time of 7.26 years**



CONCLUSION !

The 9-year locoregional recurrence risk was low.

1. Efficacia a lungo termine

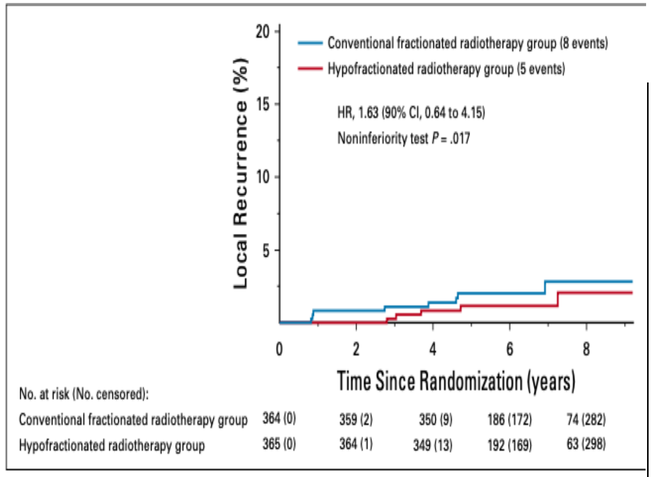
original reports

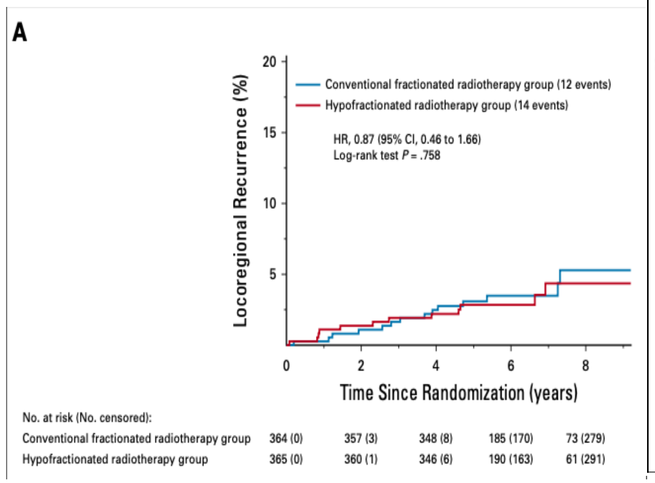
Hypofractionated Versus Conventional Fractionated Radiotherapy After Breast-Conserving Surgery in the Modern Treatment Era: A Multicenter, Randomized Controlled Trial From China

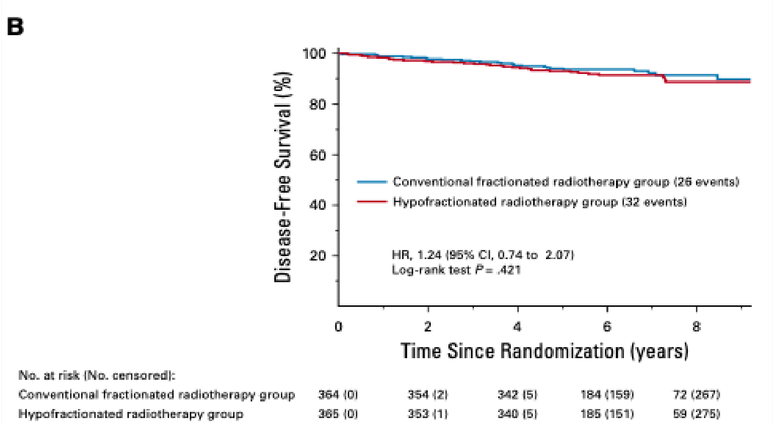
Shu-Lian Wang, MD[1]; Hui Fang, MD[1]; Chen Hu, PhD[2]; Yong-Wen Song, MD[1]; Wei-Hu Wang, MD[1]; Jing Jin, MD[1]; Yue-Ping Liu, MD[1]; Hua Ren, MD[1]; Juan Liu, MD[3]; Gao-Feng Li, MD[4]; Xiang-Hui Du, MD[5]; Yu Tang, MD[1]; Hao Jing, MD[1]; Yu-Chao Ma, MD[1]; Zhou Huang, MD[1]; Bo Chen, MD[1]; Yuan Tang, MD[1]; Ning Li, MD[1]; Ning-Ning Lu, MD[1]; Shu-Nan Qi, MD[1]; Yong Yang, MD[1]; Guang-Yi Sun, MD[1]; Xin-Fan Liu, MD[1]; and Ye-Xiong Li, MD[1]

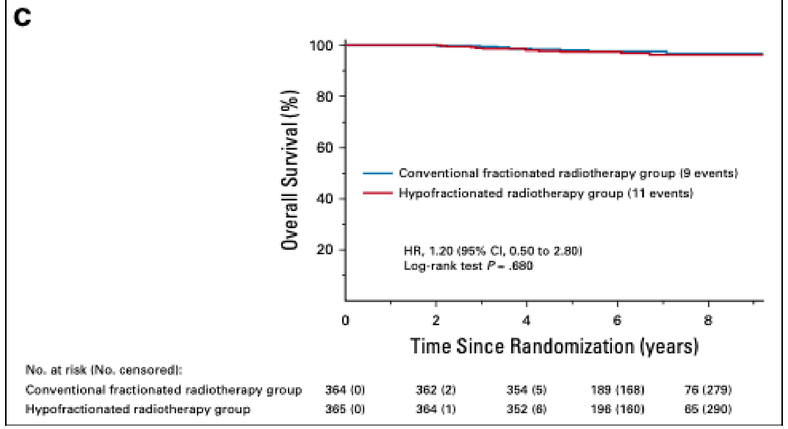
JCO 2020;

Median follow-up time of 73.5 months









CONCLUSION CFRT and HFRT with a tumor-bed boost may have similar low LR

2. Efficacia in tumori ad alto grado

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer

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central pathology
review in 989/1234 patients

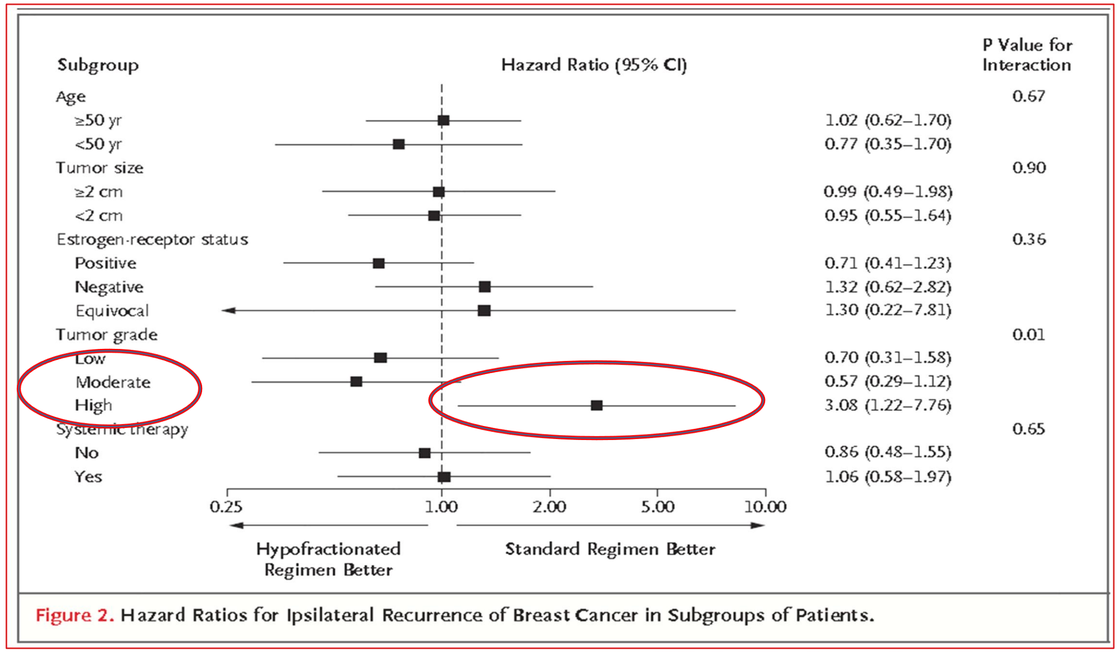

Figure 2. Hazard Ratios for Ipsilateral Recurrence of Breast Cancer in Subgroups of Patients.

Tumor factors predictive of response to hypofractionated radiotherapy in a randomized trial following breast conserving therapy

A. L. Bane[1,2*], T. J. Whelan[2], G. R. Pond[2], S. Parpia[2], G. Gohla[1], A. W. Fyles[3], J.-P. Pignol[3], K. I. Pritchard[4], S. Chambers[2] & M. N. Levine[2]

Table 3. Multivariate cox regression analysis of predictors of local recurrence ($N = 851$)

Variables	Group	Local recurrence	
		Hazard ratio (95% CI)	*P*-value[c]
Age ≥50 years		0.97 (0.51–1.85)	0.97
Tumor size >2 cm		1.19 (0.62–2.25)	0.60
Grade (Nottingham)		1.47 (0.71–3.05)	0.30
Adjuvant therapy	None	Reference	0.83[a]
	Tamoxifen	1.15 (0.64–2.07)	
	Chemotherapy	0.88 (0.34–2.31)	
Treatment = 42.5 Gy		0.80 (0.47–1.35)	0.40
Subtype	Luminal A	Reference	<0.001[b]
	Luminal B	1.71 (0.89–3.28)	
	HER2E	5.87 (2.38–14.48)	
	Basal	0.90 (0.27–2.99)	
	Unclassified	1.21 (0.41–3.58)	

[a] *P*-value is for test evaluating if receiving adjuvant therapy is different than no adjuvant therapy.
[b] *P*-value is for test evaluating whether any subtype is different from any other subtype.
[c] *P*-values are adjusted for other factors listed in this table.

2. Efficacia in tumori ad alto grado

Int. J. Radiation Oncology Biol. Phys., Vol. ■, No. ■, pp. 1–7, 2011

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2011.01.055

CLINICAL INVESTIGATION

THE IMPACT OF HYPOFRACTIONATED WHOLE BREAST RADIOTHERAPY ON LOCAL RELAPSE IN PATIENTS WITH GRADE 3 EARLY BREAST CANCER: A POPULATION-BASED COHORT STUDY

CHRISTOPHER HERBERT, F.R.C.R.,* ALAN NICHOL, F.R.C.P.C.,* IVO OLIVOTTO, F.R.C.P.C.,‡
LORNA WEIR, F.R.C.P.C.,* RYAN WOODS, M.SC.,† CAROLINE SPEERS, B.A.,†
PAULINE TRUONG, F.R.C.P.C.,‡ AND SCOTT TYLDESLEY, F.R.C.P.C.*

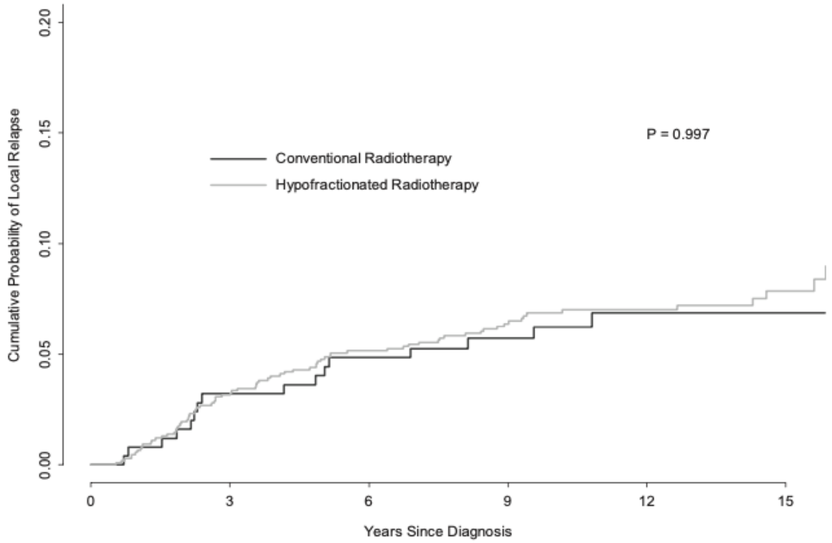

Fig. 1. Cumulative incidence of local relapse by fractionation schedule.

The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials

Joanne S Haviland, J Roger Owen, John A Dewar, Rajiv K Agrawal, Jane Barrett, Peter J Barrett-Lee, H Jane Dobbs, Penelope Hopwood, Pat A Lawton, Brian J Magee, Judith Mills, Sandra Simmons, Mark A Sydenham, Karen Venables, Judith M Bliss*, John R Yarnold*, on behalf of the START Trialists' Group†

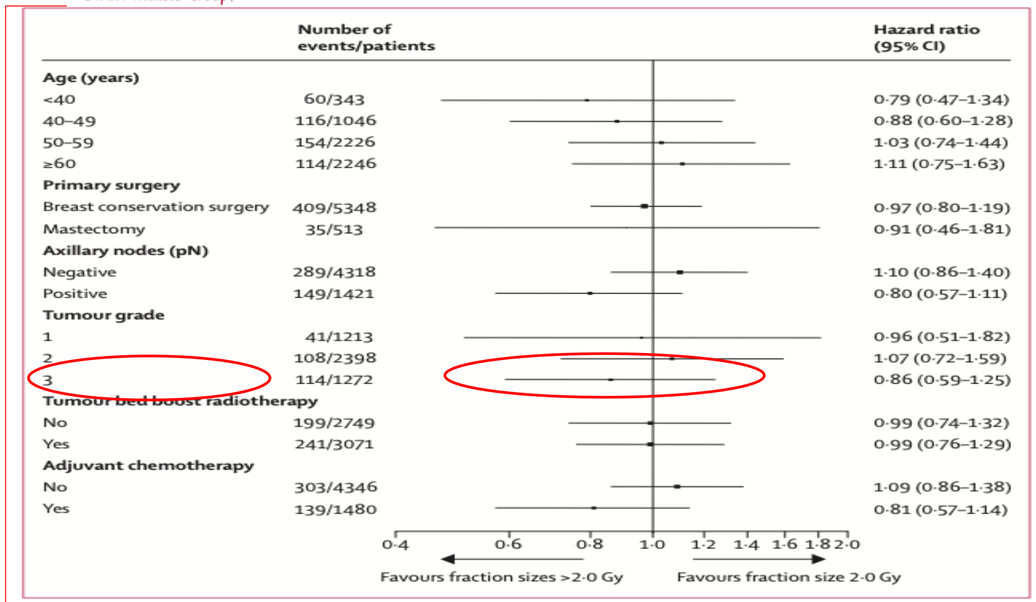

Figure 4: **Meta-analysis of local-regional relapse comparing hypofractionated regimens versus 50 Gy in 25 fractions**
Includes 5861 patients from the START pilot trial, START-A, and START-B.

3. Efficacia nei sottotipi sfavorevoli

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation

Breast Cancer Molecular Subtype as a Predictor of Radiation Therapy Fractionation Sensitivity

Nafisha Lalani, MD, MPH,* K. David Voduc, MD,*
Rachel B. Jimenez, MD,† Nathalie Levasseur, MD,‡
Lovedeep Gondara, MSc,§ Caroline Speers, MSc,§
Caroline Lohrisch, MD,‡ and Alan Nichol, MD*

Conclusions: These data support the routine use of hypofractionated radiation therapy regimens across all breast cancer subtypes.

Practical Radiation Oncology® (2022) 12, e501–e511
practical radiation oncology pro
www.practicalradonc.org

Basic Original Report

Clinical Outcomes of Hypofractionated Whole Breast Irradiation in Early Stage, Biologically High-Risk Breast Cancer

Benjamin D. Willen, MD,[a,*] Thomas J. Quinn, MD,[a]
Muayad F. Almahariq, MD, PhD,[a] Peter Y. Chen, MD,[a] M. Saada Jawad, MD,[a]
Gregory S. Gustafson, MD,[a] Eva Leung, BS,[b] Michelle Ka Yan Wu, BS,[b] and
Joshua T. Dilworth, MD, PhD[a]

[a]*Department of Radiation Oncology, Beaumont Health System, Royal Oak, Michigan; and* [b]*Oakland University William Beaumont School of Medicine, Rochester, Michigan*

Conclusions: Our data support the use of moderate HWBI in patients with early-stage, biologically high-risk breast cancer.

3. Efficacia nei sottotipi sfavorevoli

INTERNATIONAL JOURNAL OF
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CLINICAL INVESTIGATION

Disease Control After Hypofractionation Versus Conventional Fractionation for Triple Negative Breast Cancer: Comparative Effectiveness in a Large Observational Cohort

Reshma Jagsi, MD, DPhil,[a] Kent A. Griffith, MS, MPH,[b] Frank A. Vicini, MD,[c] Eyad Abu-Isa, MD,[a,d] Derek Bergsma, MD,[a,e] Amit Bhatt, MD, PhD,[f] Joshua T. Dilworth, MD, PhD,[g] Michael Dominello, DO,[h,i] Stephen Franklin, MD,[j] David K. Heimburger, MD,[k] Isaac Kaufman, MD,[l] Paul G. Kocheril, MD,[m] Annette E. Kretzler, MD,[n] Peter Paximadis, MD,[o] Jeffrey D. Radawski, MD,[p] Eleanor M. Walker, MD,[n] and Lori Pierce, MD[a]

Conclusions: Analysis of outcomes in this large observational cohort of patients with triple-negative, node-negative breast cancer treated with whole-breast irradiation revealed no differences by dose fractionation. This adds evidence to support the use of moderate hypofractionation in patients with triple-negative disease.

4. Efficacia nelle pazienti giovani

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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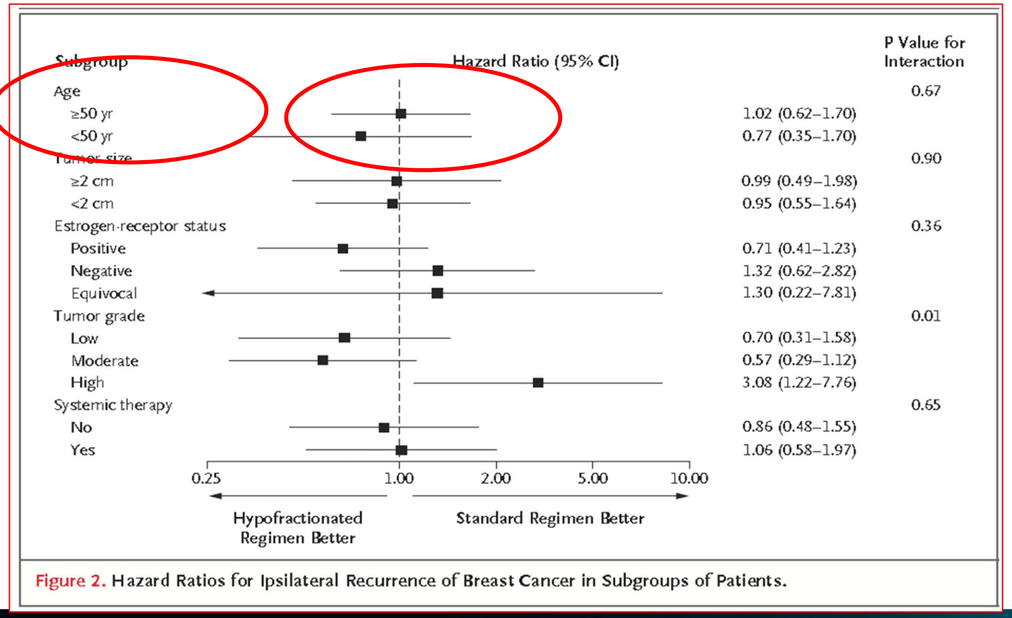
Characteristic	No. of patients in short arm (%) (n = 622)	No. of patients in long arm (%) (n = 612)
Age		
<50 y	157 (25)	148 (24)



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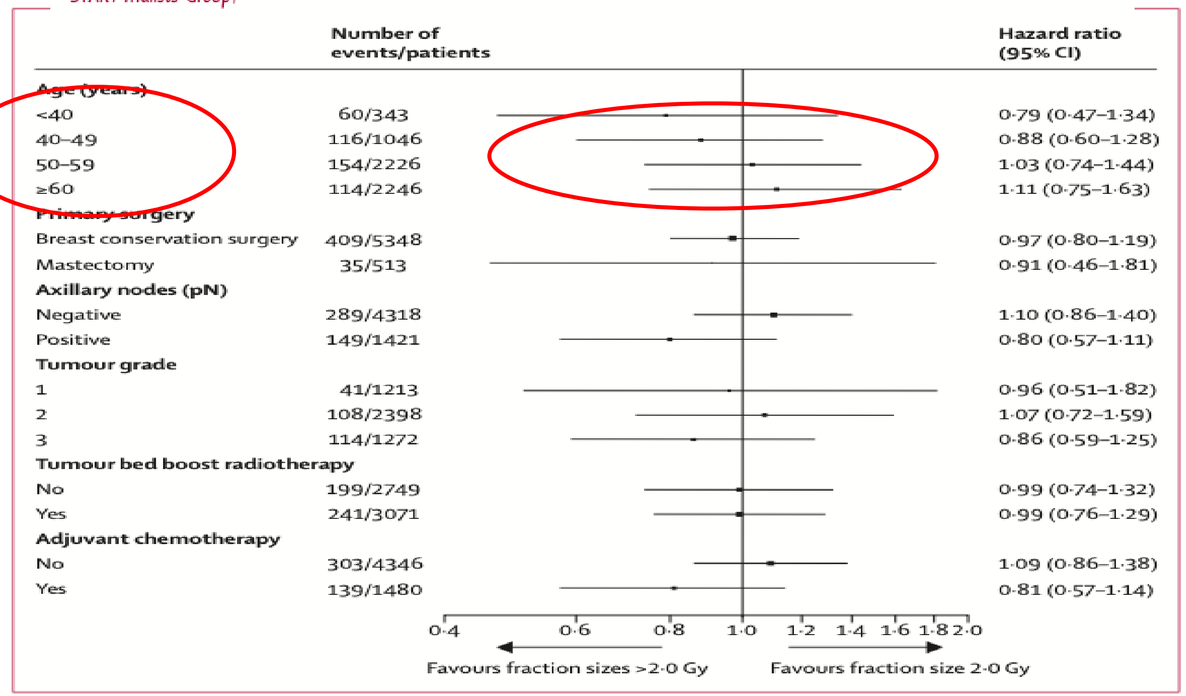

Figure 4: **Meta-analysis of local-regional relapse comparing hypofractionated regimens versus 50 Gy in 25 fractions**
Includes 5861 patients from the START pilot trial, START-A, and START-B.

5. Effetti collaterali

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No differenze:

- insorgenza di effetti collaterali
- risultato cosmetico

Table 1. Late Toxic Effects of Radiation, Assessed According to the RTOG–EORTC Late Radiation Morbidity Scoring Scheme.*

Site and Grade	5 Yr		10 Yr	
	Standard Regimen (N=424)	Hypofractionated Regimen (N=449)	Standard Regimen (N=220)	Hypofractionated Regimen (N=235)
	percent of patients			
Skin				
0†	82.3	86.1	70.5	66.8
1	14.4	10.7	21.8	24.3
2	2.6	2.5	5.0	6.4
3	0.7	0.7	2.7	2.5
Subcutaneous tissue				
0‡	61.4	66.8	45.3	48.1
1	32.5	29.5	44.3	40.0
2	5.2	3.8	6.8	9.4
3	0.9	0.9	3.6	2.5

5. Effetti collaterali

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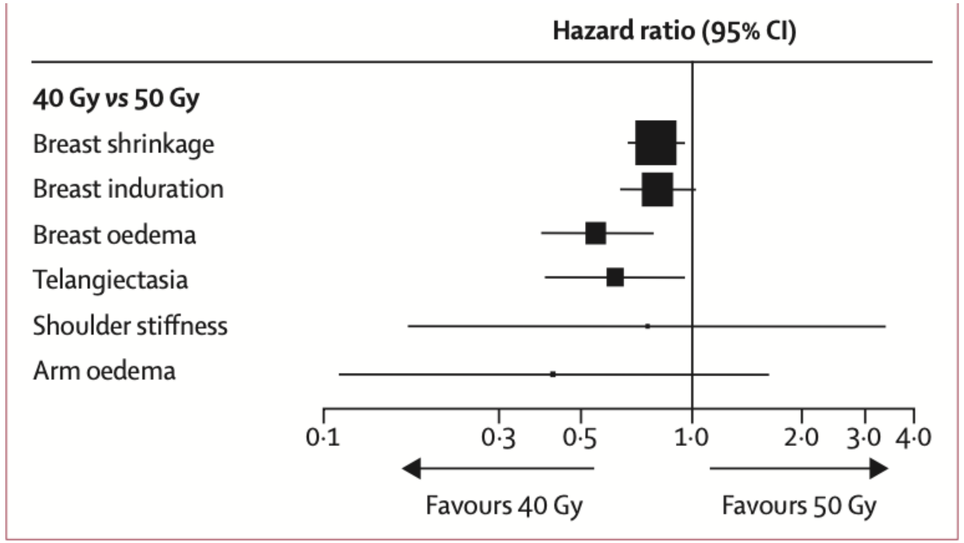


	START-A				START-B		
	50 Gy (n=749)	41·6 Gy (n=750)	39 Gy (n=737)	Total (n=2236)	50 Gy (n=1105)	40 Gy (n=1110)	Total (n=2215)
Symptomatic rib fracture*							
Reported	5 (0·7%)	8 (1·1%)	9 (1·2%)	22 (1·0%)	17 (1·5%)	24 (2·2%)	41 (1·9%)
Confirmed†	0	0	1 (0·1%)	1 (<0·1%)	3 (0·3%)	3 (0·3%)	6 (0·3%)
Symptomatic lung fibrosis							
Reported	6 (0·8%)	9 (1·2%)	8 (1·1%)	23 (1·0%)	19 (1·7%)	19 (1·7%)	38 (1·7%)
Confirmed†	0	2 (0·3%)	1 (0·1%)	3 (0·1%)	2 (0·2%)	8 (0·7%)	10 (0·5%)
Ischaemic heart disease‡							
Reported	14 (1·9%)	11 (1·5%)	8 (1·1%)	33 (1·5%)	23 (2·1%)	17 (1·5%)	40 (1·8%)
Confirmed†							
Total	7 (0·9%)	5 (0·7%)	6 (0·8%)	18 (0·8%)	16 (1·4%)	8 (0·7%)	24 (1·1%)
Left sided	4 (0·5%)	1 (0·1%)	4 (0·5%)	9 (0·4%)	5 (0·5%)	4 (0·4%)	9 (0·4%)
Brachial plexopathy	0	1 (0·1%)	0	1 (<0·1%)	0	0	0

Data are n (%). *Reported cases include seven after trauma (five in START-A, two in START-B), and ten after metastases (five in START- A and five in START-B). †After imaging and further investigations. ‡26 patients in START-A and 22 in START-B had pre-existing heart disease at enrolment and were excluded.

***Table 3*: Incidence of other late adverse effects according to fractionation schedule**

Meno effetti collaterali tardivi con ipofrazionamento

Beneficio si è mantenuto ad un follow-up di 10 anni

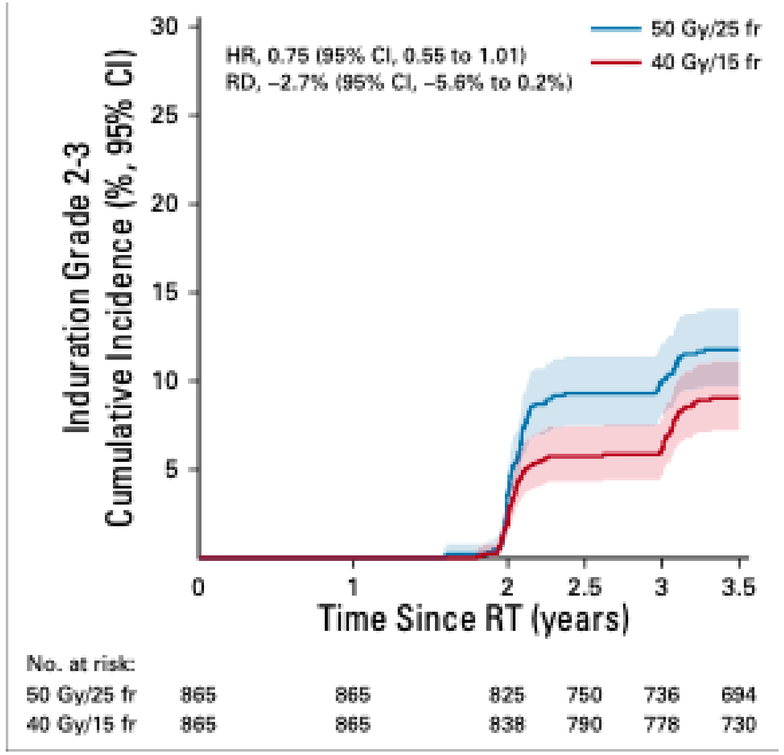
5. Effetti collaterali

original reports

Hypofractionated Versus Standard Fractionated Radiotherapy in Patients With Early Breast Cancer or Ductal Carcinoma In Situ in a Randomized Phase III Trial: The DBCG HYPO Trial

Birgitte V. Offersen, MD, PhD[1,2]; Jan Alsner, PhD[1]; Hanne M. Nielsen, PhD[2]; Erik H. Jakobsen, MD[3]; Mette H. Nielsen, PhD[4]; Mechthild Krause, MD, PhD[5]; Lars Stenbygaard, MD[6]; Ingvil Mjaaland, MD[7]; Andreas Schreiber, MD, PhD[8]; Unn-Miriam Kasti, MD[9]; and Jens Overgaard, MD, DMSc[1]; on behalf of the Danish Breast Cancer Group Radiation Therapy Committee

Median follow-up time of 7.26 years



CONCLUSION Moderately hypofractionated breast irradiation of node-negative breast cancer or DCIS did not result in more breast induration compared with standard fractionated therapy. Other normal tissue effects were minimal, with similar or less frequent rates in the 40-Gy group.

5. Effetti collaterali

original reports

Hypofractionated Versus Conventional Fractionated Radiotherapy After Breast-Conserving Surgery in the Modern Treatment Era: A Multicenter, Randomized Controlled Trial From China

Shu-Lian Wang, MD[1]; Hui Fang, MD[1]; Chen Hu, PhD[2]; Yong-Wen Song, MD[1]; Wei-Hu Wang, MD[1]; Jing Jin, MD[1]; Yue-Ping Liu, MD[1]; Hua Ren, MD[1]; Juan Liu, MD[3]; Gao-Feng Li, MD[4]; Xiang-Hui Du, MD[5]; Yu Tang, MD[1]; Hao Jing, MD[1]; Yu-Chao Ma, MD[1]; Zhou Huang, MD[1]; Bo Chen, MD[1]; Yuan Tang, MD[1]; Ning Li, MD[1]; Ning-Ning Lu, MD[1]; Shu-Nan Qi, MD[1]; Yong Yang, MD[1]; Guang-Yi Sun, MD[1]; Xin-Fan Liu, MD[1]; and Ye-Xiong Li, MD[1]

Median follow-up time of 73.5 months

Cosmetic effect at 3 years (No.)	343	345	
Global cosmetic result			.393
Excellent	49 (12.3)	44 (12.8)	
Good	262 (76.4)	263 (76.2)	
Fair	31 (9.0)	33 (9.5)	
Poor	1 (0.3)	5 (1.5)	
Breast induration			.699
Scar area	22 (6.4)	21 (6.1)	
Half breast	5 (1.5)	3 (0.9)	
Whole breast	1 (0.3)	3 (0.9)	
Breast pain (mild)	20 (5.8)	19 (5.5)	.583

TABLE 2. Adverse and Breast Cosmetic Effects of CFRT and HFRT

Adverse Events	CFRT	HFRT	P
Acute toxicity (No.)	363[a]	365	
Skin toxicity, grade			.019
1	313 (86.2)	318 (87.1)	
2	25 (6.9)	9 (2.5)	
3	2 (0.6)	2 (0.5)	
Pneumonitis/pulmonary infiltrates, grade			.219
1	50 (13.8)	38 (10.4)	
2	11 (3.0)	7 (2.2)	
Late toxicity (No.)	363[a]	365	
Lymphedema, grade			.738
1	38 (10.5)	32 (8.8)	
2	2 (0.6)	2 (0.5)	
Shoulder mobility, grade			.455
1	10 (2.8)	7 (1.9)	
2	1 (0.3)	0 (0)	
Lung fibrosis, grade			.511
1	31 (8.5)	27 (7.4)	
2	1 (0.3)	0 (0)	
Ischemic heart disease, grade			
Left-sided breast			.272
1-2	0 (0)	3 (1.5)	
3-4	2 (1.1)	1 (0.5)	
Right-sided breast			
1-2	2 (1.1)	1 (0.6)	.512
3-4	0 (0)	1 (0.6)	

There were no significant differences in acute and late toxicities, except that the HFRT group had less grade 2-3 acute skin toxicity than the CFRT group ($P = .019$).

5. Effetti collaterali

INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY · BIOLOGY · PHYSICS
www.redjournal.org

CLINICAL INVESTIGATION

The Impact of Chemotherapy on Toxic Effects and Cosmetic Outcome in Patients Receiving Whole Breast Irradiation: An Analysis Within a Statewide Quality Consortium

Joshua T. Dilworth, MD, PhD,* Kent A. Griffith, MS, MPH,† Lori J. Pierce, MD,‡ Reshma Jagsi, MD, DPhil,‡ Thomas J. Quinn, MD,* Eleanor M. Walker, MD,§ Jeffrey D. Radawski, MD,‖ Michael M. Dominello, DO,¶ Greg S. Gustafson, MD,# Jean M. Moran, PhD,‡ James A. Hayman, MD,‡ and Frank A. Vicini, MD**

Conclusions: In this cohort, use of chemotherapy before WBI was generally well tolerated. CWBI with chemotherapy but not HWBI with chemotherapy was associated with higher rates of moist desquamation. Rates of acute breast pain and impaired cosmetic outcome at 1 year were comparable in patients receiving chemotherapy before either CWBI or HWBI. These data support the use of HWBI after chemotherapy.

5. Effetti collaterali dopo irradiazione dei linfonodi regionali

Hypofractionated versus conventional fractionated postmastectomy radiotherapy for patients with high-risk breast cancer: a randomised, non-inferiority, open-label, phase 3 trial

Lancet Oncol 2019; 20: 352–60

Shu-Lian Wang*, Hui Fang*, Yang-Wen Song, Wei-Hu Wang, Chen Hu, Yue-Ping Liu, Jing Jin, Xin-Fan Liu, Zi-Hao Yu, Hua Ren, Ning Li, Ning-Ning Lu, Yu Tang, Yuan Tang, Shu-Nan Qi, Guang-Yi Sun, Ran Peng, Shuai Li, Bo Chen, Yang Yang, Ye-Xiong Li

Interpretation Postmastectomy hypofractionated radiotherapy was non-inferior to and had similar toxicities to conventional fractionated radiotherapy in patients with high-risk breast cancer. Hypofractionated radiotherapy could provide more convenient treatment and allow providers to treat more patients.

	Conventional fractionated radiotherapy group (n=409)	Hypofractionated radiotherapy group (n=401)	p value
Late toxicity			
Skin toxicity	..	..	0·669
Grade 1–2	90 (22%)	86 (21%)	..
Grade 3	0	1 (<1%)	..
Lymphoedema	..	..	0·961
Grade 1–2	81 (20%)	78 (19%)	..
Grade 3	3 (1%)	3 (1%)	..
Shoulder dysfunction	..	..	0·734
Grade 1–2	13 (3%)	7 (2%)	..
Grade 3	1 (<1%)	1 (<1%)	..
Lung fibrosis	..	..	0·081
Grade 1–2	42 (10%)	62 (15%)	..
Grade 3	0	0	..
Ischaemic heart disease	..	..	0·569
Grade 1–2	1 (<1%)	3 (1%)	..
Grade 3	3 (1%)	4 (1%)	..

5. Effetti collaterali dopo irradiazione dei linfonodi regionali

Radiotherapy and Oncology 126 (2018) 155–162

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Phase III randomised trial

Late normal tissue effects in the arm and shoulder following lymphatic radiotherapy: Results from the UK START (Standardisation of Breast Radiotherapy) trials

Joanne S Haviland [a,*], Mariella Mannino [b], Clare Griffin [a], Nuria Porta [a], Mark Sydenham [a], Judith M. Bliss [a,1], John R. Yarnold [c,1], on behalf of the START Trialists' Group

[a] Institute of Cancer Research Clinical Trials and Statistics Unit (ICR-CTSU), Division of Clinical Studies, The Institute of Cancer Research, London, UK; [b] Società per l'Assistenza al Malato Oncologico Terminale (SAMOT), Palermo, Italy; [c] Division of Radiotherapy and Imaging, The Institute of Cancer Research, London, UK

Conclusions: The START trial results suggest that appropriately-dosed hypofractionated LNRT is safe in the long-term, according to patient and physician-assessed arm and shoulder symptoms. These findings are consistent with those reported after the same schedules delivered to the breast/chest wall.

Analisi retrospettiva: 864/5,861 (14.7%) pazienti trattate con BCS (662) o mastectomia (202); no standardizzazione volumi linfonodali, differenti nello studio

Ad un follow-up mediano di 10 anni, gli effetti collaterali da RT a livello di braccio e spalla sono stati valutati dal medico e dalla paziente (questionario EORTC QLQ-BR23 e domande specifiche al protocollo)

No differenze tra le due schedule di radioterapia: ipofrazionamento su linfonodi regionali è stato considerato «safe»

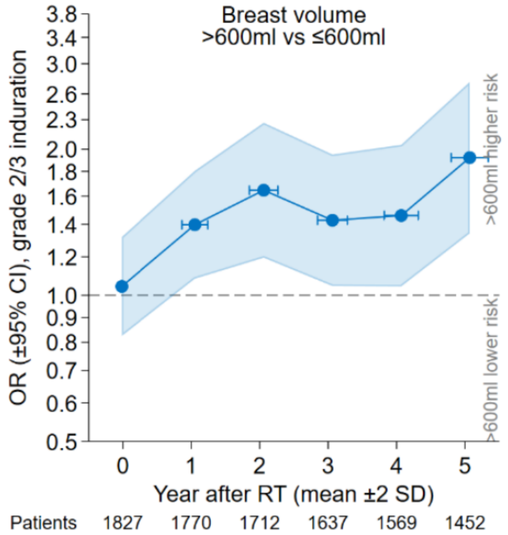
5. Effetti collaterali in mammelle voluminose

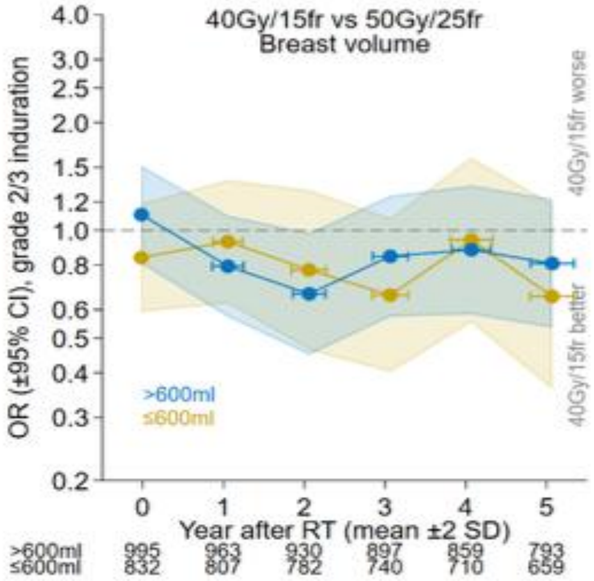
original reports

Hypofractionated Versus Standard Fractionated Radiotherapy in Patients With Early Breast Cancer or Ductal Carcinoma In Situ in a Randomized Phase III Trial: The DBCG HYPO Trial

Birgitte V. Offersen, MD, PhD[1,2]; Jan Alsner, PhD[1]; Hanne M. Nielsen, PhD[2]; Erik H. Jakobsen, MD[3]; Mette H. Nielsen, PhD[4]; Mechthild Krause, MD, PhD[5]; Lars Stenbygaard, MD[6]; Ingvil Mjaaland, MD[7]; Andreas Schreiber, MD, PhD[8]; Unn-Miriam Kasti, MD[9]; and Jens Overgaard, MD, DMSc[1]; on behalf of the Danish Breast Cancer Group Radiation Therapy Committee

of 40 Gy in 15 fr for early breast cancer and DCIS does not increase the risk of breast morbidity irrespective of the use of chemotherapy, trastuzumab, letrozole, or radiotherapy boost and breast size. When evaluating both morbidity and





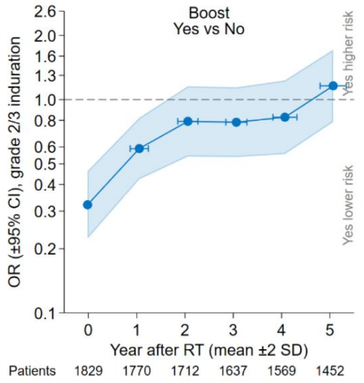
BOOST

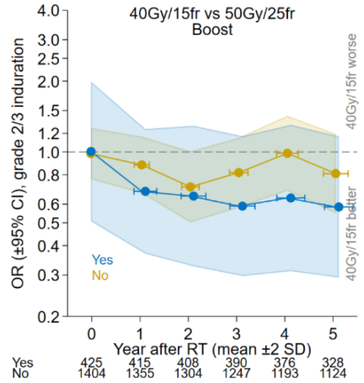
original reports

Hypofractionated Versus Standard Fractionated Radiotherapy in Patients With Early Breast Cancer or Ductal Carcinoma In Situ in a Randomized Phase III Trial: The DBCG HYPO Trial

Birgitte V. Offersen, MD, PhD[1,2]; Jan Alsner, PhD[1]; Hanne M. Nielsen, PhD[2]; Erik H. Jakobsen, MD[3]; Mette H. Nielsen, PhD[4]; Mechthild Krause, MD, PhD[5]; Lars Stenbygaard, MD[6]; Ingvil Mjaaland, MD[7]; Andreas Schreiber, MD, PhD[8]; Unn-Miriam Kasti, MD[9]; and Jens Overgaard, MD, DMSc[1]; on behalf of the Danish Breast Cancer Group Radiation Therapy Committee

10/16 Gy in 2 Gy/fr





original reports

Hypofractionated Versus Conventional Fractionated Radiotherapy After Breast-Conserving Surgery in the Modern Treatment Era: A Multicenter, Randomized Controlled Trial From China

Shu-Lian Wang, MD[1]; Hui Fang, MD[1]; Chen Hu, PhD[2]; Yong-Wen Song, MD[1]; Wei-Hu Wang, MD[1]; Jing Jin, MD[1]; Yue-Ping Liu, MD[1]; Hua Ren, MD[1]; Juan Liu, MD[3]; Gao-Feng Li, MD[4]; Xiang-Hui Du, MD[5]; Yu Tang, MD[1]; Hao Jing, MD[1]; Yu-Chao Ma, MD[1]; Zhou Huang, MD[1]; Bo Chen, MD[1]; Yuan Tang, MD[1]; Ning Li, MD[1]; Ning-Ning Lu, MD[1]; Shu-Nan Qi, MD[1]; Yong Yang, MD[1]; Guang-Yi Sun, MD[1]; Xin-Fan Liu, MD[1]; and Ye-Xiong Li, MD[1]

tumor-bed boost, either at a dose of 50 Gy in 25 fractions over weeks with a boost of 10 Gy in five fractions over 1 week (CFRT) or 43.5 Gy in 15 fractions over 3 weeks with boost of 8.7 Gy in three daily fractions (HFRT). The primary endpoint was 5-year local recurrence (LR), and

Dose-escalated simultaneous integrated boost radiotherapy in early breast cancer (IMPORT HIGH): a multicentre, phase 3, non-inferiority, open-label, randomised controlled trial

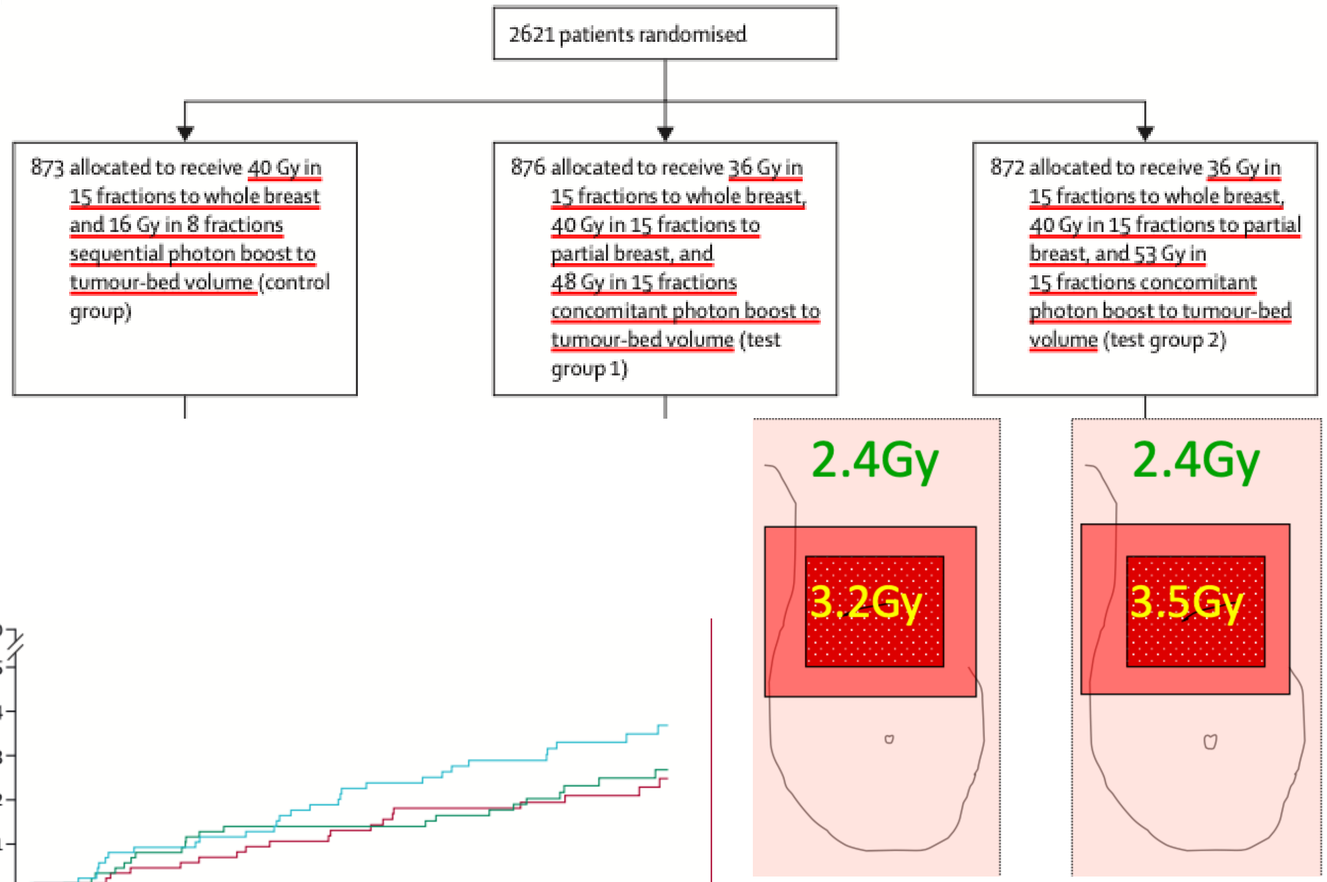
Charlotte E Coles*, Joanne S Haviland*, Anna M Kirby, Clare L Griffin, Mark A Sydenham, Jenny C Titley, Indrani Bhattacharya, A Murray Brunt, H Y Charlie Chan, Ellen M Donovan, David J Eaton, Marie Emson, Penny Hopwood, Monica L Jefford, Sara V Lightowlers, Elinor J Sawyer, Isabel Syndikus, Yat M Tsang, Nicola I Twyman, John R Yarnold†, Judith M Bliss†, on behalf of the IMPORT Trial Management Group‡

Lancet 2023; 401: 2124–37
Published Online June 8, 2023
https://doi.org/10.1016/S0140-6736(23)00619-0

Summary

Background A tumour-bed boost delivered after whole-breast radiotherapy increases local cancer-control rates but requires more patient visits and can increase breast hardness. IMPORT HIGH tested simultaneous integrated boost against sequential boost with the aim of reducing treatment duration while maintaining excellent local control and similar or reduced toxicity.

sequential) as the main variable in the trial. At 5 years, hypofractionated SIB (48 Gy) shows non-inferiority in terms of ipsilateral local relapse compared with sequential boost with incidence of relapse much lower than anticipated, and with low late adverse effect rates in all groups. There was no advantage for escalating to 53 Gy SIB, which was associated with increased breast induration. By contrast, 48 Gy SIB showed similar or reduced normal tissue toxicity compared with control. Follow-up is ongoing and reporting of 10-year results is envisaged.



Courtesy Dr Coles

	Consensus agreement	Strength
1. Whole breast irradiation		
1a. Moderate hypofractionated whole breast irradiation should be offered regardless of:		
I. Age at breast cancer diagnosis	91·3%	Strong consensus
II. Pathological tumour stage	91·3%	Strong consensus
III. Breast cancer biology	91·3%	Strong consensus
IV. Surgical margins status	100%	Unanimous consensus
V. Tumour bed boost	100%	Unanimous consensus
VI. Breast size	91·3%	Strong consensus
VII. Invasive or pre-invasive DCIS disease	91·3%	Strong consensus
VIII. Oncoplastic breast conserving surgery	91·3%	Strong consensus
IX. Use of systemic therapy	95·6%	Strong consensus

European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer

Icro Meattini, Carlotta Becherini, Liesbeth Boersma, Orit Kaidar-Person, Gustavo Nader Marta, Angel Montero, Birgitte Vrou Offersen, Marianne C Aznar, Claus Belka, Adrian Murray Brunt, Samantha Dicuonzo, Pierfrancesco Franco, Mechthild Krause, Mairead MacKenzie, Tanja Marinko, Livia Marrazzo, Ivica Ratosa, Astrid Scholten, Elżbieta Senkus, Hilary Stobart, Philip Poortmans, Charlotte E Coles**

High-quality randomised clinical trials testing moderately fractionated breast radiotherapy have clearly shown that *Lancet Oncol* 2022; 23: e21–31

2. Chest wall irradiation		
2a. Moderate hypofractionation can be offered for chest wall irradiation without breast reconstruction	95·6%	Strong consensus
2b. Moderate hypofractionation can be offered for chest wall irradiation regardless of time and type of breast reconstruction	86·9%	Consensus

3. Nodal irradiation		
3a. Moderate hypofractionation should be offered for nodal irradiation	82·6%	Consensus

https://doi.org/10.1007/s11547-022-01563-9
https://doi.org/10.1007/s11547-022-01563-9

POSITION PAPER

Check for updates

The Italian Association for Radiotherapy and Clinical Oncology (AIRO) position statements for postoperative breast cancer radiation therapy volume, dose, and fractionation

Icro Meattini[1,2] · Isabella Palumbo[3] · Carlotta Becherini[2] · Simona Borghesi[4] · Francesca Cucciarelli[5] · Samantha Dicuonzo[6] · Alba Fiorentino[7] · Ruggero Spoto[8] · Philip Poortmans[9,10] · Cynthia Aristei[3] · Lorenzo Livi[1,2]

	50 Gy in 25 fractions	40–42.5 Gy in 15–16 fractions
Whole breast irradiation	Not recommended	Recommended°
Partial breast irradiation	Not recommended	Recommended°
Chest wall irradiation without reconstruction	Not recommended ^	Recommended°
Chest wall irradiation with reconstruction	Not recommended ^	Recommended°
Regional nodal irradiation	Not recommended ^	Recommended°

L’ IPOFRAZIONAMENTO CON SCHEDULA SETTIMANALE È PIÙ FAST

original reports

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 Harnett, 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]

50 Gy/25 fr (5 weeks)
30 Gy/5 fr (5 weeks)
28 Gy/5 fr (5 weeks)

TABLE 5. 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)

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-

The once weekly 28.5 Gy five-fraction schedule can be considered for patients who would struggle to attend daily, for instance due to frailty

L' ULTRA-IPOFRAZIONAMENTO È PIÙ FAST

Ultra-ipofrazionamento e controllo tumorale

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

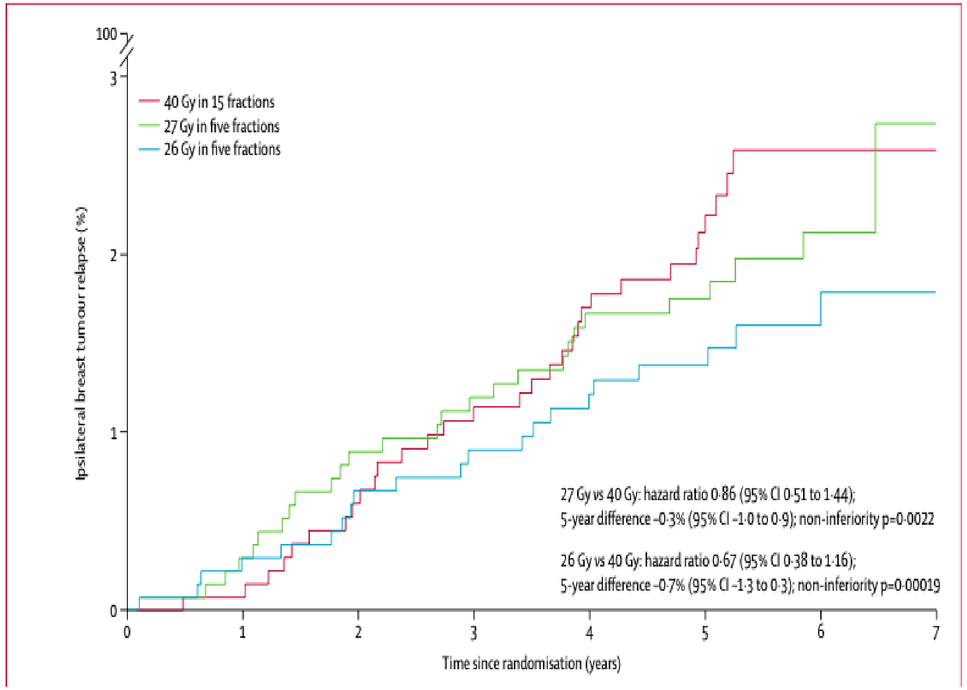
Adrian Murray Brunt, Joanne S Haviland*, Duncan A Wheatley, Mark A Sydenham, Abdulla Alhasso, David J Bloomfield, Charlie Chan, Mark Chum, Susan Cleator, Charlotte E Coles, Andrew Goodman, Adrian Harnett, Penelope Hopwood, Anna M Kirby, Chena C Kirwan, Carolyn Morris, Zohal Nabi, Elinor Sawyer, Navita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

www.thelancet.com **Published online April 28, 2020** **https://doi.org/10.1016/S0140-6736(20)30932-6**

Arruolate 4,096 pazienti

Malattia pT1-3, pN0-1

La schedula con 5 frazioni non è risultata inferiore a 40 Gy in 15 frazioni



Ultra-ipofrazionamento ed effetti collaterali

Nel 97% delle pazienti è stata effettuata almeno 1 valutazione clinica all'anno per monitorare l'insorgenza di effetti collaterali

Ogni effetto moderato/severo è stato osservato nel:

9.9% dopo 40 Gy

15.4% dopo 27 Gy

11.9% dopo 26 Gy

26 Gy sono raccomandati

Ultra-ipofrazionamento ed effetti collaterali

	Number of moderate or marked events/total number of assessments over follow-up	Odds ratio for schedule (95% CI)	p value for comparison with 40 Gy	p value for comparison between 27 Gy and 26 Gy	Odds ratio for years of follow-up (95% CI); p value
Any adverse event in the breast or chest wall*	..	..	..	..	0·98 (0·96–1·00); 0·055
40 Gy	651/6121 (10·6%)	1 (ref)	..	..	..
27 Gy	1004/6303 (15·9%)	1·55 (1·32–1·83)	<0·0001	..	..
26 Gy	774/6327 (12·2%)	1·12 (0·94–1·34)	0·20	0·0001	..
Breast distortion†	..	..	..	..	0·99 (0·95–1·02); 0·38
40 Gy	232/5724 (4·0%)	1 (ref)	..	..	..
27 Gy	363/5953 (6·1%)	1·51 (1·15–1·97)	0·0028	..	..
26 Gy	299/5945 (5·0%)	1·20 (0·91–1·60)	0·19	0·083	..
Breast shrinkage†	..	..	..	..	1·03 (1·00–1·06); 0·023
40 Gy	330/5728 (5·8%)	1 (ref)	..	..	..
27 Gy	503/5944 (8·5%)	1·50 (1·20–1·88)	0·0004	..	..
26 Gy	369/5943 (6·2%)	1·05 (0·82–1·33)	0·71	0·0018	..
Breast induration (tumour bed)†	..	..	..	..	1·00 (0·96–1·04); 0·95
40 Gy	185/5713 (3·2%)	1 (ref)	..	..	..
27 Gy	304/5948 (5·1%)	1·56 (1·19–2·05)	0·0013	..	..
26 Gy	236/5937 (4·0%)	1·19 (0·90–1·59)	0·23	0·047	..
Breast induration (outside tumour bed)†	..	..	..	..	0·96 (0·90–1·02); 0·17
40 Gy	45/5712 (0·8%)	1 (ref)	..	..	..
27 Gy	137/5943 (2·3%)	2·79 (1·74–4·50)	<0·0001	..	..
26 Gy	97/5930 (1·6%)	1·90 (1·15–3·14)	0·013	0·059	..

Ultra-ipofrazionamento ed effetti collaterali

Telangiectasia	..	..	..	..	1·21 (1·14–1·29); <0·0001
40 Gy	63/6087 (1·0%)	1 (ref)	..	..	..
27 Gy	100/6272 (1·6%)	1·68 (1·07–2·65)	0·025	..	..
26 Gy	102/6300 (1·6%)	1·53 (0·96–2·43)	0·070	0·65	
Breast or chest wall oedema	..	..	..	..	0·73 (0·69–0·78); <0·0001
40 Gy	89/6097 (1·5%)	1 (ref)	..	..	..
27 Gy	217/6287 (3·4%)	2·18 (1·57–3·03)	<0·0001	..	..
26 Gy	155/6318 (2·4%)	1·47 (1·03–2·09)	0·032	0·0097	..
Breast or chest wall discomfort	..	..	..	..	0·93 (0·89–0·97); 0·0003
40 Gy	234/6086 (3·8%)	1 (ref)	..	..	..
27 Gy	269/6285 (4·3%)	1·10 (0·86–1·40)	0·44	..	..
26 Gy	250/6309 (4·0%)	0·98 (0·76–1·26)	0·86	0·35	..

E' stato stressato di accettare con cautela l'ultra-ipofrazionamento

Comment

*Antonin Levy, *Sofia Rivera*

1-week hypofractionated adjuvant whole-breast radiotherapy: towards a new standard?

Correspondence

Breast cancer radiation therapy

**Birgitte Vrou Offersen, Jens Overgaard*
**Michael Douek,*
Shiroma De Silva-Minor, Lucy Davies,
Bleddyn Jones

Strahlenther Onkol
https://doi.org/10.1007/s00066-020-01744-3

REVIEW ARTICLE

Moderate hypofractionation remains the standard of care for whole-breast radiotherapy in breast cancer: Considerations regarding FAST and FAST-Forward

David Krug[1] · René Baumann[1,2] · Stephanie E. Combs[3,4,5] · Marciana Nona Duma[6] · Jürgen Dunst[1] · Petra Feyer[7] · Rainer Fietkau[8] · Wulf Haase[9] · Wolfgang Harms[10] · Thomas Hehr[11] · Marc D. Piroth[12] · Felix Sedlmayer[13] · Rainer Souchon[14] · Vratislav Strnad[8] · Wilfried Budach[15] · Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO)

A favore dell'ultra-ipofrazionamento

Correspondence

Breast cancer radiation therapy

Shearwood McClelland III

any change in clinical practice in which radiotherapy duration is shortened has the potential to greatly reduce radiotherapy disparities and considerably improve quality of life for all vulnerable populations facing racial, ethnic, or socioeconomic disparities, or a combination of all three, in health care.

Because it has been well established that one life is saved for every four local recurrences of breast cancer prevented by radiotherapy,[5] the impact of the FAST-Forward trial in further decreasing the timeframe of hypofractionated radiotherapy might save millions of lives worldwide.

Ultra-ipofrazionamento è stato raccomandato per ridurre il rischio di infezione da COVID-19 in pazienti e personale sanitario

Clinical Oncology 32 (2020) 279–281

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Editorial

International Guidelines on Radiation Therapy for Breast Cancer During the COVID-19 Pandemic

C.E. Coles *, C. Aristei ††, J. Bliss §, L. Boersma ¶, A.M. Brunt ||, S. Chatterjee **, G. Hanna †††‡, R. Jagsi §§, O. Kaidar Person ¶¶, A. Kirby ||||, I. Mjaaland ***, I. Meattini ††††‡, A.M. Luis §§§, G.N. Marta ¶¶¶|||||, B. Offersen ****, P. Poortmans ††††, S. Rivera ‡‡‡§§§§

La pandemia ha contribuito a scegliere di utilizzare l' ultra-ipofrazionamento

Clinical Oncology 33 (2021) e166–e171

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Clinical Oncology

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Editorial

Accelerated Adaptation of Ultrahypofractionated Radiation Therapy for Breast Cancer at the Time of the COVID-19 Pandemic

M. Machiels *†, R. Weytjens *†, W. Bauwens *, W. Vingerhoed *, C. Billiet *†, P. Huget *, D. Verellen *†, P. Dirix *†, P. Meijnders *†, P. Poortmans *†, O. Kaidar-Person ‡§¶

https://www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Clinical and Translational Radiation Oncology 47 (2024) 100807

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

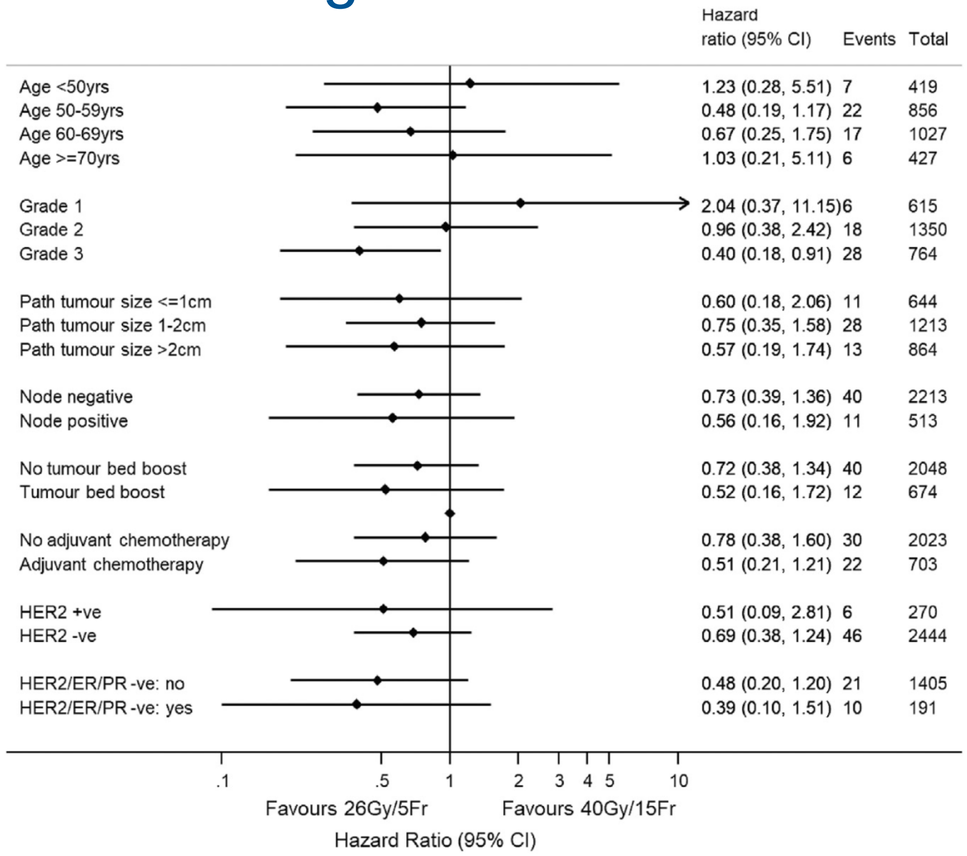
Original Research Article

Implementation of ultra-hypofractionated radiotherapy schedules for breast cancer during the COVID-19 pandemic in the Netherlands

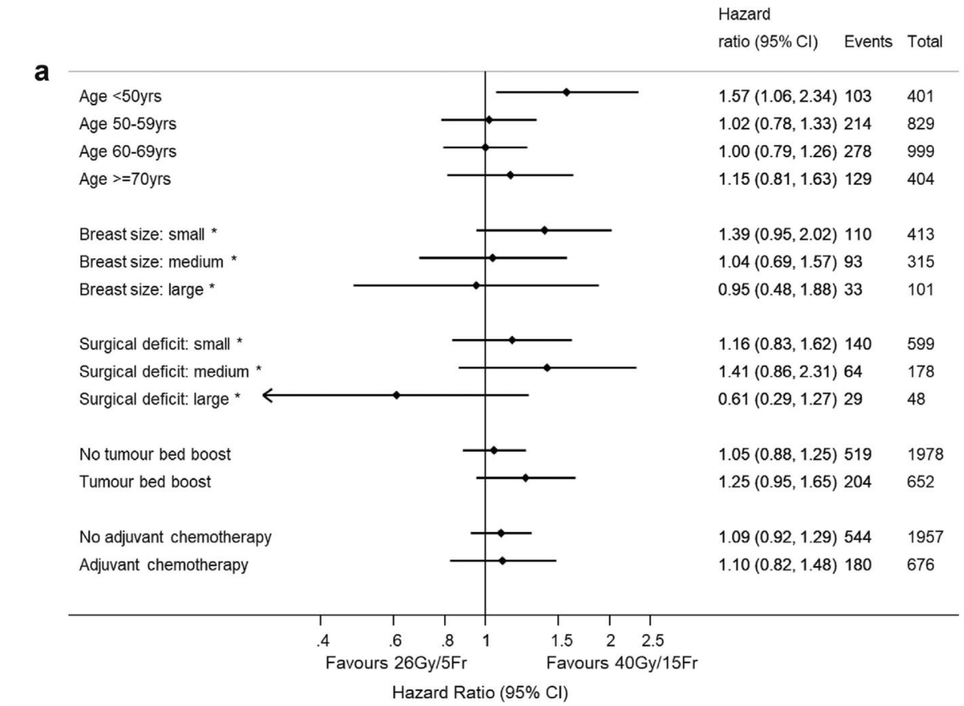
Anouk H. Eijkelboom [a,b,*], Marcel R. Stam [c], Desirée H.J.G. van den Bongard [d], Margriet G.A. Sattler [e], Enja J. Bantema-Joppe [f], Sabine Siesling [a,b], Marissa C. van Maaren [a,b,*]

Retrospective subgroup analyses provided no evidence of a differential:

Oncological Outcome



Breast/Chest Wall Normal Tissue Effects



* Assessed from baseline photographs

Brunt et al. Clin Oncol 2021

Although the number of events is small and results should be interpreted with caution, there is no suggestion of concern relating to either five-fraction schedule

www.rcr.ac.uk

Postoperative radiotherapy for breast cancer: hypofractionation
RCR consensus statements

May 2021

Consensus statement 1

Statement	Voting outcome
Offer 26 Gy in five fractions over one week for whole breast radiotherapy.	Very strongly supported

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*

Consensus statement 2

Statement	Voting outcome
Offer 26 Gy in five fractions over one week for chest wall radiotherapy.	Very strongly supported

Consensus statement 3

Statement	Voting outcome
Consider 26 Gy in five fractions over one week for chest wall radiotherapy with reconstruction.	Strongly supported

	40 Gy in 15 fractions (n=1361)	27 Gy in five fractions (n=1367)	26 Gy in five fractions (n=1368)
Mastectomy	91 (6·7%)	89 (6·5%)	84 (6·1%)
Mastectomy with immediate reconstruction	8 (0·6%)	11 (0·8%)	7 (0·5%)
Autologous reconstruction	5/8 (62·5%)	7/11 (63·6%)	3/7 (42·9%)
Implant-based reconstruction	2/8 (25·0%)	4/11 (27·3%)	4/7 (57·1%)
Reconstruction type not specified	1/8 (12·5%)	0	0

However, it was noted that there was no biological reason why patients with an immediate reconstruction should have a higher risk of normal tissue toxicity/capsular contracture with 26 Gy in five fractions compared with 40 Gy in 15 fractions.

Ultra-ipofrazionamento dopo terapia sistemica neoadiuvante

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 Chum, Susan Clester, Charlotte E Coles, Andrew Goodman, Adrian Hamett, Penelope Hopwood, Anna M Kirby, Chris C Kirwan, Carolyn Morris, Zohal Nabi, Elinor Sawyer, Navita Samaiah, Liba Stones, Isabel Syndikus, Judith M Bliss†, John R Yarnold†, on behalf of the FAST-Forward Trial Management Group*

	40 Gy in 15 fractions (n=1361)	27 Gy in five fractions (n=1367)	26 Gy in five fractions (n=1368)
Neoadjuvant chemotherapy received‡			
Yes	48 (3·5%)	56 (4·1%)	43 (3·1%)
No	1312 (96·4%)	1311 (95·9%)	1323 (96·7%)
Unknown	1 (0·1%)	0	2 (0·1%)

Ultra-ipofrazionamento e irradiazione dei linfonodi regionali

Un sotto-studio ha utilizzato l'ultra-ipofrazionamento in pazienti irradiate su:

1. Linfonodi ascellari o sovraclaveari dopo biopsia del linfonodo sentinella
2. Livelli 3 - 4 dopo dissezione ascellare

Endpoint primario: safety

Analisi ad interim ad un follow-up di 2-3 anni: no differenze in insorgenza di effetti collaterali a livello di braccia o spalle dopo 26 Gy in 5 frazioni o 40 Gy in 15 frazioni

La non inferiorità potrà comunque essere definitivamente sancita ad un'analisi a 5 anni

Wheatley et al. R&O 2022; 170 (Suppl 1) OC-0101

Ultra-ipofrazionamento e irradiazione dei linfonodi regionali

Recruiting

Efficacy and Safety of Ultra_HYPofractionated RadiotHerapy in Women With BrEast CaNcer Receiving Regional Nodal Radiation vs Nodal Moderate Hypofractionated Radiotherapy (HYPHEN)

ClinicalTrials.gov ID NCT05665920

Sponsor Instituto Brasileiro de Controle do Cancer

Information provided by Eduardo Barbieri, Instituto Brasileiro de Controle do **Cancer** (Responsible Party)

Last Update Posted 2022-12-29

Recruiting

Hypofractionated LocoRegional Radiotherapy in Breast Cancer (RHEAL)

ClinicalTrials.gov ID NCT04228991

Sponsor Ontario Clinical Oncology Group (OCOG)

Information provided by Ontario Clinical Oncology Group (OCOG) (Responsible Party)

Last Update Posted 2024-11-18

European Society for Radiotherapy and Oncology Advisory Committee in Radiation Oncology Practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer

Icro Meattini, Carlotta Becherini, Liesbeth Boersma, Orit Kaidar-Person, Gustavo Nader Marta, Angel Montero, Birgitte Vrou Offersen, Marianne C Aznar, Claus Belka, Adrian Murray Brunt, Samantha Dicuonzo, Pierfrancesco Franco, Mechthild Krause, Mairead MacKenzie, Tanja Marinko, Livia Marrazzo, Ivica Ratosa, Astrid Scholten, Elżbieta Senkus, Hilary Stobart, Philip Poortmans, Charlotte E Coles**

Lancet Oncol 2022; 23: e21–31

High-quality randomised clinical trials testing moderately fractionated breast radiotherapy have clearly shown that

	Consensus agreement	Strength
1. Whole breast irradiation		
1b. Ultrahypofractionated (26 Gy in five fractions) whole breast irradiation can be offered as (1) standard of care or (2) within a randomised controlled trial or prospective registration cohort	86·9%	Consensus
2. Chest wall irradiation		
2c. Ultrahypofractionation (26 Gy in five fractions) for chest wall irradiation without breast reconstruction can be offered as (1) standard of care or (2) within a randomised controlled trial or prospective registration cohort	78·3%	Consensus
2d. Ultrahypofractionation (26 Gy in five fractions) for chest wall irradiation after breast reconstruction can be offered within a randomised controlled or prospective registration cohort trial	90·5%	Strong consensus
3. Nodal irradiation		
3b. Ultrahypofractionation (26 Gy in five fractions) should not be offered for nodal irradiation until ongoing trials results are reported	87·0%	Consensus

https://doi.org/10.1007/s11547-022-01563-9
https://doi.org/10.1007/s11547-022-01563-9

POSITION PAPER

The Italian Association for Radiotherapy and Clinical Oncology (AIRO) position statements for postoperative breast cancer radiation therapy volume, dose, and fractionation

Icro Meattini[1,2] · Isabella Palumbo[3] · Carlotta Becherini[2] · Simona Borghesi[4] · Francesca Cucciarelli[5] · Samantha Dicuonzo[6] · Alba Fiorentino[7] · Ruggero Spoto[8] · Philip Poortmans[9,10] · Cynthia Aristei[3] · Lorenzo Livi[1,2]

Table 1 Volume, dose, fractionation AIRO breast cancer group recommendations

	26 Gy in 5 fractions
Whole breast irradiation	Recommended°
Partial breast irradiation	Recommended°*
Chest wall irradiation without reconstruction	Recommended
Chest wall irradiation with reconstruction	Not recommended
Regional nodal irradiation	Not recommended

STUDI RANDOMIZZATI DI CONFRONTO TRA IPOFRAZIONAMENTO MODERATO VS ULTRA-IPOFRAZIONATO

Radiotherapy and Oncology 174 (2022) 59–68

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

HYPORT adjuvant acute toxicity and patient dosimetry quality assurance results – Interim analysis

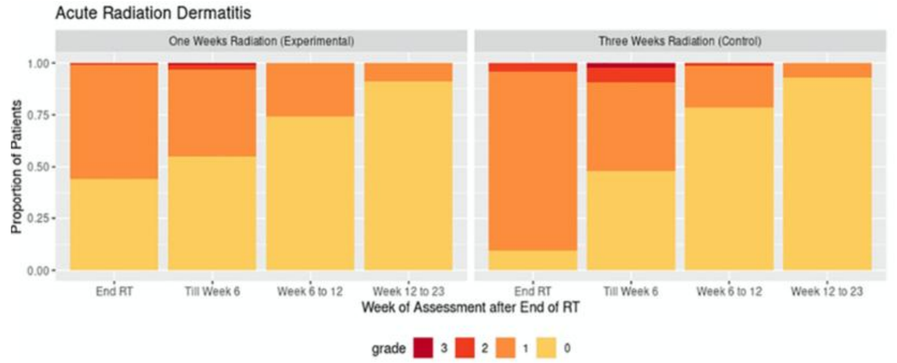
Santam Chakraborty [a], Sanjoy Chatterjee [b,*], Hyport Adjuvant Author Group [1] Selvamani Backianathan [d], Punita Lal [e], Subhash Gupta [f], Rosina Ahmed [g], Shagun Misra [e], Patricia Solomon [d], Rajesh Balakrishan [d], Subecha Bhushal [c], Debashree Guha [h], K.J. Maria Das [i], Anurupa Mahata [c], Samar Mandal [c], Abha Kumari [c], Henry Finlay Godson [d], Sandip Ganguly [j], Abha Kumari [c], C. Shamsudden [k], M. Dinesh [k], Debdeep Dey [l]

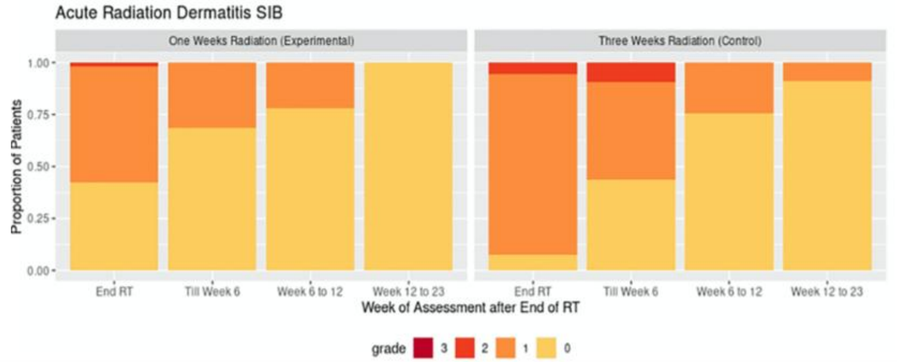
Background: HYPORT adjuvant trial is a randomised phase III open-label noninferiority trial comparing standard moderately hypofractionated 3 week adjuvant radiation therapy in breast cancer with a novel 1-week schedule. The trial was initiated in March 2019 and is open to recruitment with a total sample size of 2100. We report the results of dosimetric quality assurance, acute toxicity and pre planned first interim safety analysis in the first 271 patients.

Methods: Stage I–III breast cancer planned for adjuvant radiation therapy to the breast/chest-wall (along with regional nodes as indicated) were randomised to receive 40 Gy/15 fractions/3 weeks or 26 Gy/5 fractions/1 week. For simultaneous integrated boost, the patients in the control arm received 8 Gy/15 fractions/3 weeks, while those in the experimental arm received 6 Gy/5 fractions/1 week (to the tumour bed). For sequential boost, the prescribed dose was 12 Gy/4 fractions/4 days in both arms. Compliance to pre specified dosimetric parameters and acute toxicities were evaluated.

Result: Data of the first 271 patients was analysed of whom 104 patients received tumour bed boost using SIB. All mandatory dosimetric criteria were met apart from one patient with a higher contralateral breast dose due to optimal internal mammary nodal coverage. Overall three patients (1.1%) experienced grade 3 radiation dermatitis (none received SIB), no other Grade 3 or higher toxicities reported.

Conclusion: This acute toxicity interim analysis demonstrates that hypofractionated adjuvant radiotherapy with SIB for patients with breast cancer is feasible, and associated with minimal severe acute toxicities.





Clinical and Translational Radiation Oncology 46 (2024) 100764

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Ultra-hypofractionated one-week locoregional radiotherapy for patients with early breast cancer: Acute toxicity results

Ivica Ratosa [a,b,c,1], Angel Montero [c,d,1,*], Raquel Ciervide [c], Beatriz Alvarez [c], Mariola García-Aranda [c], Jeannette Valero [c], Xin Chen-Zhao [c], Mercedes Lopez [c], Daniel Zucca [e], Ovidio Hernando [c], Emilio Sánchez [c], Miguel Angel de la Casa [e], Rosa Alonso [c], Pedro Fernandez-Leton [e], Carmen Rubio [c]

Purpose: Moderate hypofractionated radiotherapy is the standard of care for all patients with breast cancer, irrespective of stage or prior treatments. While extreme hypofractionation is accepted for early-stage tumours, its application in irradiating locoregional lymph nodes remains controversial.

Materials and methods: A prospective registry analysis from July 2020 to September 2023 included 276 patients with early-stage breast cancer treated with one-week ultra-hypofractionation (UHF) at 26 Gy in 5 fractions on the whole breast (58.3 %) or thoracic wall (41.7 %) and ipsilateral regional lymph nodes and simultaneous integrated boost (58.3 %). Primary endpoint was assessment of acute adverse events (AEs). Secondarily, onset of early-delayed toxicity was assessed. A minimum 6-month follow-up was required for assessing potential treatment-related early-delayed complications. Acute or late complications attributable to treatment were assessed at inclusion using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria.

Results: With a median follow-up of 19 months (range 1–49 months), 159 (57.6 %) patients reported AEs, predominantly grade (G) 1 (n = 139, 50.4 %) and G2 (n = 20, 7.8 %). Skin acute toxicity was common (G1/2: 134, G3: 14), while breast oedema occurred in 10 patients (G1: 9, G2: 1), and 15.9 % reported breast pain (G1: 42, G2: 2). Ipsilateral arm oedema was observed in 1.8 % patients. For patients with a follow-up beyond 6 months (n = 213), 23.4 % patients reported G1/G2 skin AEs, 8.8 % had G1/G2 breast/chest wall oedema, and 8.9 % experienced arm lymphedema. There were no cases of brachial plexopathy or G3 toxicity in this group of patients.

Conclusions: One-week UHF adjuvant locoregional radiation is well-tolerated, displaying low-toxicity profiles comparable to other studies using similar irradiation schedules.

Clinical and Translational Oncology
https://doi.org/10.1007/s12094-024-03786-w

RESEARCH ARTICLE

Ultra-hypofractionated 5-fraction radiation therapy for early breast cancer into whole breast and regional nodes: experience in a tertiary hospital

Eva María Tejada Ortigosa[1] · Inés Ollinger Casin[1] · Isabela Gaztelu Blanco[1] · Gema Muñiz Romero[2] · Roberto de Haro Piedra[1]

Abstract

Introduction Post-surgery radiotherapy to the breast and regional lymph nodes decreases locoregional tumour recurrence and related mortality. The FAST-Forward approach, with 5 daily fractions, shows non-inferiority to the conventional 15-fraction scheme with similar safety. Authors suggest Simultaneous Integrated Boost (SIB) for the tumour bed and regional nodal irradiation (RNI) for comparable toxicity.

Objectives and purposes To describe acute and delayed toxicity in adjuvant radiotherapy patients using FAST-Forward scheme with SIB and analyze associations with patient characteristics.

Materials and methods An observational, descriptive, retrospective study on 120 early breast cancer patients (pT1-3, pN0-1, M0), treated with surgery and adjuvant radiotherapy using the FAST-Forward scheme with SIB at our center. Some also received RNI. Study conducted from June 2021 to October 2023.

Results Median age: 55 years (range 30–86). Main histological type: infiltrating ductal carcinoma (80%), with Luminal A as predominant molecular subtype (58.5%). Stage IA tumours (61%), pT1c (40%), G2 (50%). Treatment included: neoadjuvant chemotherapy (18.3%), adjuvant chemotherapy (23.5%), hormonal treatment (82.5%), surgery (99%). Radiotherapy with SIB in 90% of conservative surgeries with a median dose 30 Gy (range: 29–33.6). There was no significant association between acute/chronic toxicity and SIB found. However, there was increased risk of acute induration with neoadjuvant chemotherapy. Adjuvant chemotherapy was linked to significant rates of acute and delayed hyperpigmentation. The acute toxicity in first 6 months post-radiotherapy was only G1. The most frequent late toxicities were G1 indurations, edema, hyperpigmentation.

Conclusions The FAST-Forward scheme with SIB and RNI in 5 daily fractions seems well-tolerated without severe acute or delayed toxicity.

Breast Cancer: Targets and Therapy
Dovepress
open access to scientific and medical research
Open Access Full Text Article
ORIGINAL RESEARCH

Ultra-Hypofractionated Whole Breast Radiotherapy with Automated Hybrid-VMAT Technique: A Pilot Study on Safety, Skin Toxicity and Aesthetic Outcomes

Mariangela Boccardi[1], Savino Cilla[2], Mara Fanelli[3], Carmela Romano[2], Paolo Bonome[1], Milena Ferro[1], Donato Pezzulla[1], Roberto Di Marco[4], Francesco Deodato[1,5]*, Gabriella Macchi

Purpose: The most prevalent treatment-related side effect related to adjuvant radiotherapy (RT) for breast cancer is acute skin toxicity in the irradiated area. The purpose of this single-institution pilot study is to provide preliminary clinical results on the feasibility and safety of a breast ultra-hypofractionated radiation treatment delivered using an automated hybrid-VMAT technique. Skin damage was assessed both with clinical examination and objectively using a Cutometer equipment.

Patients and Methods: Patients received 26 Gy to the whole breast and 30 Gy to the tumoral bed in 5 fractions using an automated hybrid-VMAT approach with the option for the breath hold technique if necessary. Acute and late toxicities were clinically evaluated at baseline, 1- and 6-months after treatment using the CTC-AE v.5.0 scale. An instrumental evaluation of the skin elasticity was performed using a Cutometer® Dual MP580. Two parameters per patient, R0 (the total skin firmness) and Q1 (the elastic recovery), were registered at the different timelines.

Results: From June 2022 to January 2024, 30 patients, stage T1-T2, N0 were enrolled in the study. Four out of 30 (13.3%) patients reported G2 acute skin toxicities. At 6 months, G2 late toxicity was registered in 3 patients (10%). A total of 2160 measures of R0 and Q1 were recorded. At 1 month after treatment, no correlation was found between measured values of R0 and Q1 and clinical evaluation. At 6 months after treatment, clinical late toxicity ≥1 was strongly associated with decreased R0 and Q1 values ≥24% ($p = 0.003$) and ≥18% ($p = 0.022$), respectively.

Conclusion: Ultra-hypofractionated whole-breast radiotherapy, when supported by advanced treatment techniques, is both feasible and safe. No severe adverse effects were observed at any of the different timeframes. Acute and late skin toxicities were shown to be lower in contrast to data presented in the literature.

RADIOTERAPIA ADIUVANTE IPOFRAZIONATA SECONDO SCHEMA ULTRA-IPOFRAZIONATO DOPO CHIRURGIA CONSERVATIVA IN PAZIENTI AFFETTE DA NEOPLASIA DELLA MAMMELLA

Studio **osservazionale retrospettivo e prospettico** di tipo "no profit" per valutare **fattibilità, efficacia, tossicità, risultato cosmetico e qualità di vita**, nelle pazienti affette da carcinoma della mammella che dopo chirurgia conservativa devono essere irradiate solamente a livello della ghiandola mammaria residua con schema di irradiazione ultra-ipofrazionato secondo **protocollo "FAST-forward".**

OBIETTIVO PRIMARIO → **TOSSICITÀ ACUTA e CRONICA**

OBIETTIVI SECONDARI → **SOPRAVVIVENZA** (globale e libera da malattia), **INCIDENZA di RECIDIVA** (locale, loco-regionale e a distanza)

→ **RISULTATO ESTETICO** e **QUALITÀ di VITA**

Protocollo FAST-forward

Dose singola **5,2 Gy**;

Dose totale **26 Gy**

in **5 frazioni** giornaliere consecutive

±

Sovradosaggio

- **Sequenziale**

(7,6 Gy in 2 fr consecutive; dose singola 3,8 Gy)

o

- **SIB**

(30 Gy in 5 fr consecutive; dose singola 6 Gy)

Durata del follow up: 5 anni

- ✓ **VALUTAZIONE FOTOGRAFICA:** prima dell'inizio del trattamento RT e dopo 1, 2 e 4 anni (secondo il metodo di Haviland et al.)
- ✓ **VALUTAZIONE DELLA TOSSICITÀ ACUTA E CRONICA:** secondo la scala CTCAE versione 5.0 ad ogni visita clinica
- ✓ **VALUTAZIONE COSMETICA:** secondo scala di Harvard, sia da parte del medico che da parte della paziente, ad ogni visita clinica di controllo
- ✓ **VALUTAZIONE DELLA QUALITÀ DI VITA:** mediante questionari EORTC QLQ-C30 e QLQ-BR23 ad ogni visita clinica di controllo

Da Marzo 2020 a Settembre 2024 arruolate1798 pazienti in 25 centri Italiani

età mediana 71 anni (range 19-93)
76,8% pT1, 80,3% pN0
68,1% carcinoma invasivo
79,3% G1-G2,
prevalentemente Luminal A
Nella maggior parte dei casi non è stato prescritto un boost su letto operatorio

Follow up mediano: 12 mesi (range 1-55)

Eventi intramammari: 3 (2/3 associate a recidiva linfonodale)
Recidive linfonodali: 3 (2 + 1)
Metastasi a distanza: 7
Altre neoplasie: 29
Decessi: 15 (1 per BC)

Table 1– Acute and late toxicity

	ACUTE		LATE					
Toxicity	Grading	N° (%) (1798 pts)	6 months (1300 pts)	12 months (823 pts)	18 months (427 pts)	24 months (310 pts)	36 months (127 pts)	48 months (43 pts)
Erythema	G1	519 (28.9%)	45 (3.5%)	11 (1.3%)	4 (0.9%)	2 (0.6%)	-	-
	G2	51 (2.8%)	6 (0.5%)	1 (0.1%)	1 (0.2%)	-	-	-
	G3	7 (0.4%)	-	-	-	-	-	-
Skin ulceration	G1	37 (2.1%)	6 (0.5%)	3 (0.4%)	-	-	-	-
	G2	10 (0.5%)	-	-	-	-	-	-
	G3	2 (0.1%)	-	-	-	-	-	-
Pruritus	G1	62 (3.4%)	10 (0.8%)	4 (0.5%)	-	-	-	-
	G2	6 (0.3%)	2 (0.2%)	-	-	-	-	-
Oedema	G1	109 (6.1%)	128 (9.8%)	49 (5.6%)	21 (4.9%)	14 (4.5%)	1 (0.8%)	1 (2.1%)
	G2	15 (0.8%)	26 (2%)	8 (0.9%)	3 (0.7%)	-	-	-
	G3	1 (0.05%)	-	1 (0.1%)	1 (0.2%)	-	-	-
Breast induration	G1	-	129 (9.9%)	80 (9.7%)	54 (12.6%)	40 (12.9%)	15 (11.8%)	-
	G2	-	13 (1%)	6 (0.7%)	4 (0.9%)	2 (0.6%)	-	-
Skin dyschromia	G1	-	170 (13.1%)	55 (6.9%)	24 (5.6%)	12 (3.9%)	3 (2.3%)	2 (4.6%)
	G2	-	7 (0.5%)	1 (0.1%)	1 (0.2%)	-	-	-
Telangiectasia	G1	-	4 (0.3%)	1 (0.1%)	-	2 (0.6%)	1 (0.8%)	-
	G2	-	-	-	1 (0.2%)	1 (0.3%)	-	-

Table 2 Statistical Analysis					
BIVARIATE ANALYSIS					
Risk factors	**Acute Toxicity**	**6 Months Toxicity**	**12 Months Toxicity**	**18 Months Toxicity**	**24 Months Toxicity**
Young age	p<0.0001				
Smoking habits	p=0.002	p<0.0001	p<0.0001	p=0.002	p=0.031
Boost administration	p<0.0001	p=0.001			
PTV breast	p<0.0001	p<0.0001			
PTV boost		p=0.001	p=0.013	p=0.024	
MULTIVARIATE ANALYSIS					
Risk factors					
Young age	p<0.0001, OR 0.968; CI95%0.959-0.978				
Smoking habits	p=0.005, OR 1.618; CI95% 1.161-2.255				
Boost administration	p=0.001 OR 1.299; CI95%1.107-1.524				
PTV breast	p<0.0001, OR1.001; CI95%1.000-1.001				
PTV boost		p=0.001, OR 1.008; CI95%1.003-1.012	p=0.024, OR1.006; CI95%1.001-1.011		

L' ULTRA-IPOFRAZIONAMENTO È TOO FAST?

Based on the low a/β ratio of breast cancer in relation to the late-reacting normal tissues, five-fraction regimens are unlikely to represent the limit of hypofractionation

But what are the incentives to reduce fraction number further?
Overall local relapse rates of 2% at 5 years and low overall toxicity rates following 26 Gy in five fractions are unlikely to be improved upon

Given that breast cancer remains both common and a substantial proportion of radiotherapy departments' workloads, could further societal and health economic benefits be gained by reducing the number of patient visits, say from five to two?

Yarnold et al. Clin Oncol 2022

Beyond this, are there subgroups of patients in whom higher doses per fraction given might facilitate:

- *ablative (and therefore non-surgical) pathways*
- *interaction with immunological therapies to increase the therapeutic effect*

Future work is increasingly likely to be undertaken in the primary setting in which translational opportunities abound with the aim of being able to individualise the application, fractionation schedule and timing of radiotherapy to each patient's physiological and biological situation

MEDICINA DI PRECISIONE

Yarnold et al. Clin Oncol 2022

CONCLUSIONI

- L' ipofrazionamento moderato (40-42.5 Gy / 15-16 frazioni / 3 settimane) rappresenta lo standard dopo chirurgia conservativa e mastectomia senza e con ricostruzione, anche quando i linfonodi regionali devono essere irradiati

- L' ultra-ipofrazionamento (26 Gy /1 settimana) rappresenta il trattamento standard per l'irradiazione della mammella e della parete toracica senza ricostruzione

- I risultati degli studi in corso definiranno l'indicazione dell'ultra-ipofrazionamento su linfonodi regionali

CONCLUSIONI

- Convenienza delle pazienti e impatto sulla loro qualità di vita
- Migliore uso delle risorse sanitarie
- Aumento di trattamenti erogabili nei centri di radioterapia
- Timing chemio-radioterapia post-chirurgia