ACTUALITES ET CONTROVERSE EN SENOLOGIE

Radiothérapie hypofractionnée

Céline BOURGIER

Institut régional du Cancer
Montpellier | Val d'Aurelle

EBCTCG – 2011

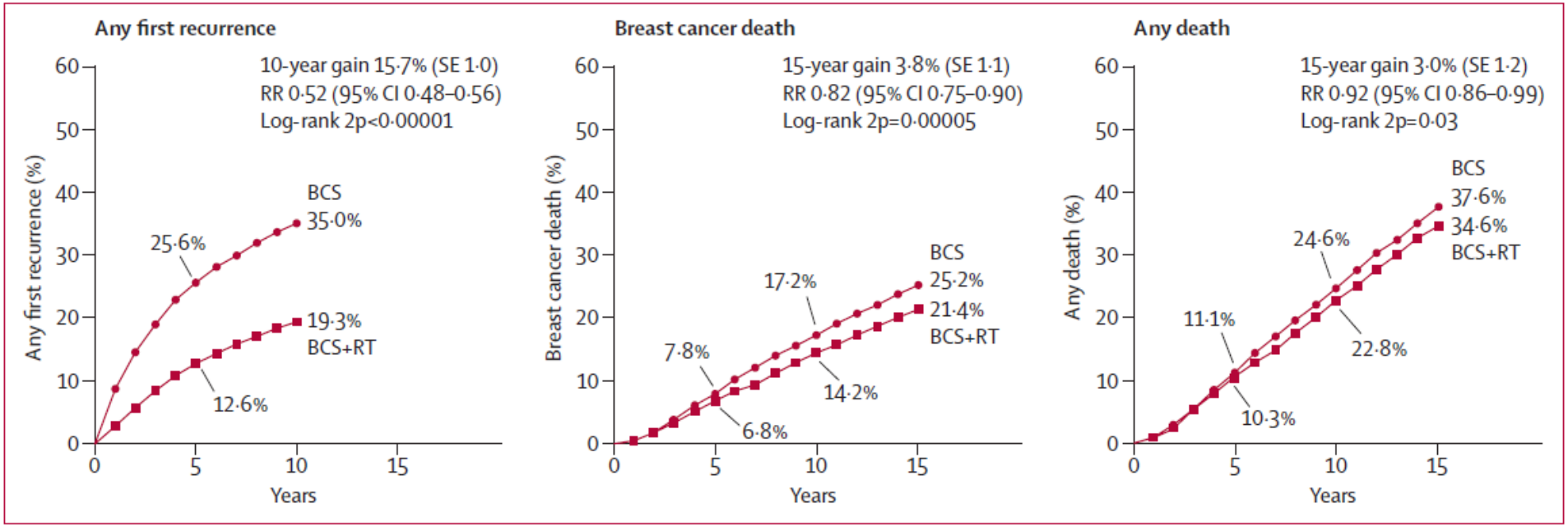
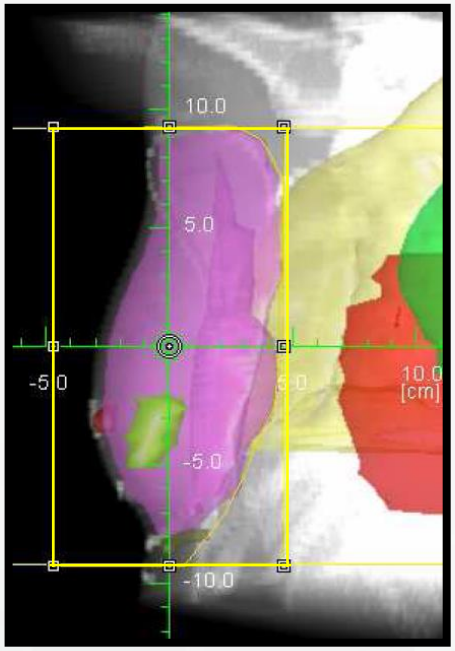


Figure 1: Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year risk of any (locoregional or distant) first recurrence and on 15-year risks of breast cancer death and death from any cause in 10 801 women (67% with pathologically node-negative disease) in 17 trials
Further details are in webappendix p 5. RR=rate ratio. Rate ratios in this figure include all available years of follow-up.

EBCTCG ***Lancet*** **2011**

APRES TRAITEMENT CONSERVATEUR



Diminution de l'étalement

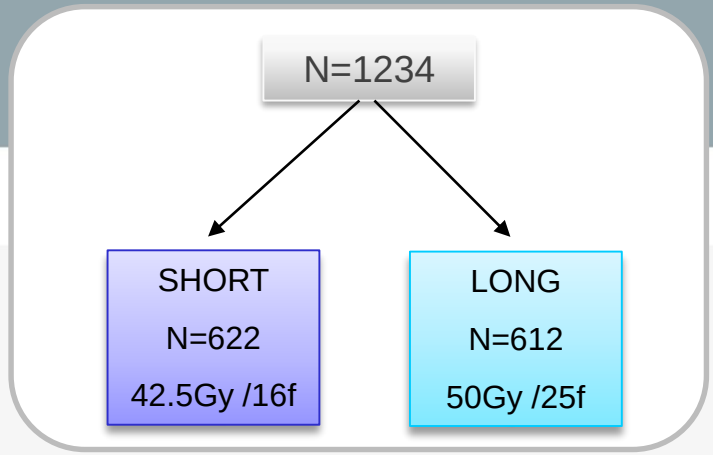
Augmentation de la dose par fraction

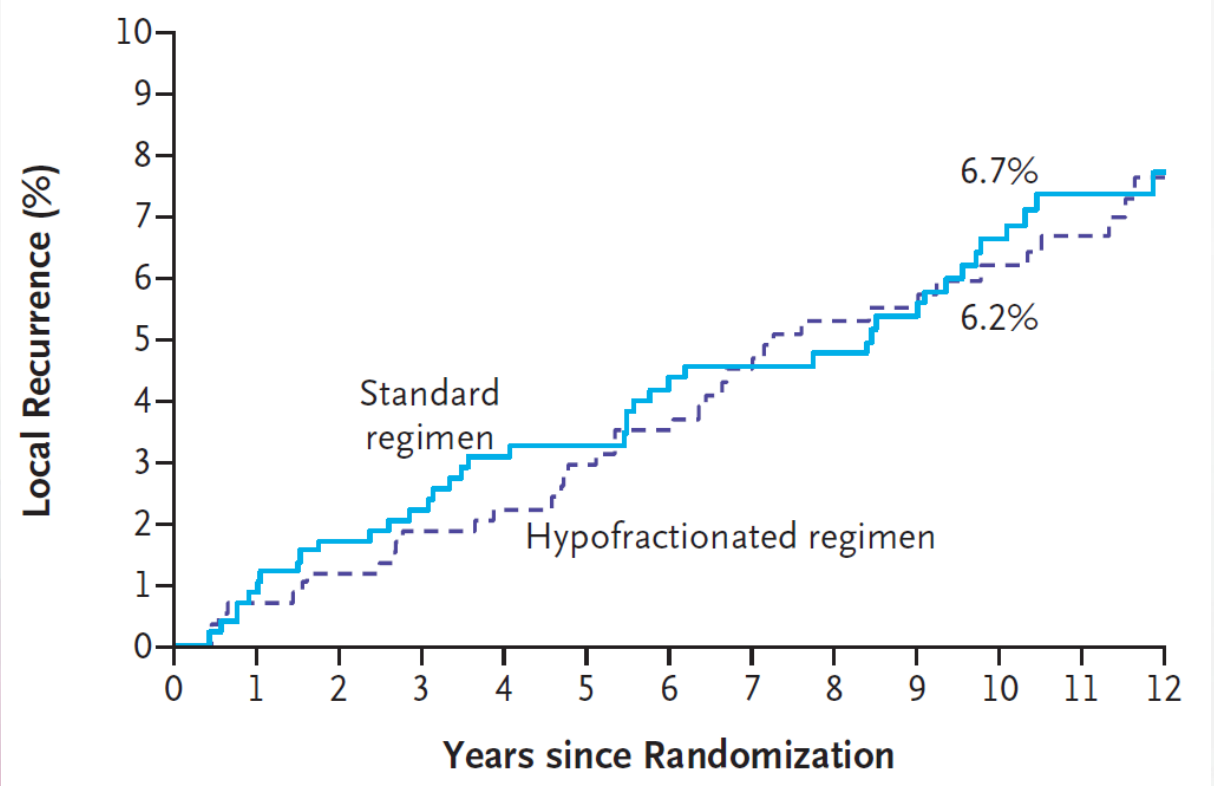
Diminution du volume d'irradiation traité

RADIOTHERAPIE HYPOFRACTIONNEE DE L'ENSEMBLE DU SEIN

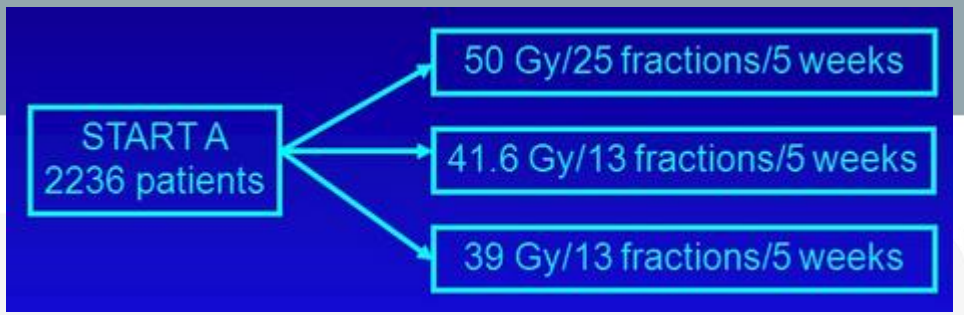
Études prospectives validées
Long suivi +++

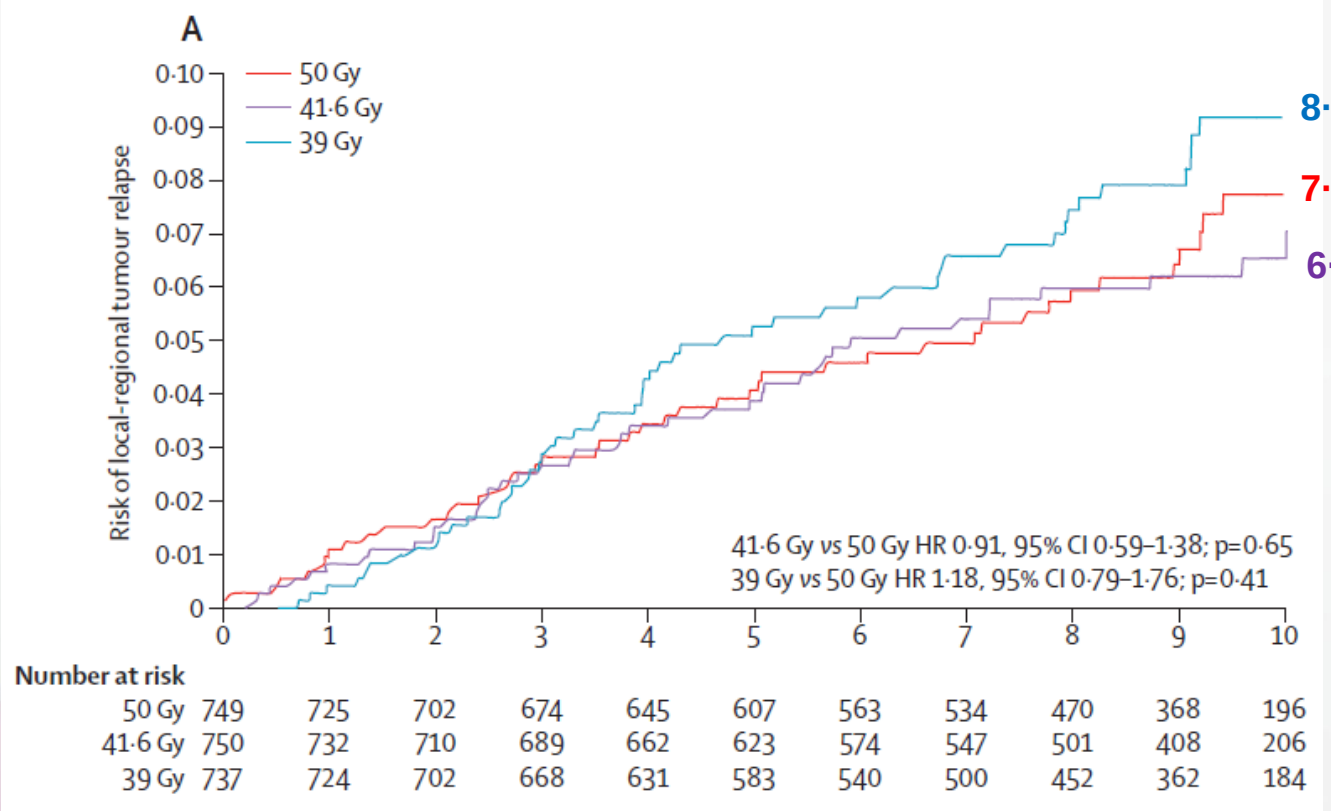
EFFICACITE



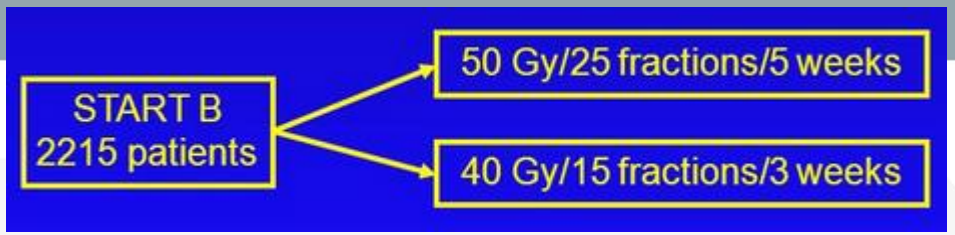


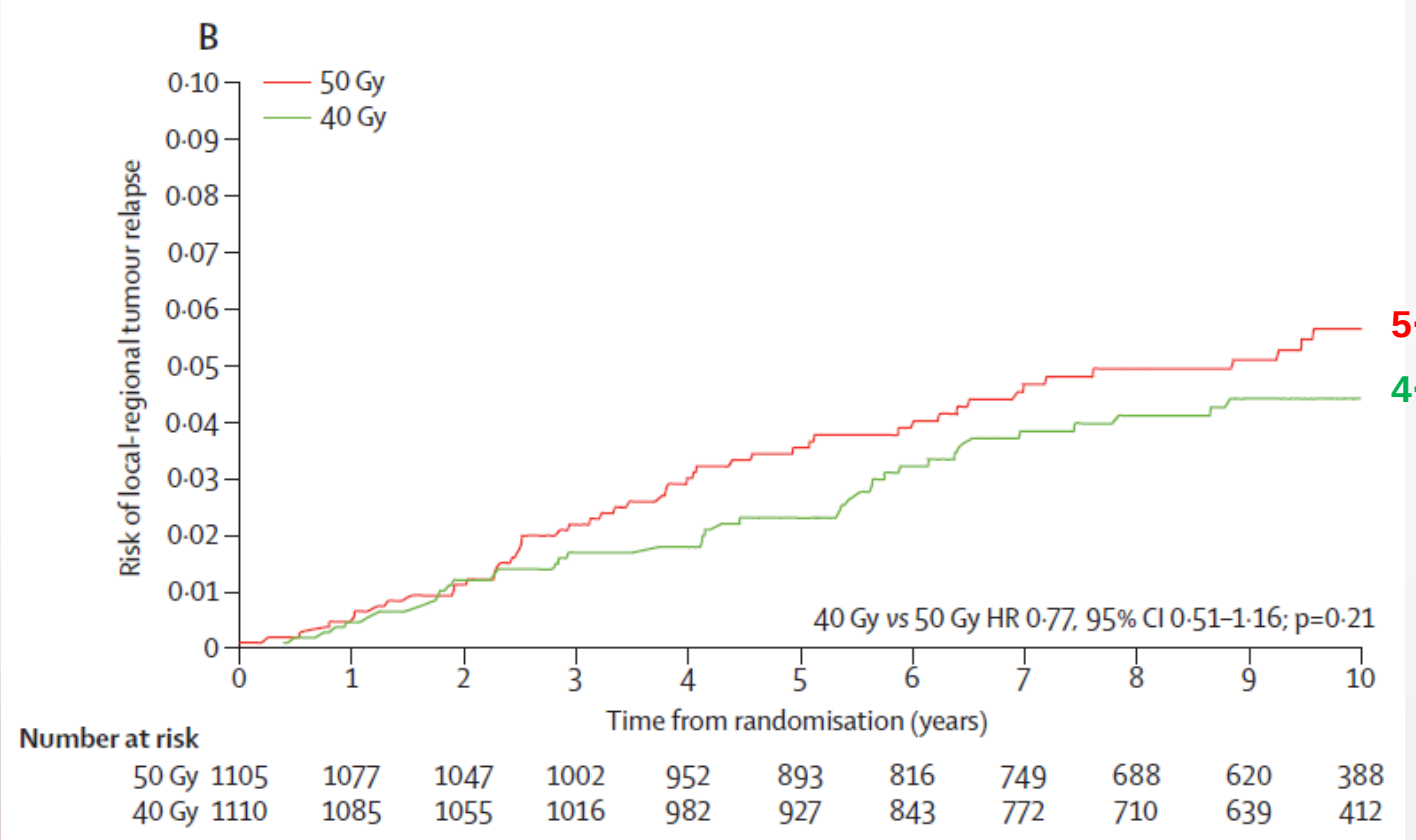
Whelan NEJM 2010





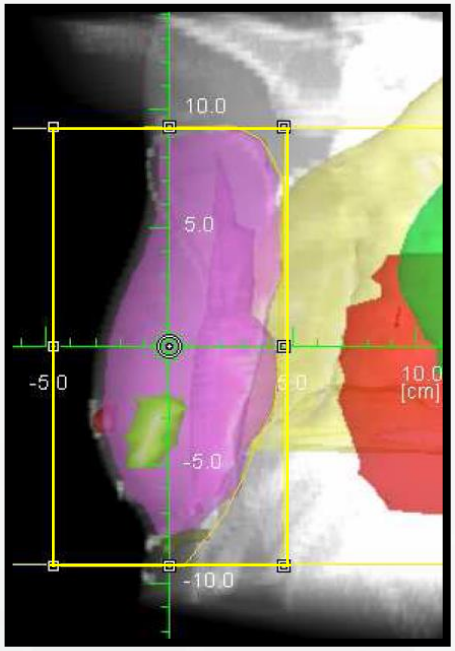
Haviland, Lancet Oncol 2013





Haviland, Lancet Oncol 2013

APRES TRAITEMENT CONSERVATEUR



Diminution de l'étalement

Augmentation de la dose par fraction

Diminution du volume d'irradiation traité

RADIOTHERAPIE HYPOFRACTIONNEE
DE L'ENSEMBLE DU SEIN

Études prospectives validées
Long suivi +++

EFFETS SECONDAIRES TARDIFS

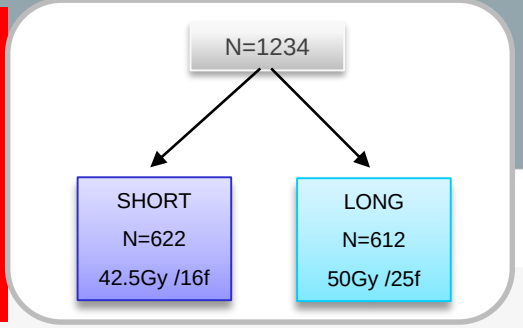


Table 1. Late Toxic Effects of Radiation, Assessed According to the RTOG–EORTC Late Radiation Morbidity Scoring Scheme.*

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

3%

4-6%

Whelan NEJM 2010

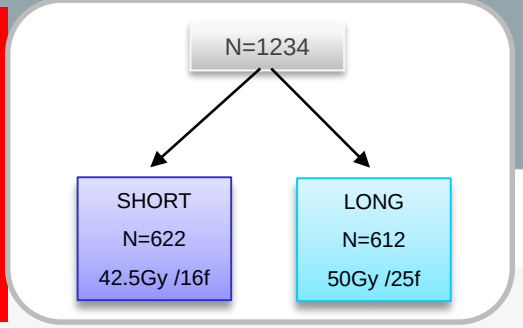


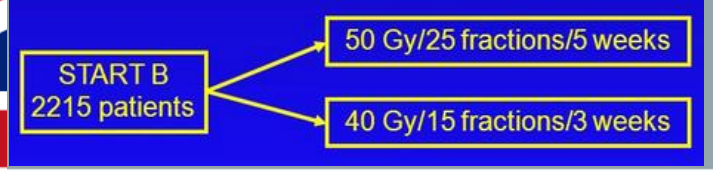
Table 1. Late Toxic Effects of Radiation, Assessed According to the RTOG–EORTC Late Radiation Morbidity Scoring Scheme.*

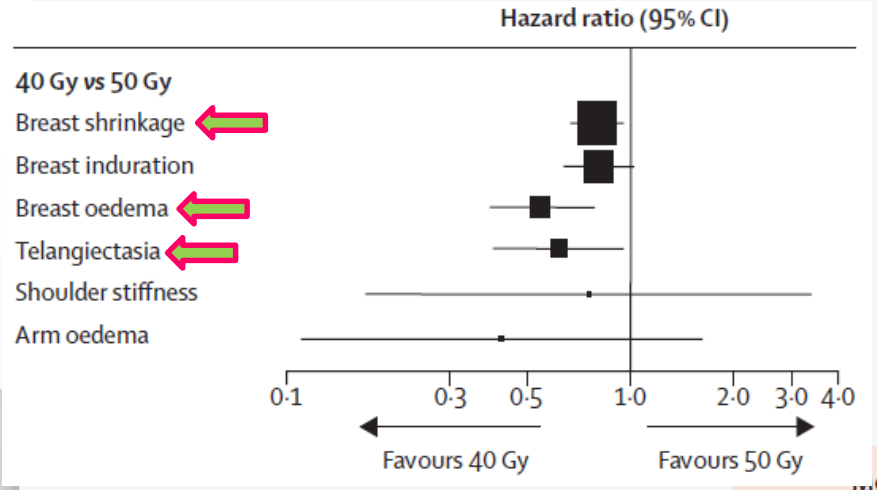
Site and Grade	5 Yr		10 Yr	
	Standard Regimen (N=424)	Hypofractionated Regimen (N=449)	Standard Regimen (N=220)	Hypofractionated Regimen (N=235)
	percent of patients			
Skin				
0†	82.3	86.1	70.5	66.8
1	14.4	10.7	21.8	24.3
2	2.6	2.5	5.0	6.4
3	0.7	0.7	2.7	2.5
Subcutaneous tissue				
0‡	61.4	66.8	45.3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

7-9%

10-12%

Whelan NEJM 2010





	...oderate or marked events (n/patients; %)	Estimated proportion of patients with event by 5 years (%; 95% CI)	Estimated proportion of patients with event by 10 years (%; 95% CI)	Crude hazard ratio (95% CI)	p value*
Breast shrinkage†					
50 Gy	256/1003 (25·5%)	15·8% (13·6–18·3)	31·2% (27·9–34·9)	1·00	..
40 Gy	221/1006 (22·0%)	11·4% (9·5–13·6)	26·2% (23·1–29·6)	0·80 (0·67–0·96)	0·015
Breast induration (tumour bed)†					
50 Gy	153/1003 (15·3%)	12·1% (10·2–14·4)	17·4% (14·9–20·3)	1·00	..
40 Gy	129/1006 (12·8%)	9·6% (7·9–11·6)	14·3% (12·1–16·9)	0·81 (0·64–1·03)	0·084
Telangiectasia					
50 Gy	52/1081 (4·8%)	3·8% (2·8–5·2)	5·8% (4·4–7·7)	1·00	..
40 Gy	34/1094 (3·1%)	1·8% (1·1–2·8)	4·2% (2·9–5·9)	0·62 (0·40–0·96)	0·032
Breast oedema†					
50 Gy	86/1003 (8·6%)	8·1% (6·6–10·1)	9·0% (7·3–11·0)	1·00	..
40 Gy	49/1006 (4·9%)	4·7% (3·5–6·2)	5·1% (3·9–6·7)	0·55 (0·39–0·79)	0·001

HYPOFRACTIONNEMENT ET AIRES GANGLIONNAIRES?

Quelques données – START trials

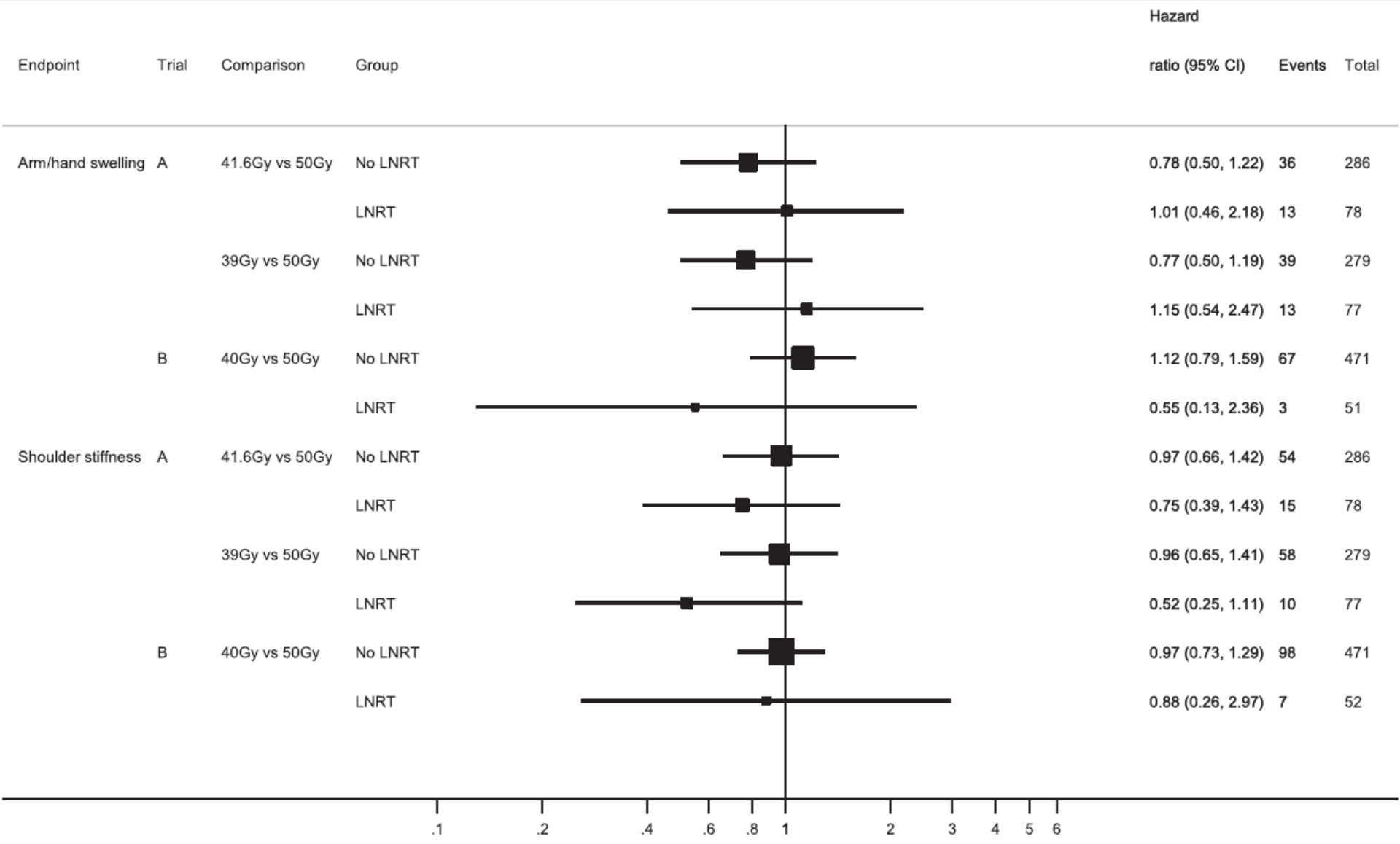
N= 864 /5861 (14.7%) patients

Baseline and treatment characteristics of patients who received lymphatic radiotherapy in the START-pilot, START-A and START-B trials.

	START-pilot Total *n* = 385 (%)	START-A Total *n* = 318 (%)	START-B Total *n* = 161 (%)
Age (years)			
Median (IQR) [range]	52.4 (45.5–60.5) [25.4–78.5]	56.2 (48.7–65.4) [25.7–81.9]	56.6 (50.7–65.2) [24.7–86.8]
Primary surgery			
Breast conserving surgery	385 (100.0)	171 (53.8)	106 (65.8)
Mastectomy	0	147 (46.2)	55 (34.2)
Pathological node status			
Positive	129 (33.5)	274 (86.2)	144 (89.4)
Negative	21 (5.5)	34 (10.7)	9 (5.6)
Not known (no axillary surgery)	233 (60.5)	9 (2.8)	8 (5.0)
Not known (missing data)	2 (0.5)	1 (0.3)	0
If positive, number of involved nodes			
Median (IQR) [range]	2 (1–5) [1–19]	3 (1–6) [1–25]	3 (1–6) [1–23]
Adjuvant therapy			
None	0	5 (1.6)	4 (2.5)
Tamoxifen only	145 (37.7)	59 (18.6)	67 (41.6)
Chemotherapy only	19 (4.9)	56 (17.6)	16 (9.9)
Tamoxifen + chemotherapy	44 (11.4)	184 (57.9)	74 (46.0)
Other endocrine therapy**/Not known	177 (46.0)	14 (4.3)	0
Lymphatic treatment			
Surgery + Axilla only	1 (0.3)	0 (0.0)	48 (29.8)
Surgery + SCF only	93 (24.2)	285 (89.6)	90 (56.0)
Surgery + Axilla + SCF	58 (15.1)	24 (7.6)	15 (9.3)
No surgery + Axilla only	0 (0.0)	1 (0.3)	0 (0.0)
No surgery + SCF only	2 (0.5)	3 (0.9)	2 (1.2)
No surgery + Axilla + SCF	231 (59.9)	5 (1.6)	6 (3.7)

Haviland Radiotherapy and Oncology 2018

Quelques données – START trials



Haviland Radiotherapy and Oncology 2018

Cohortes rétrospectives
British Columbia Cancer Agency & Cancer Control Alberta

Objectif principal:

Enquête transversale pour évaluer les symptômes et l'aspect fonctionnel du membre supérieur d'après la perception des patientes

- 1759 patientes éligibles
- Envoi d'un questionnaire, réponse des patientes pour 45.5%
  - ✓ Au total 708 patientes éligibles à cette étude

- HF (2.25-2.5 Gy/fx) *versus* CF; ≤2 Gy/fx

Leong, IJROBP 2017

Cohortes rétrospectives
British Columbia Cancer Agency & Cancer Control Alberta

Table 3 Comparisons of presence of patient-reported arm symptoms (score ≥1) and function between hypofractionated and conventionally fractionated nodal radiation therapy

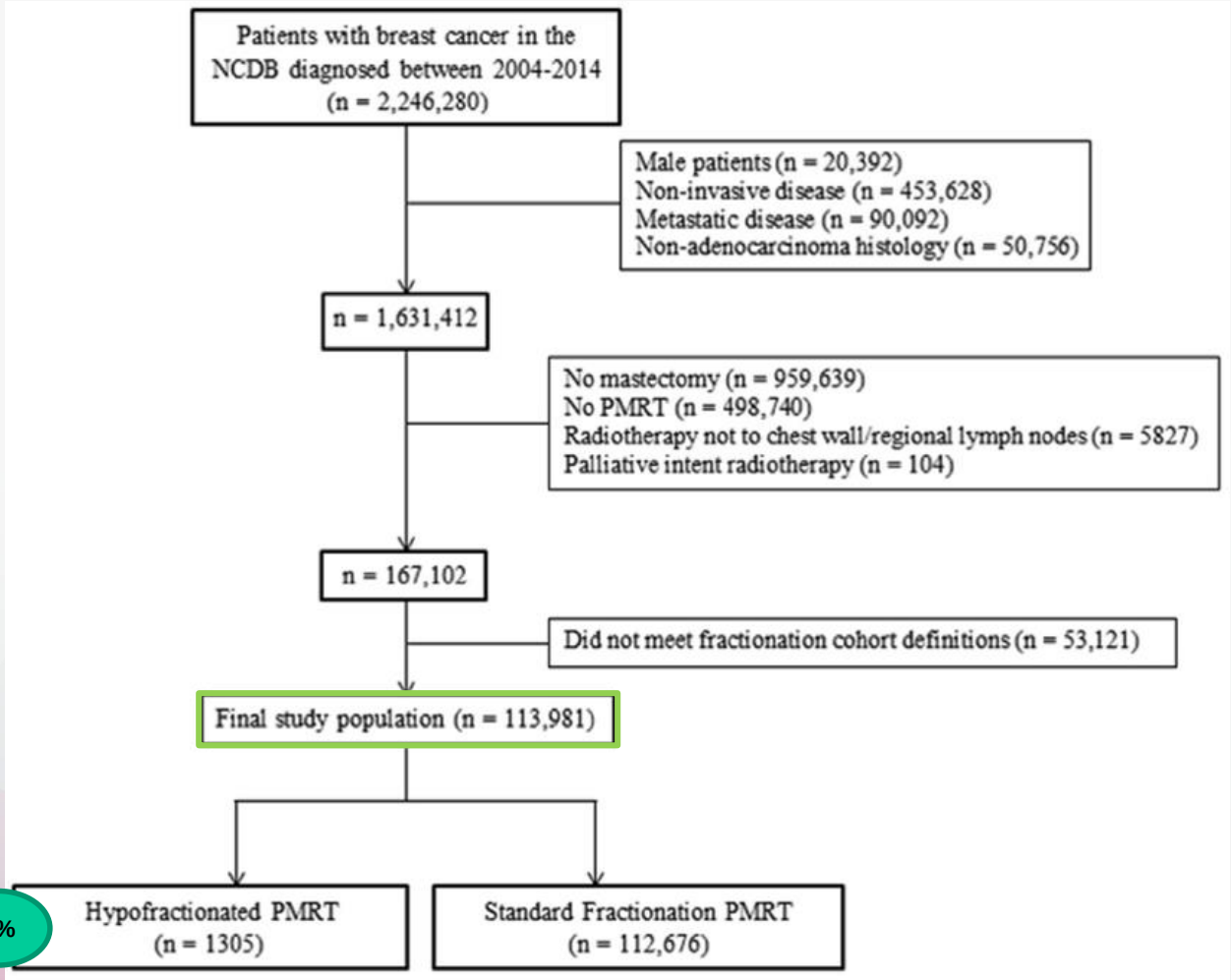
SASS question (Q)		HFRT (%)	CFRT (%)	*P*
Q1	Arm swelling	33	35	.86
Q2	Arm pain	33	37	.22
Q3	Shoulder pain	30	32	.45
Q4	Arm stiffness	37	39	.57
Q5	Shoulder stiffness	35	42	.04
Q6	Arm dysfunction	48	54	.06
Q7	Arm numbness	44	48	.39
Q8	Arm movement	43	52	.02
Q9a	Hair brushing	24	29	.13
Q9b	Sweater pullover	28	31	.56
Q9c	Bra fastening	36	40	.27
Q9d	Back zipper	44	48	.47
Q9e	Reach overhead	38	49	.004

Leong, IJROBP 2017

HYPOFRACTIONNEMENT APRES MASTECTOMIE?

HF-RT and PMRT

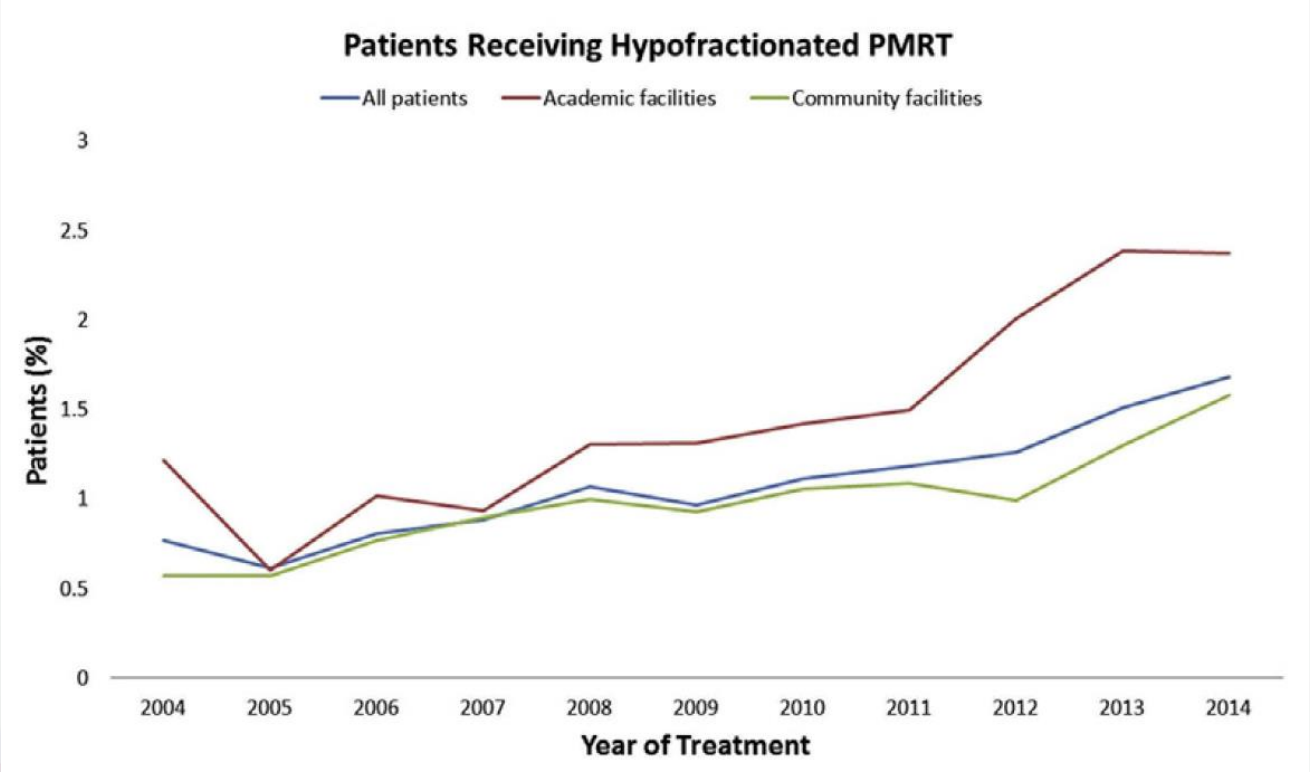
- Pourquoi s'y intéresser? *Données issues du National Cancer Database*



Venigalla Clinical Breast Cancer 2018

HF-RT and PMRT

- Pourquoi s'y intéresser?



struction and receipt of chemotherapy were negative predictors. **Conclusion:** Because of the absence of high-level evidence to support its use, hypofractionated PMRT was uncommonly utilized in the United States from 2004 to 2014, although a small increase in use was noted over time. Findings from this study might be useful in designing

Venigalla Clinical Breast Cancer 2018

ORIGINAL REPORT
JOURNAL OF CLINICAL ONCOLOGY
VOLUME 35 · NUMBER 18 · JUNE 20, 2017

Hypofractionated Postmastectomy Radiation Therapy Is Safe and Effective: First Results From a Prospective Phase II Trial

ClinicalTrials.gov Identifier: NCT01417286

- **Primary aim/end point :**
  - ✓ To ensure that the total serious toxicity rate (greater than grade 2, CTCAE v.4) from the experimental fractionation, at any time point, was similar to standard PMRT

- **Schéma de radiothérapie:**
  - ✓ Dose totale= 36.63 Gy (en 11 fractions)
  - ✓ Dose par fraction= 3.33 Gy
  - ✓ Étalement= 11jours

- 69 patientes, Stage II – IIIa
- Période d'inclusion: Déc 2010 – Déc 2014

Khan, JCO 2017

ORIGINAL REPORT
JOURNAL OF CLINICAL ONCOLOGY
VOLUME 35 · NUMBER 18 · JUNE 20, 2017

Hypofractionated Postmastectomy Radiation Therapy Is Safe and Effective: First Results From a Prospective Phase II Trial

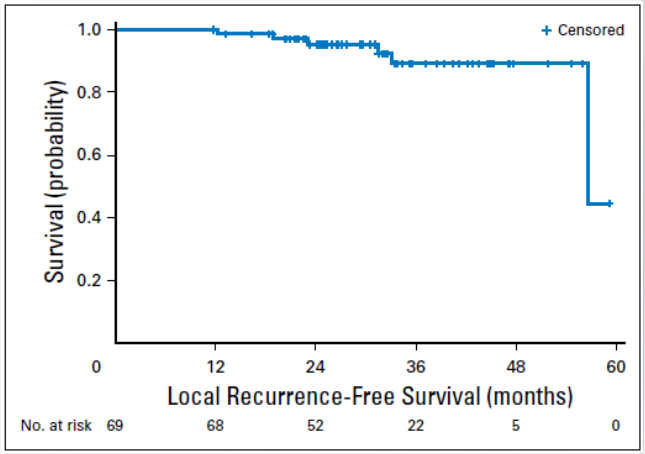
ClinicalTrials.gov Identifier: NCT01417286

- No grade 3 toxicity

Table 2. Treatment-Related Grade 2 Toxicities

Toxicity	No.	%
Skin	16	24.0
Fatigue	5	7.5
Pain	3	4.5
Lymphedema	3	4.5
Subcutaneous	1	1.4
Other*	1	1.4

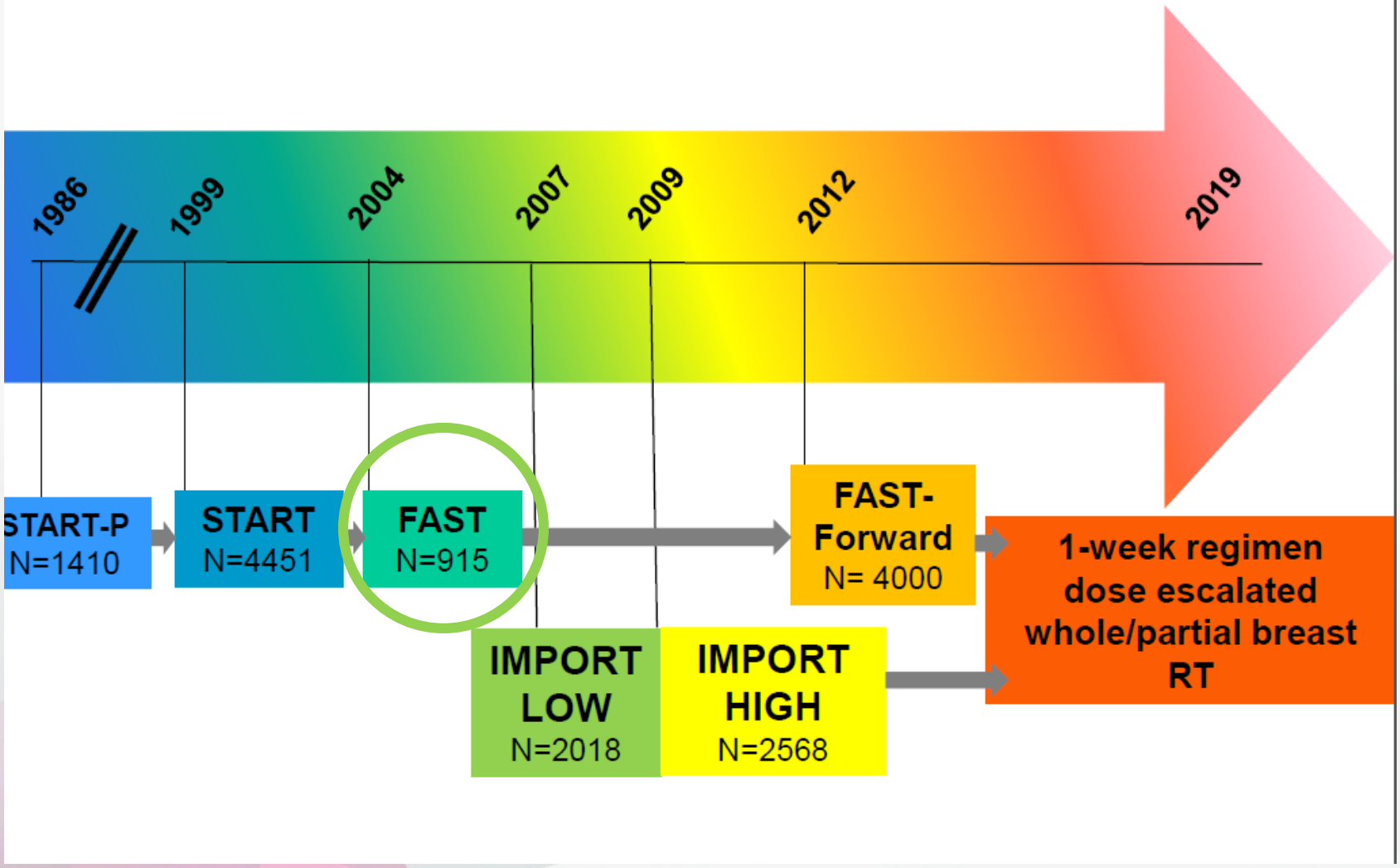
*Hot flashes.



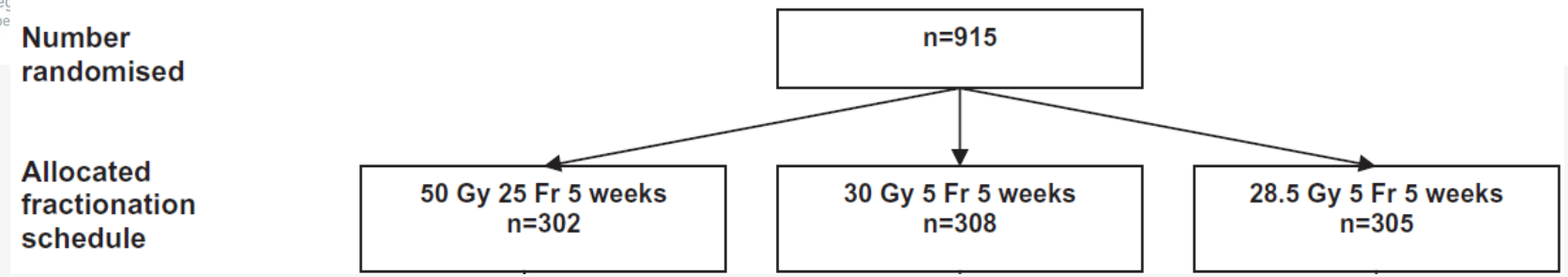
Khan, JCO 2017

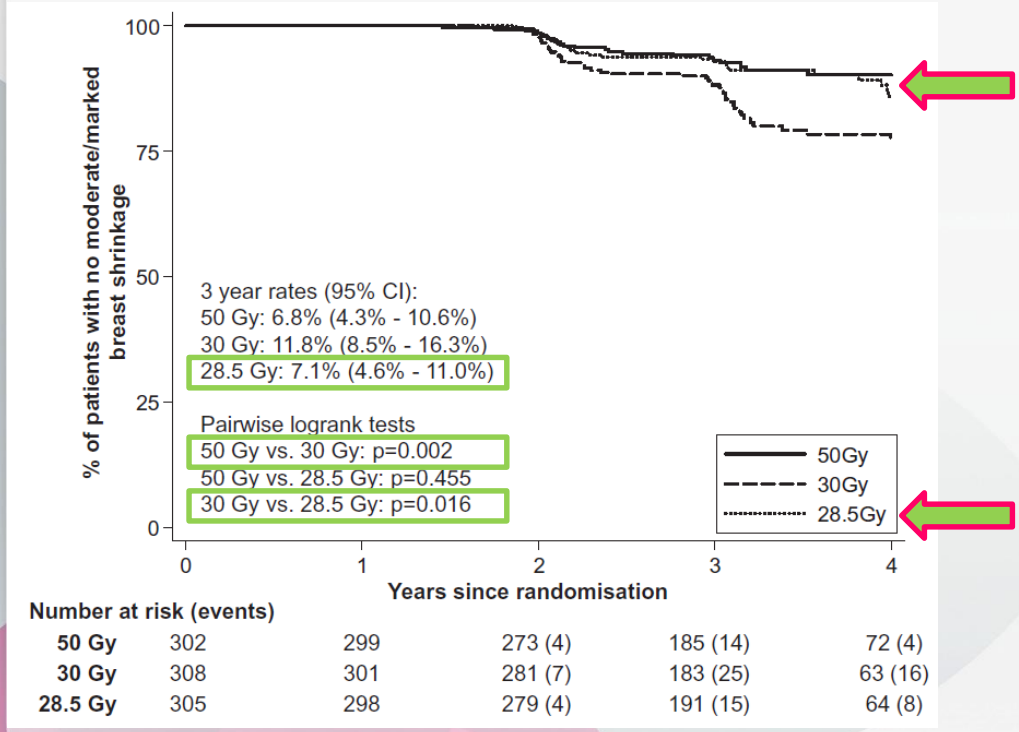
ESSAIS CLINIQUES PASSES, EN COURS, A VENIR…

Timeline of UK Breast RT trials



UK FAST Trial: CRUKE/04/015



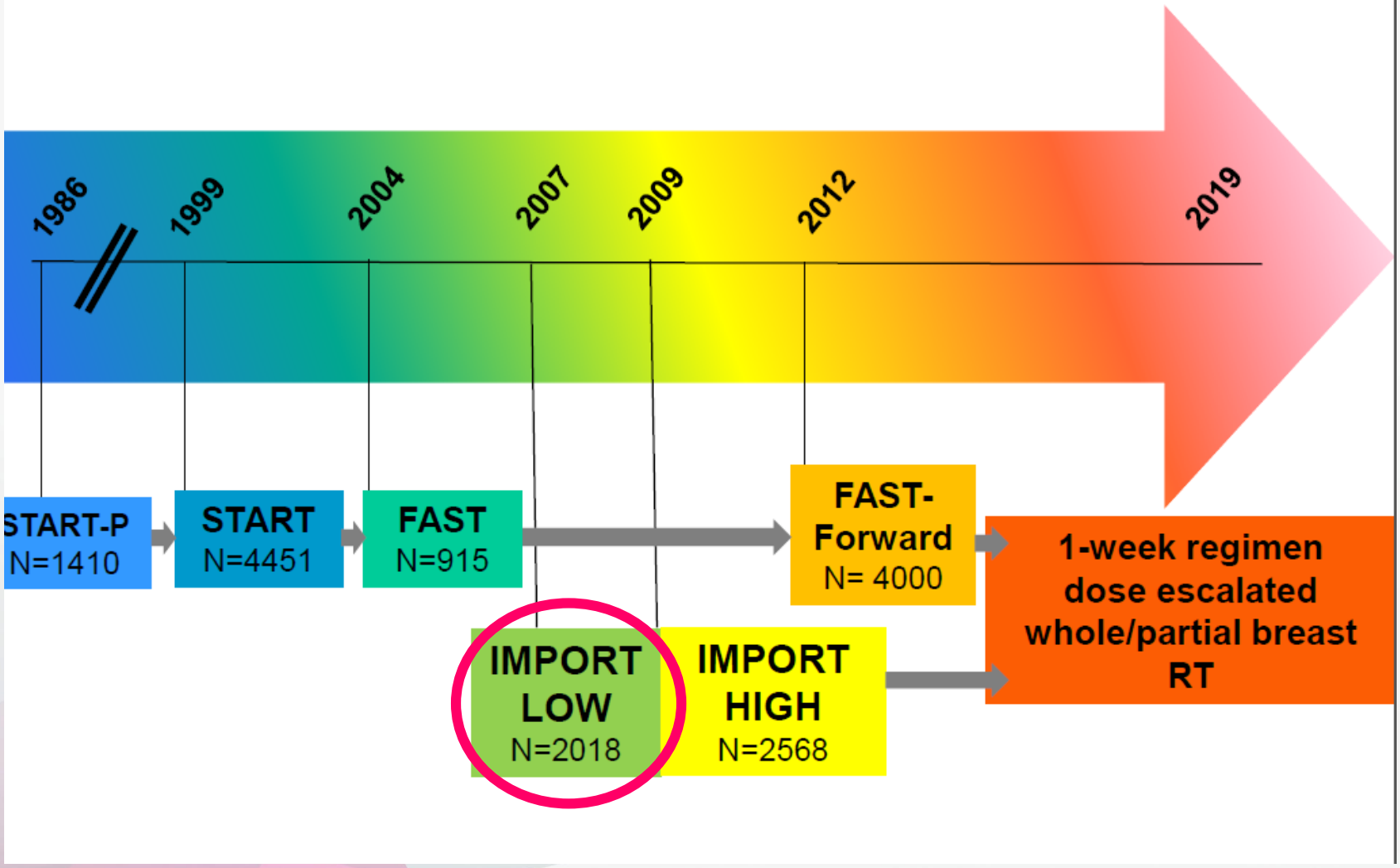


Relapses, second primary cancers and deaths by fractionation schedule.

	Fractionation schedule			Total
	50 Gy	30 Gy	28.5 Gy	
Relapses				
Local (breast skin or parenchyma)	2	0	0	2
Regional (axilla or supraclavicular fossa)	1	0	2	3
Distant	5	2	10	17
Second primary cancer	3	3	2	8
Deaths	6	5	12	23
Breast cancer	2	2	6	10
Other cause[a]	4	3	6	13

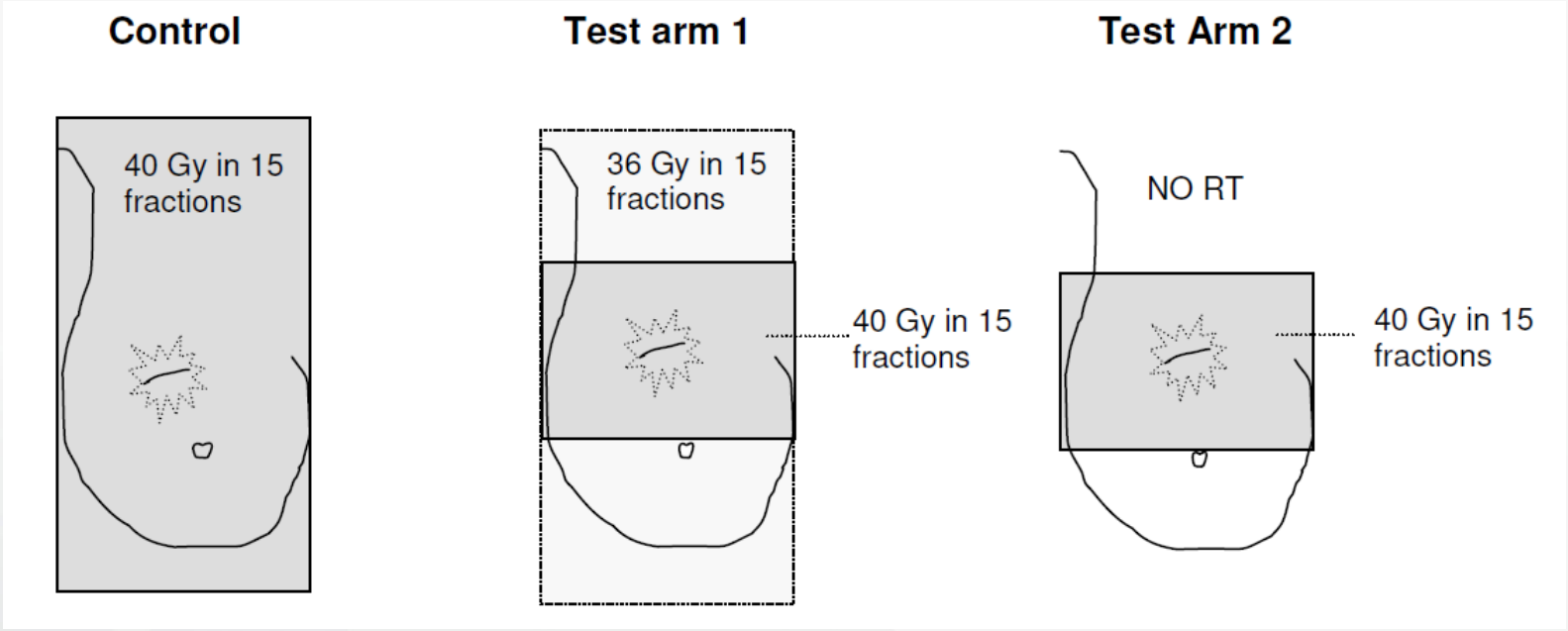
Yarnold Radiotherapy and Oncology 2011

Timeline of UK Breast RT trials



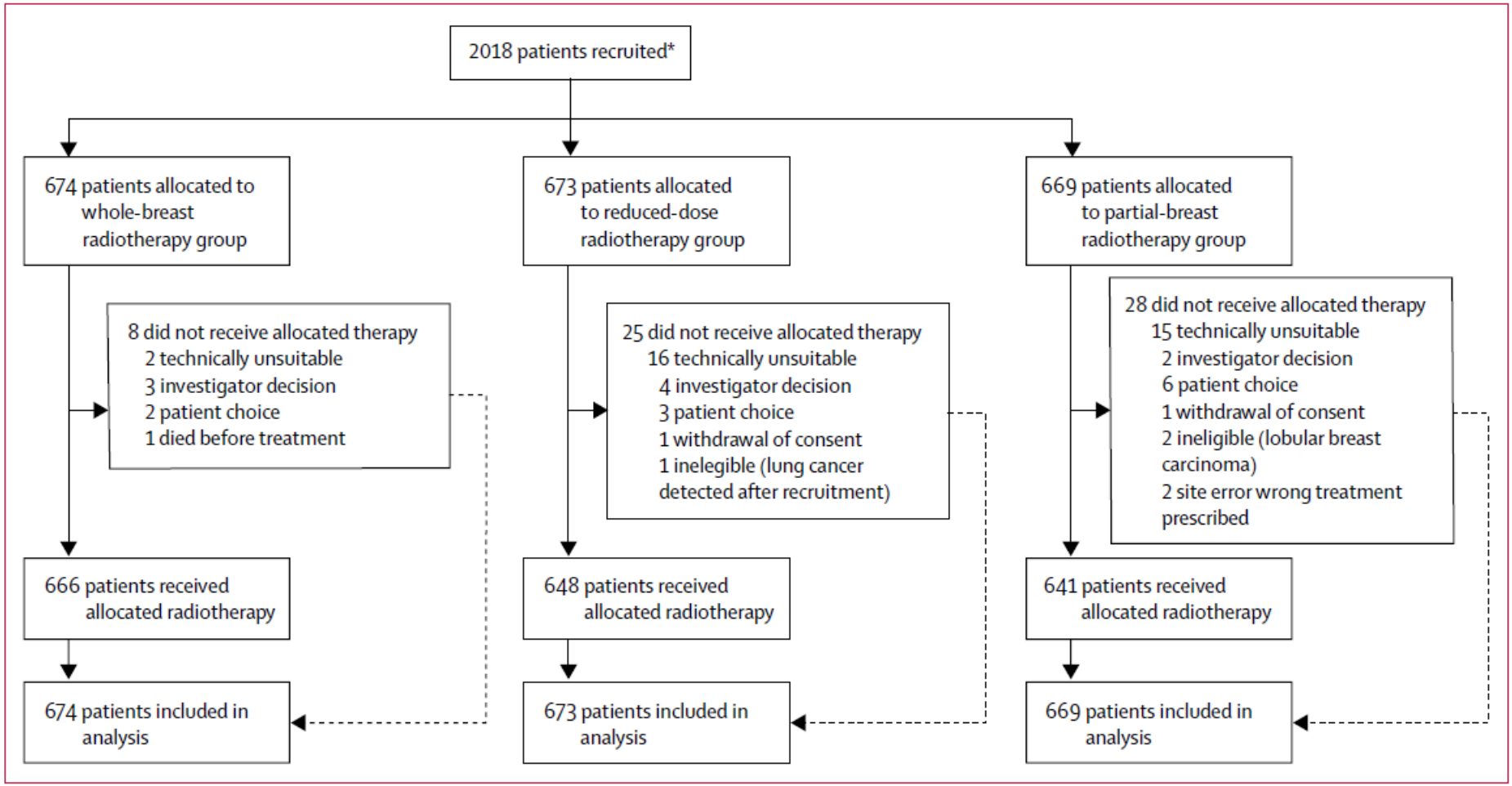
IMPORT LOW

Intensity Modulated and Partial Organ RadioTherapy



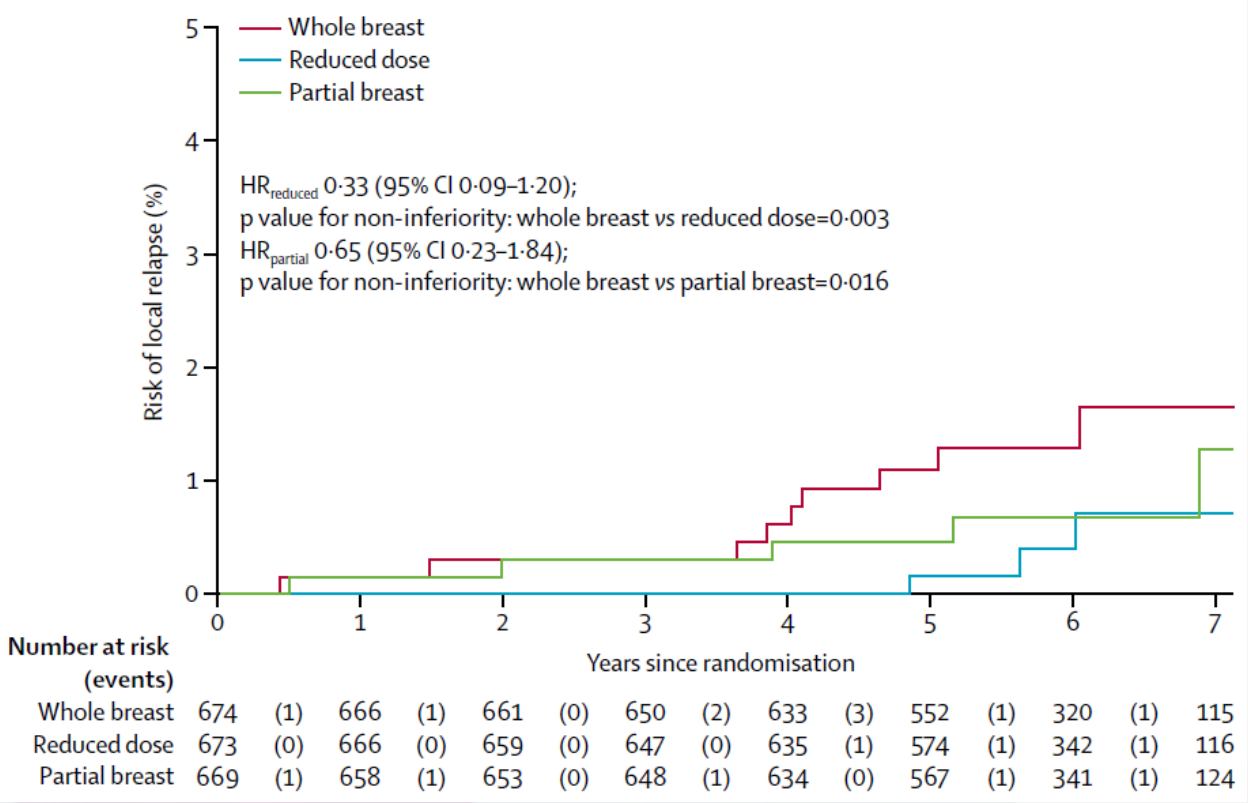
Intensity Modulated and Partial Organ Radiotherapy following Breast Conservation Surgery for Early Breast Cancer in patients with a low risk of local relapse

IMPORT LOW



Coles, Lancet 2017

IMPORT LOW



POPULATION

- Age: 62 ans
- Grade SBR1/ 2 : 90%
- Ré-excision chir: 13%
- pN0: 96%
- IDC: 86%
- RE+: 95%
- Her2-: 96%
- Hormonothérapie: 91%

Coles, Lancet 2017

- **Topographie des récidives locales**

	Whole breast (n=674)	Reduced dose (n=673)	Partial breast (n=669)	Total (n=2016)
Local relapse	9* (1%)	3† (<1%)	6 (1%)	18 (1%)
Within radiotherapy field‡	9 (1%)	1 (<1%)	4 (1%)	14 (1%)
Borderline with radiotherapy field	0	0	1 (<1%)	1 (<1%)
Not documented	0	2 (<1%)	1 (<1%)	3 (<1%)

- **Autres récidives**

Contralateral breast second primary	12 (2%)	13 (2%)	13 (2%)	38 (2%)

Coles, Lancet 2017

- **Autres récidives: seconds cancers (hors cancer du sein)**

Non-breast second primary	35 (5%)	37 (5%)	24 (4%)	96 (5%)
Colorectal	10§ (1%)	7 (1%)	3 (<1%)	20 (1%)
Lung	11§ (2%)	4 (1%)	4 (1%)	19 (1%)
Gynaecological	5 (1%)	8 (1%)	4 (1%)	17 (1%)
Other¶	4 (1%)	3 (<1%)	1 (<1%)	8 (<1%)
Oesophagus	0	3 (<1%)	3 (<1%)	6 (<1%)
Pancreas	1 (<1%)	2 (<1%)	3 (<1%)	6 (<1%)
Lymphoma	0	2 (<1%)	3 (<1%)	5 (<1%)
Genitourinary	3 (<1%)	1 (<1%)	0	4 (<1%)
Head and neck	1 (<1%)	2 (<1%)	0	3 (<1%)
Liver	0	2 (<1%)	1 (<1%)	3 (<1%)
Cancer of unknown primary	0	0	2 (<1%)	2 (<1%)
Peritoneal	0	2 (<1%)	0	2 (<1%)
Sarcoma	1 (<1%)	1‖ (<1%)	0	2 (<1%)

Coles, Lancet 2017

- **Causes de décès**

Deaths	40 (6%)	39 (6%)	37 (6%)	116 (6%)
Breast cancer	9** (1%)	7†† (1%)	10‡‡ (1%)	26 (1%)
Second cancer	14 (2%)	16 (2%)	12 (2%)	42 (2%)
Cardiac	5 (1%)	2 (<1%)	2 (<1%)	9 (<1%)
Cerebrovascular accident	1 (<1%)	2 (<1%)	1 (<1%)	4 (<1%)
Pulmonary embolism	0	2 (<1%)	0	2 (<1%)
Other	11 (2%)	10 (1%)	10 (1%)	31 (2%)
Unknown	0	0	2 (<1%)	2 (<1%)

Coles, Lancet 2017

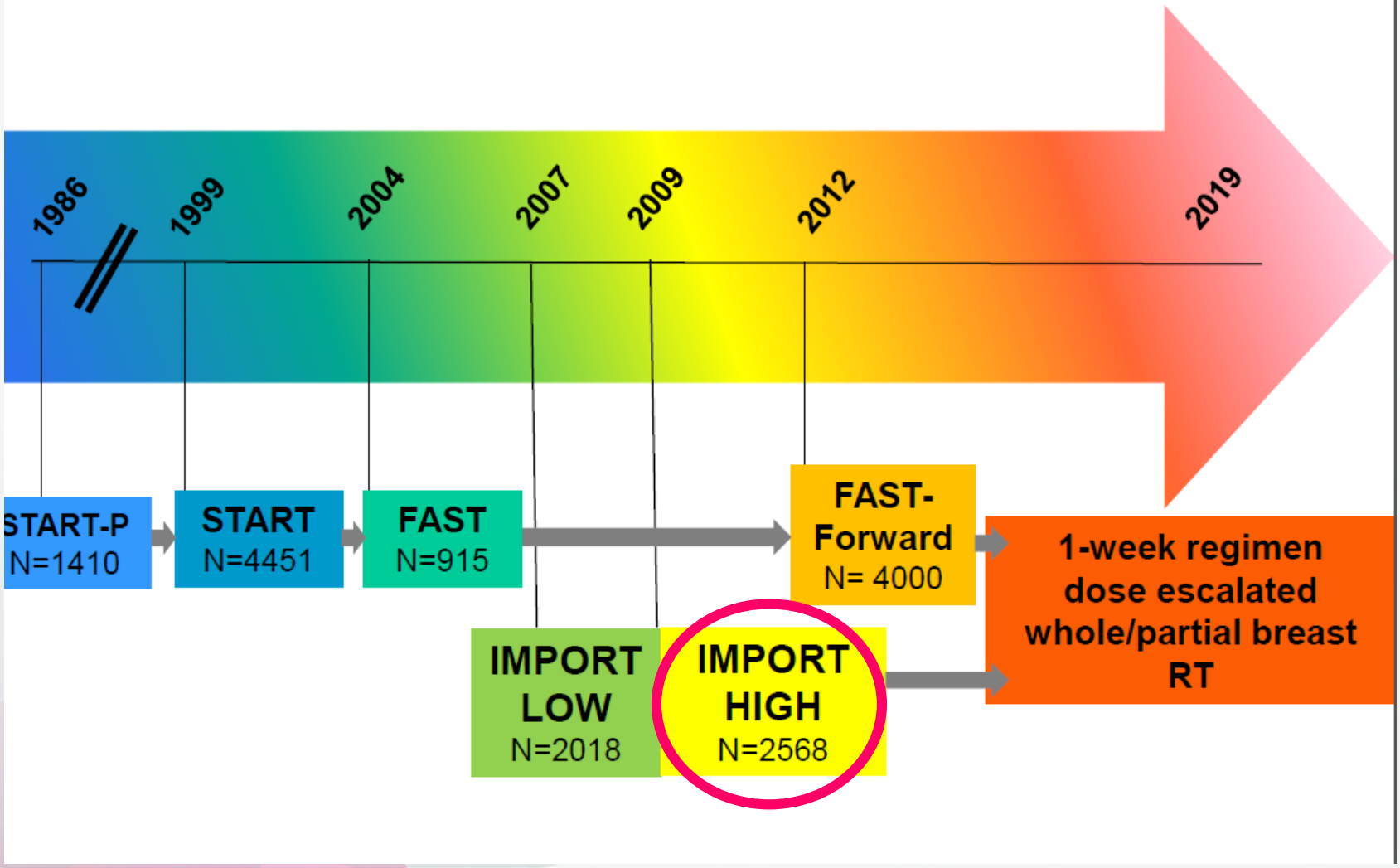
Institut régional du Cancer Montpellier | Val d'Aurelle

- **Effets secondaires tardifs**

	Cumulative number of adverse events			Adverse events at 5 years	
	n/N (%)	5-year cumulative incidence*, % (95% CI)	HR (95% CI), p value†	n/N (%)	p value‡
Protocol-specific items					
Breast appearance changed					
Whole breast	158/411 (38%)	47·7% (41·1–54·8)	1	80/295 (27%)	..
Reduced dose	123/433 (28%)	36·7% (30·6–43·6)	0·74 (0·54–1·00), p=0·051	66/325 (20%)	0·047
Partial breast	113/421 (27%)	35·1% (28·7–42·5)	0·64 (0·46–0·89), p=0·007	49/331 (15%)	<0·0001
Breast smaller					
Whole breast	119/411 (29%)	37·3% (30·9–44·4)	1	66/294 (22%)	..
Reduced dose	110/433 (25%)	31·9% (26·3–38·4)	0·83 (0·59–1·16), p=0·280	63/326 (19%)	0·373
Partial breast	104/421 (25%)	34·7% (27·5–43·0)	0·78 (0·54–1·11), p=0·162	56/331 (17%)	0·086
Breast harder or firmer					
Whole breast	115/411 (28%)	35·3% (28·4–43·3)	1	27/292 (9%)	..
Reduced dose	74/433 (17%)	21·0% (16·2–26·9)	0·53 (0·36–0·79), p=0·002	23/325 (7%)	0·376
Partial breast	58/421 (14%)	15·3% (12·0–19·5)	0·47 (0·32–0·71), p<0·0001	15/330 (5%)	0·024
Shoulder stiffness					
Whole breast	56/411 (14%)	19·3% (14·0–26·5)	1	12/296 (4%)	..
Reduced dose	56/433 (13%)	19·3% (13·9–26·4)	0·93 (0·64–1·35), p=0·701	22/328 (7%)	0·161
Partial breast	58/421 (14%)	15·3% (12·0–19·5)	1·06 (0·73–1·54), p=0·756	13/331 (4%)	0·999
Skin appearance changed					
Whole breast	63/411 (15%)	21·0% (15·5–27·9)	1	22/294 (7%)	..
Reduced dose	59/433 (14%)	17·9% (13·2–24·0)	1·07 (0·68–1·68), p=0·775	23/325 (7%)	0·878
Partial breast	49/421 (12%)	14·6% (10·4–20·5)	0·87 (0·54–1·40), p=0·569	12/330 (4%)	0·051

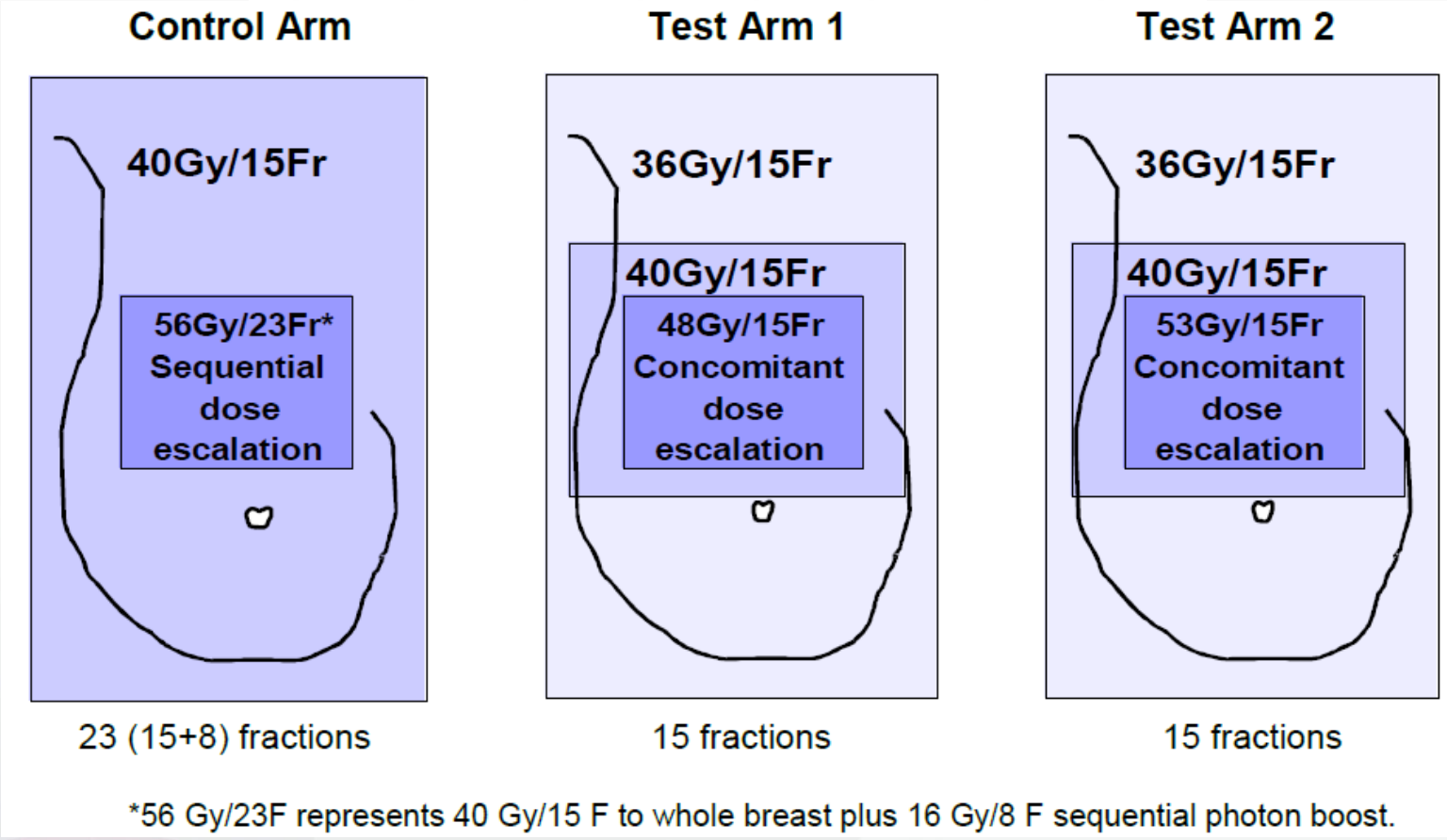
Coles, Lancet 2017

Timeline of UK Breast RT trials



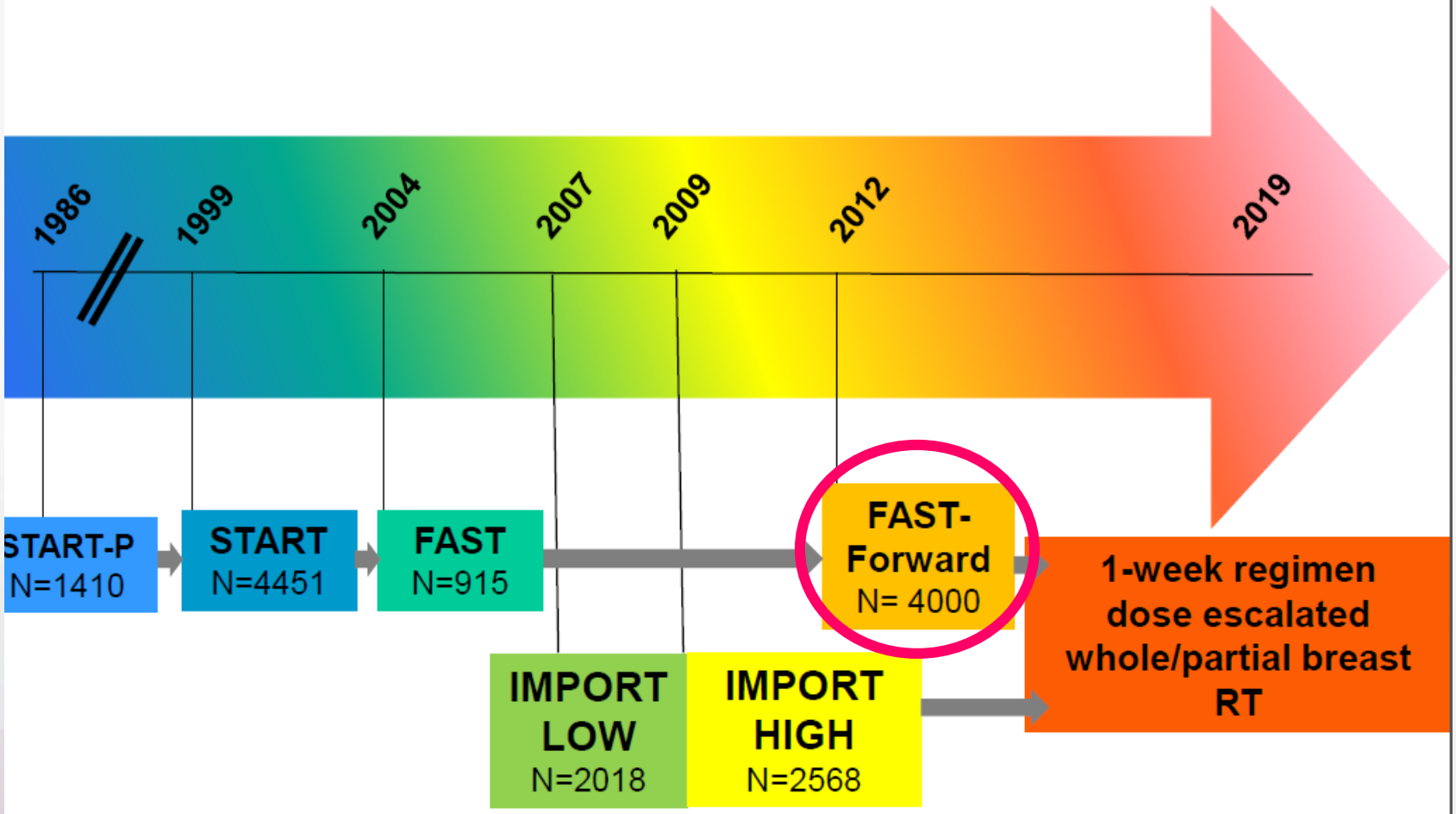
IMPORT HIGH

Intensity Modulated and Partial Organ RadioTherapy



Dose escalated intensity modulated radiotherapy following Breast Conservation Surgery for Early Breast Cancer in patients with a high risk of local relapse

Timeline of UK Breast RT trials



FAST-Forward

Control Group	Test Group 1	Test Group 2
40.05 Gy in 15 Fr 3 weeks 2.67 Gy/F	27.0 Gy in 5 Fr 1 week 5.4 Gy/F	26.0 Gy in 5 Fr 1 week 5.2 Gy/F

Main end-point: ipsilateral local recurrence

Brunt Radiotherapy and Oncology 2016

UK FAST-Forward Trial

- Toxicité aigue

Acute toxicity substudy 2 – Worst acute CTCAE score according to treatment.

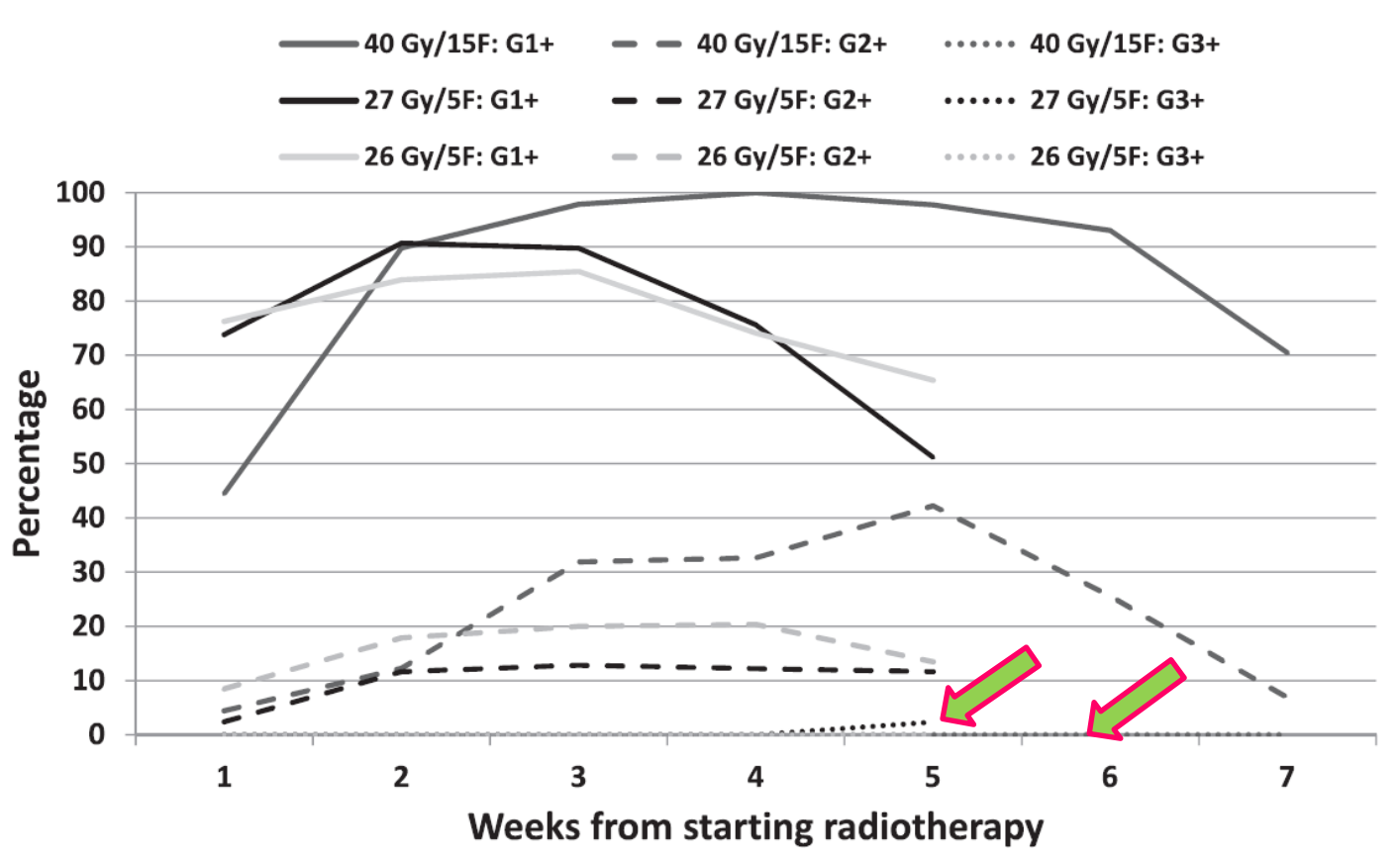
CTCAE grade	40 Gy/15F *N* = 43 *N* (%)[a]	27 Gy/5F *N* = 41 *N* (%)[a]	26 Gy/5F *N* = 53 *N* (%)[a]
0	0	3 (7)	3 (6)
1	21 (49)	26 (63)	31 (58)
2	22 (51)	11 (27)	19 (36)
3	0	1 (2)[b]	0
4	0	0	0
Proportion grade 3+ (upper limit of one-sided 95% CI)	0 (6.7)%	2.4 (11.1)%	0 (5.5)%

[a] Percentages calculated from those evaluable.
[b] Grade 3 toxicity reported at 4 weeks post-RT resolved to grade 1 one week later.

Brunt Radiotherapy and Oncology 2016

UK FAST-Forward Trial

- **Délai apparition des toxicités aigues de grade 3+** (i.e, grade 3 apparue 4 semaines après XRT et résolutive en 1 semaine) en fonction du fractionnement



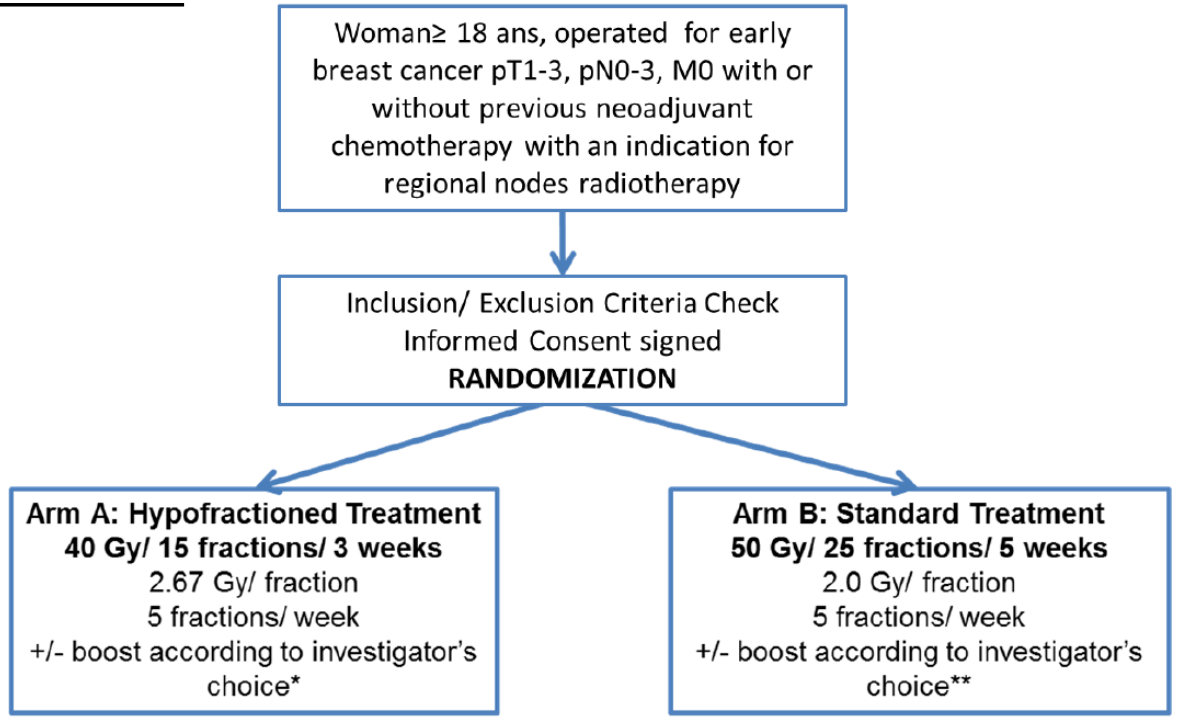
Brunt Radiotherapy and Oncology 2016

Hypofractionated vs Standard Radiotherapy in breast cancer with an indication for Regional Lymph Node Irradiation about lymphedema occurrence (HYPOG-01)

ClinicalTrials.gov Identifier: NCT03127995

Primary endpoint: arm lymphedema
Standard arm= 10% at 3 years

Non-inferiority randomized phase 3 trial
(non-inferiority limit HR=1.545)



TAKE HOME MESSAGE

- **Après traitement conservateur**

Table 1 Patients for whom consensus supports use of HF-WBI: A comparison of the 2011 and 2018 ASTRO Guidelines *

Factor	2011 Guideline	2018 Guideline
Age	≥50 years	Any
Stage	T1-2 N0	Any stage provided intent is to treat the whole breast without an additional field to cover the regional lymph nodes
Chemotherapy	None	Any chemotherapy
Dose homogeneity	±7% in the central axis	Volume of breast tissue receiving >105% of the prescription dose should be minimized regardless of dose-fractionation

ASTRO, American Society for Radiation Oncology; HF-WBI, hypofractionated whole-breast irradiation.

Smith Practical Radiation Oncology: May-June 2018

- **En cours d'évaluation:**
  - ✓ Après mastectomie
  - ✓ Irradiation des aires ganglionnaires