ACTUALITÉS EN RADIOTHÉRAPIE

Mardi 04 février 2025

Limoges

Alexandre Nivet

Réunion « Actualités dans la prise en charge du cancer du sein »

Liens d’intérêts

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†*

***Lancet Oncol* 2013; 14: 1086–94**

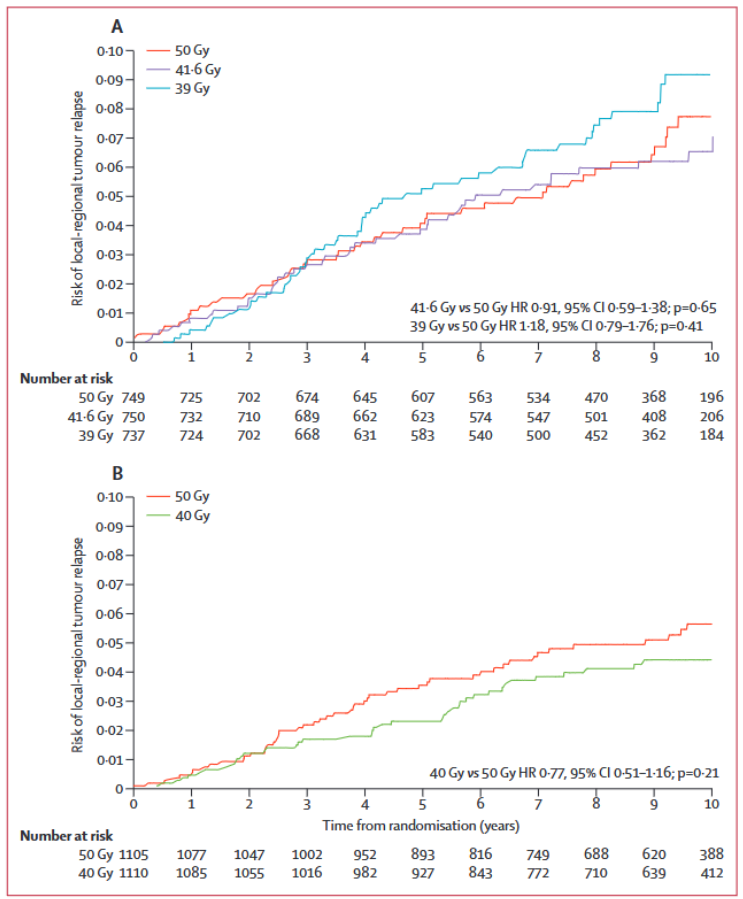


Figure 1: **Cumulative risk of local-regional tumour relapse**
In START-A (A) and START-B (B).

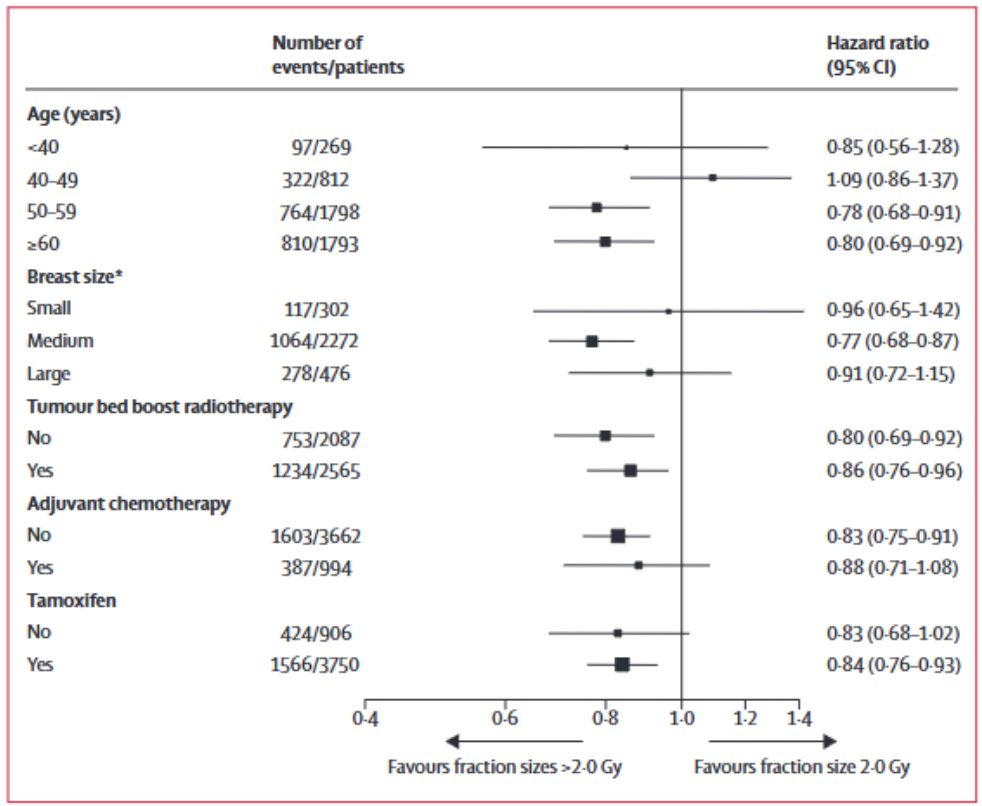


Figure 5: **Meta-analysis of any moderate or marked physician-assessed normal tissue effects in the breast comparing hypofractionated regimens versus 50 Gy in 25 fractions**
Includes 4672 patients from START pilot trial, START-A, and START-B. *Assessed from baseline photographs.

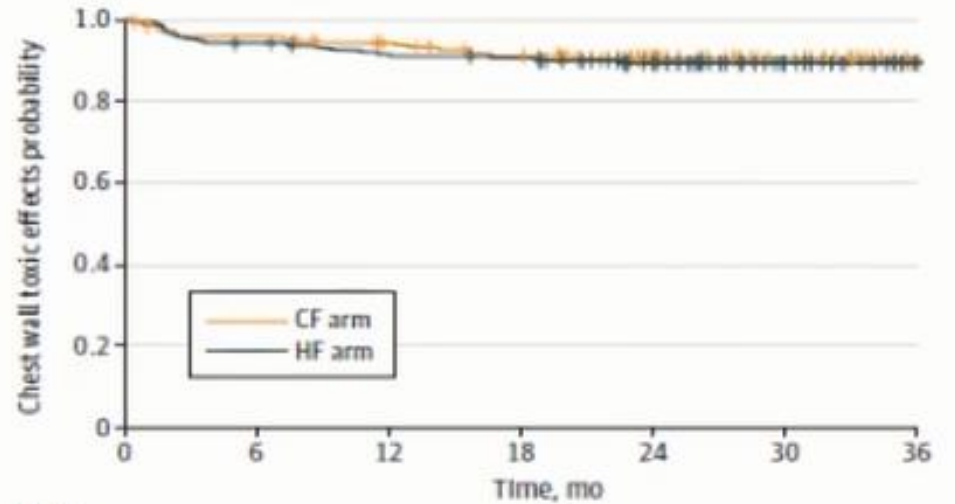
Hypofractionated vs Conventionally Fractionated Postmastectomy Radiation After Implant-Based Reconstruction

JAMA Oncol. 2024;10(10):1370-1378. doi:10.1001/jamaoncol.2024.2652

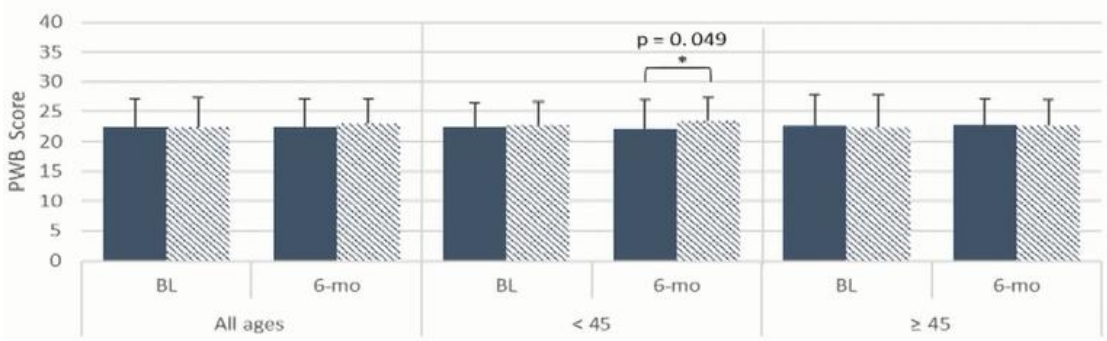
A Randomized Clinical Trial

Julia S. Wong, MD[1,2,3]; Hajime Uno, PhD[1,2]; Angela C. Tramontano, MPH[1]; et al

Figure 2. Kaplan-Meier Plot for Freedom From Chest Wall Toxic Effects by Treatment Arm



CF indicates conventionally fractionated; HF, hypofractionated.

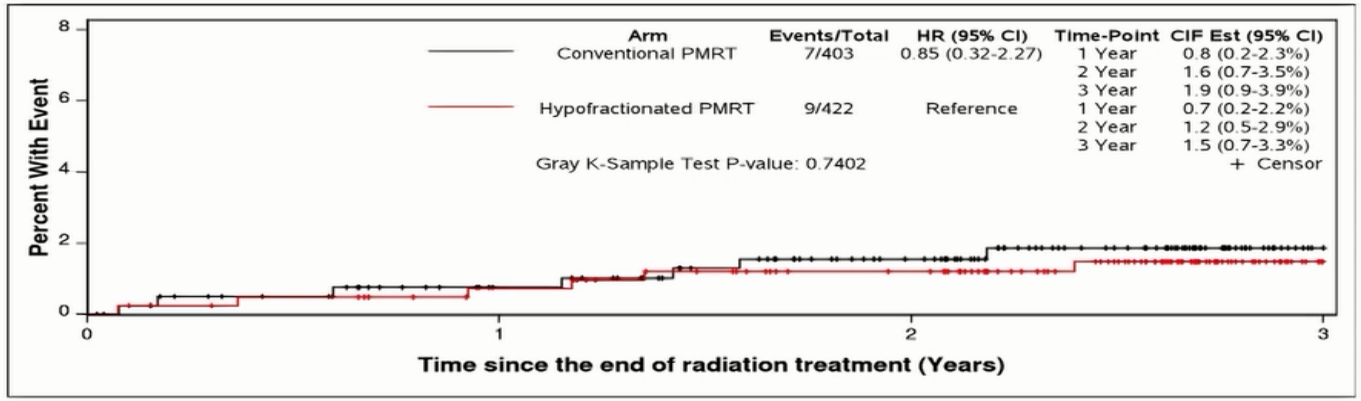


Characteristic	No. (%)	
	Conventional therapy (n = 201)	Hypofractionated therapy (n = 199)
Radiation therapy		
Chest wall and nodes	160 (87.4)	170 (90.0)
Chest wall alone	23 (12.6)	19 (10.1)
Missing due to study withdrawal	9	5
Technique		
IMRT	78 (41.0)	82 (42.9)
Three-dimensional conformal	112 (59.0)	109 (57.1)
Missing	2	3
Time from surgery to radiation therapy, median (IQR), mo	2.7 (1.8-5.3)	2.4 (1.8-4.9)

RT CHARM: Alliance A221505/ MAC.23

Session PL01: Phase III Randomized Trial of Hypofractionated Post Mastectomy Radiation with Breast Reconstruction

	Conventional PMRT (N = 403)	Hypofractionated PMRT (N = 422)	Total (N = 825)	Difference (95% Confidence Interval)
Complication				Z = 3.373 p-value = 0.0004
Yes	49 (12.2%)	60 (14.2%)	109 (13.2%)	-2.1% (-6.7%, 2.6%)
No	354 (87.8%)	362 (85.8%)	716 (86.8%)	
Implant				
Autologous (+/- implant)	12 / 135 (8.9%)	12 / 142 (8.5%)	24 / 277 (8.7%)	0.4% (-6.2%, 7.1%) Z = 3.085, p-value = 0.0044
Implant Only	37 / 268 (13.8%)	48 / 280 (17.1%)	85 / 548 (15.5%)	-3.3% (-9.4%, 2.7%) Z = 2.160, p-value = 0.0154



Hypofractionated Whole-Breast Irradiation with Simultaneous Integrated Boost for Breast Cancer: Primary Analysis of the HYPOSIB-Trial (ARO 2013-05)

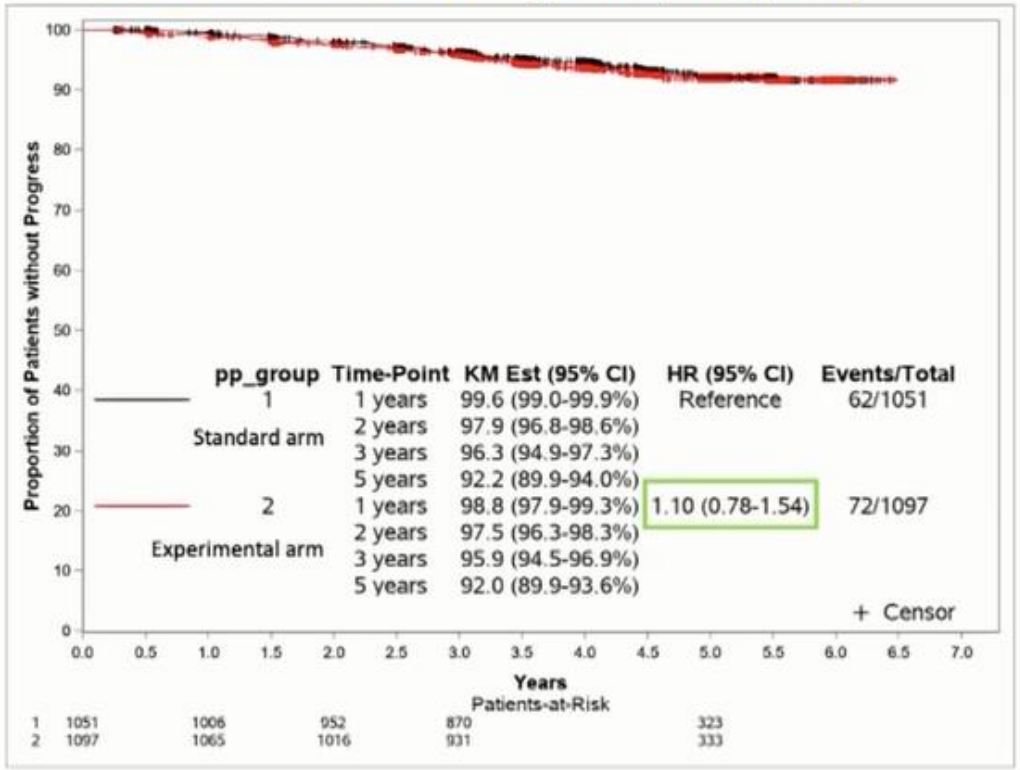
Experimental arm	Fractionation
Hypofractionated whole-breast radiotherapy	16 x 2.5 Gy = 40 Gy
Simultaneous integrated boost	16 x 0.5 Gy = 48 Gy

Standard arm (investigator's choice)	Fractionation	Use
Hypofractionated whole-breast radiotherapy	16 x 2.66 Gy = 42.5 Gy	34%
Sequential boost	5-8 x 2 Gy = 10-16 Gy	
Convent. fract. whole-breast radiotherapy	28 x 1.8 Gy = 50.4 Gy	55%
Simultaneous integrated boost	28 x 0.3-0.45 Gy = 58.8-63 Gy	
Convent. fract. whole-breast radiotherapy	28 x 1.8 Gy = 50.4 Gy	11%
Sequential boost	5-8 x 2 Gy = 10-16 Gy	

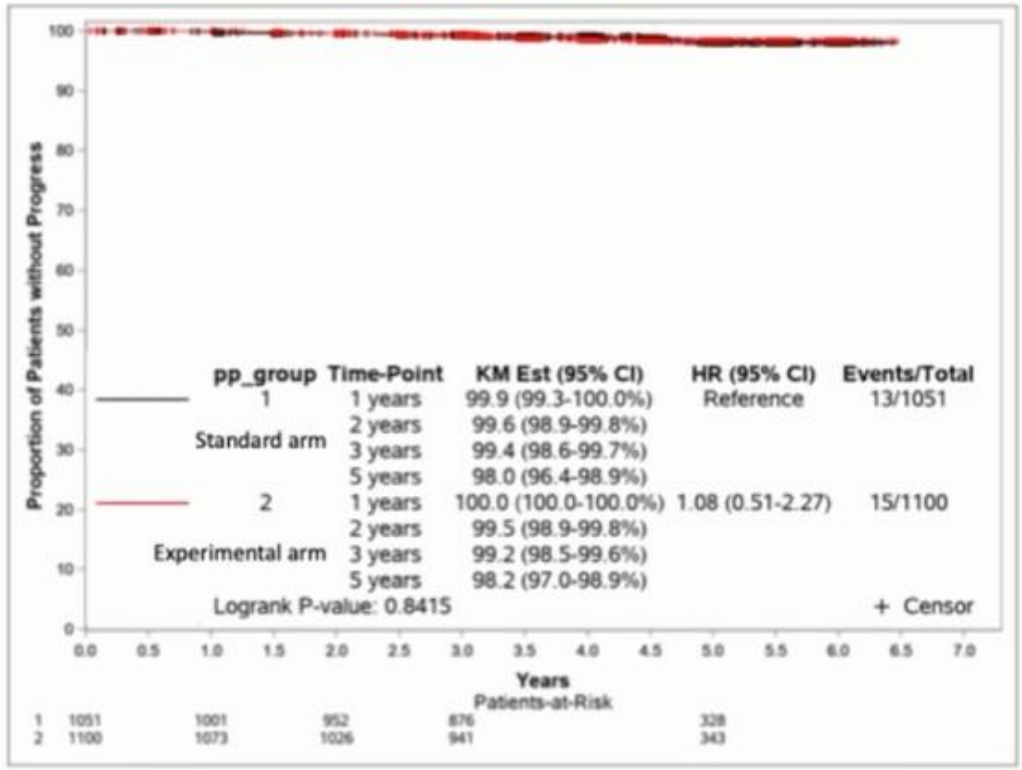
	Total (n = 2179)	Experimental arm (n = 1108)	Standard arm (n = 1071)
Age (mean)	57.6 (SD 10.3)	57.3 (SD 10.4)	57.9 (SD 10.3)
Postmenopausal	63.8%	62.2%	65.5%
pT1a-c	71.5%	70.4%	72.4%
pT2	20.3%	20.6%	20.1%
pN0	93.8%	93.7%	94.0%
G3	23.0%	23.6%	22.5%
ER pos.	85.0%	84.2%	85.8%
SLNE	94.8%	95.1%	94.5%
Systemic therapy			
Neoadjuvant CHT	18.5%	19.2%	17.8%
Adjuvant CHT	15.7%	16.8%	14.5%
Anti-HER2	9.4%	9.4%	9.5%
Endocrine Therapy	75.1%	74.5%	76.5%

Hypofractionated Whole-Breast Irradiation with Simultaneous Integrated Boost for Breast Cancer: Primary Analysis of the HYPOSIB-Trial (ARO 2013-05)

Disease-free survival (primary endpoint)



Local control



Hypofractionated Whole-Breast Irradiation with Simultaneous Integrated Boost for Breast Cancer: Primary Analysis of the HYPOSIB-Trial (ARO 2013-05)

Adverse Event	Experiment. arm	Standard arm	OR [95%-KI]	p-value*
Skin toxicity	43 (3.85%)	61 (5.48%)	0.69 [0.46-1.03]	0.0706
Fibrosis	83 (21.07%)	98 (23.17%)	0.89 [0.64-1.23]	0.4699
Telangiectasia	19 (1.70%)	19 (1.70%)	1.00 [0.53-1.90]	0.9978
Nausea	41 (3.67%)	37 (3.32%)	1.11 [0.71-1.75]	0.6449
Hot flashes	529 (47.4%)	501 (44.85%)	1.11 [0.94-1.31]	0.2271
Pain	240 (21.51%)	235 (21.04%)	1.03 [0.84-1.26]	0.7875
Feeling of pressure	128 (11.47%)	122 (10.94%)	1.05 [0.81-1.37]	0.6927

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

	Moderate or marked events*	Kaplan-Meier estimate of cumulative incidence of moderate or marked events (%, 95% CI)†		HR (95% CI), p value	
		By 3 years	By 5 years	Test groups vs control‡§	Test group 2 vs 1¶‖
Any adverse event in the breast**					
Control group	283/817 (34·6%)	23·5% (20·7–26·7)	33·1% (29·8–36·7)	1 (ref)	..
Test group 1	271/836 (32·4%)	20·8% (18·2–23·8)	29·9% (26·8–33·3)	0·90 (0·76–1·06), p=0·21	1 (ref)
Test group 2	302/834 (36·2%)	25·8% (23·0–29·0)	34·5% (31·2–38·0)	1·06 (0·90–1·24), p=0·50	1·18 (1·00–1·39), p=0·026

Locoregional hypo vs normofractionated radiation therapy in breast early cancer

5 years results of the **HypoG-01** phase 3
UNICANCER trial

Non inferiority, phase III, 29 centers

N= 1265 randomized patients

Woman≥18 years, operated for T1-3, N0-3, M0 breast cancer with an indication for **regional nodes RT**

R

Hypofractionated RT:
40 Gy/ 15 fr/ 3 weeks
+/- boost (investigator's choice)

Normofractionated RT:
50 Gy/ 25 fr/ 5 weeks
+/- boost (investigator's choice)

Primary endpoint: 3-year cumulative incidence of **Arm lymphedema**

Primary endpoint: 3-year cumulative incidence of **Arm lymphedema**

Stratification:
- Mastectomy vs lumpectomy
- Radiotherapy technique
- Center of treatment
- Nodes cleared : 0, 1-3, ≥4
- BMI ≤25 vs >25

Locoregional hypo vs normofractionated radiation therapy in breast early cancer

5 years results of the **HypoG-01** phase 3
UNICANCER trial

Primary endpoint

- **Arm lymphedema** defined as ≥10% increase in arm circumference 15 cm proximal and/or 10 cm distal of the olecranon relative to baseline, compared to the contralateral circumference

Secondary endpoints

- **Overall Survival (OS)**
- **Loco Regional-Free survival (LRFS)**
- **Distant disease-Free survival (DDFS)**
- **Breast cancer specific survival (BCSS)**
- **Shoulder range of motion** impairment defined as a reduction ≥25° in active abduction or flexion

Locoregional hypo vs normofractionated radiation therapy in breast early cancer

5 years results of the **HypoG-01** phase 3
UNICANCER trial

Non inferiority of hypofractionated RT

In per protocol analysis :

Median follow up: **4.8 years**

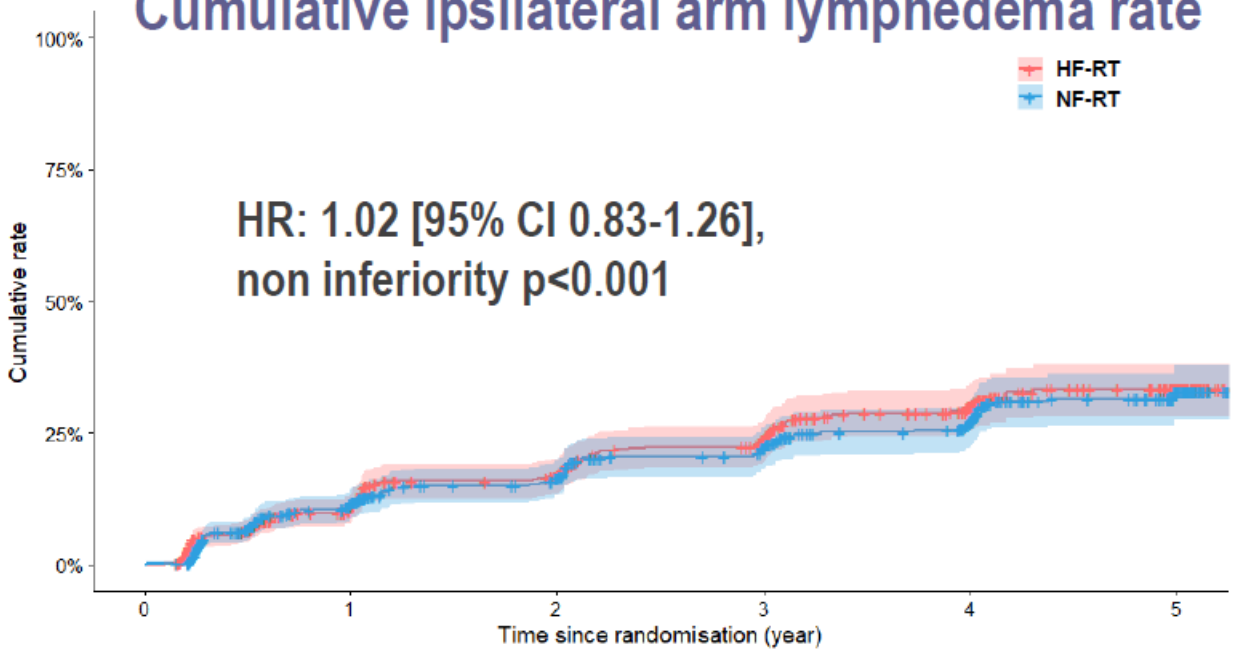
Arm lymphedema occurred in 275/ 1113 pts with baseline and end of RT measurements

Non inferiority in cumulative ipsilateral arm lymphedema rate p<0.001

Cumulative 5-year rate (PP):

- **33.3%** (95% CI: 28.7 - 38.4) in HF
- **32.8%** (95% CI: 27.9 - 38.1) in NF

Cumulative ipsilateral arm lymphedema rate

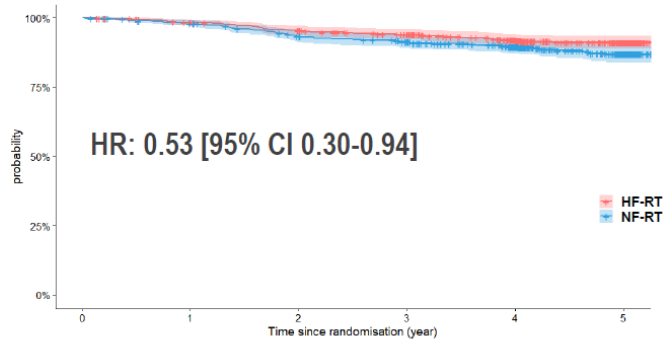


Number at risk						
HF-RT	562	415	343	291	205	91
NF-RT	551	394	330	275	210	95

Locoregional hypo vs normofractionated radiation therapy in breast early cancer

5 years results of the **HypoG-01** phase 3 UNICANCER trial

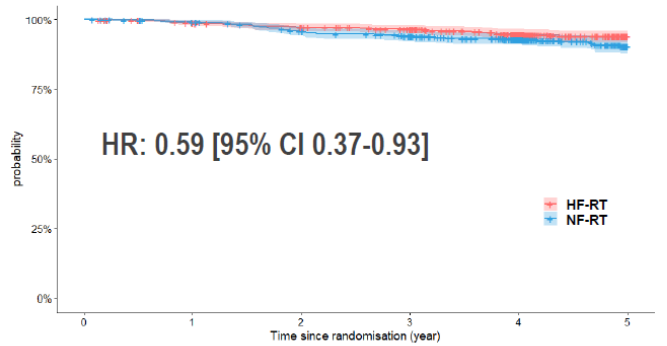
Breast Cancer-Specific Survival



Number at risk

HF-RT	614	590	567	541	438	201
NF-RT	607	586	550	526	433	172

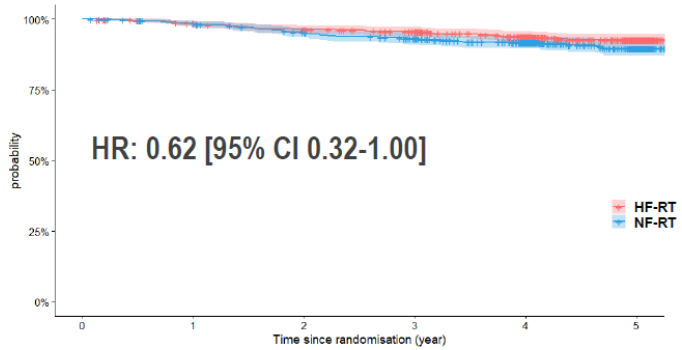
Overall Survival



Number at risk

HF-RT	614	593	577	555	444	200
NF-RT	607	591	564	537	437	170

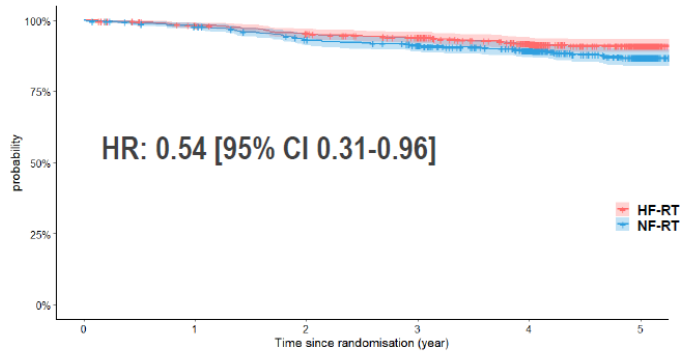
Local Recurrence-free Survival



Number at risk

HF-RT	614	591	573	550	447	223
NF-RT	607	585	560	532	438	176

Distant Disease-free Survival



Number at risk

HF-RT	614	590	567	541	438	201
NF-RT	607	586	550	526	433	172

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

Lancet 2020; 395: 1613–26

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*

	40 Gy in 15 fractions (n=1361)	27 Gy in five fractions (n=1367)	26 Gy in five fractions (n=1368)
Primary surgery			
Breast conservation surgery	1270 (93·3%)	1278 (93·5%)	1284 (93·9%)
Breast conservation surgery with oncoplastic technique	42 (3·1%)	33 (2·4%)	42 (3·1%)
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
Pathological node status			
Positive	257 (18·9%)	243 (17·8%)	256 (18·7%)
Negative	1103 (81·0%)	1124 (82·2%)	1110 (81·1%)
Unknown	1 (0·1%)	0	2 (0·1%)
Maximal extent of axillary staging			
Sentinel node biopsy or guided axillary sampling	1157 (85·0%)	1184 (86·6%)	1164 (85·1%)
Axillary clearance	200 (14·7%)	181 (13·2%)	201 (14·7%)
Other	4 (0·3%)	2 (0·1%)	1 (0·1%)
Unknown	0	0	2 (0·1%)

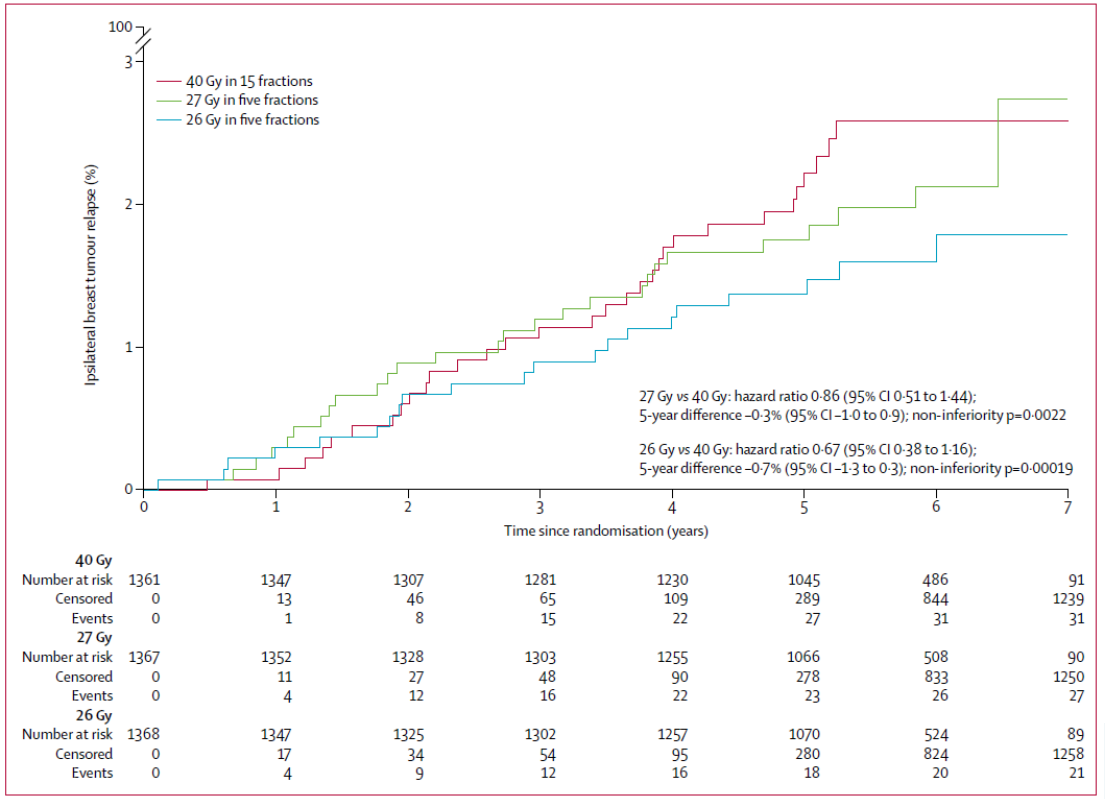


Figure 2: Cumulative risk of ipsilateral breast tumour relapse by fractionation schedule

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

Lancet 2020; 395: 1613–26

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*

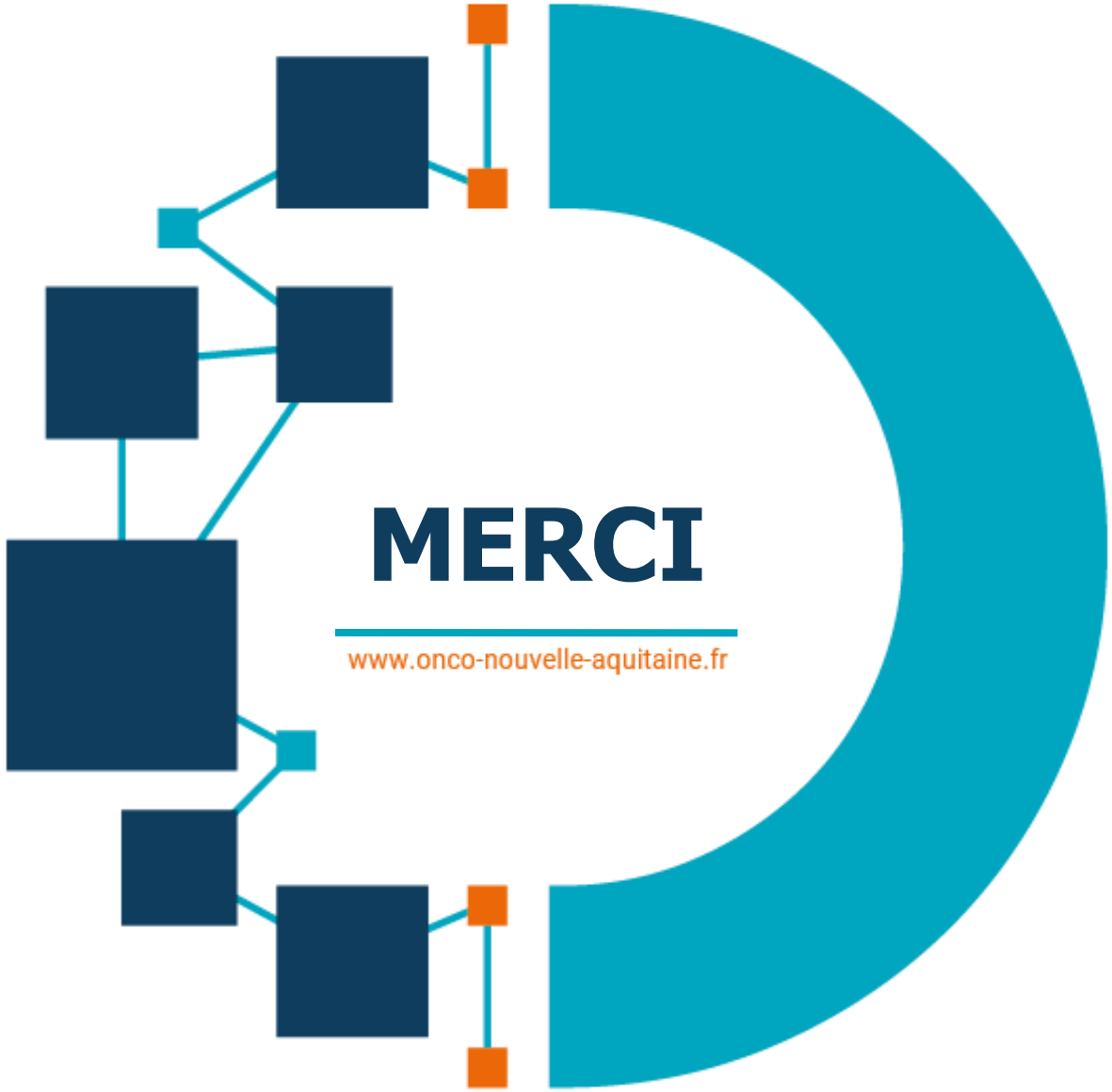
	Number of moderate or marked events/total number of assessments over follow-up	Odds ratio for schedule (95% CI)	p value for comparison with 40 Gy	p value for comparison between 27 Gy and 26 Gy	Odds ratio for years of follow-up (95% CI); p value
Any adverse event in the breast or chest wall*	..	..	..	..	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	..
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	..

Synthèse

- Hypofractionnement modérée = radiothérapie de référence
  - ➔ Sein seul
  - ➔ Sein + Boost intégré
  - ➔ Après mastectomie
  - ➔ Sein + aires ganglionnaires

  - ➔ Limite d'age ?

- Hypofractionnement extrême 5 fractions 1 semaine
  - ➔ Nouvelle référence pour radiothérapie du sein seul ?
  - ➔ Futur référence dans toutes les situations ?


MERCI
www.onco-nouvelle-aquitaine.fr