Centre Oscar Lambret

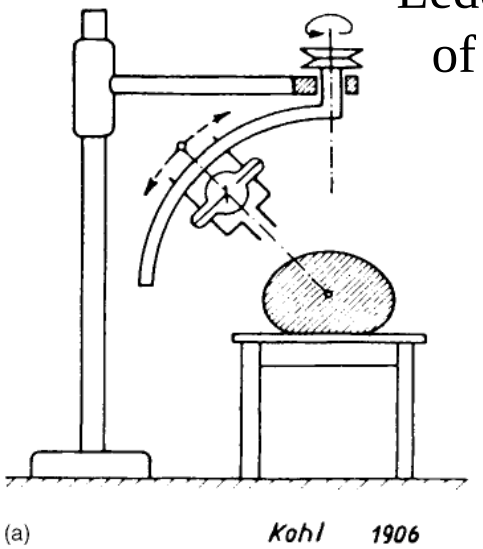
ONCO LILLE
Site de Recherche Intégrée sur le Cancer

Cancer du sein: vers de nouveaux fractionnements ?

Pr. Eric F. LARTIGAU

Centre Oscar Lambret

& Université Lille II

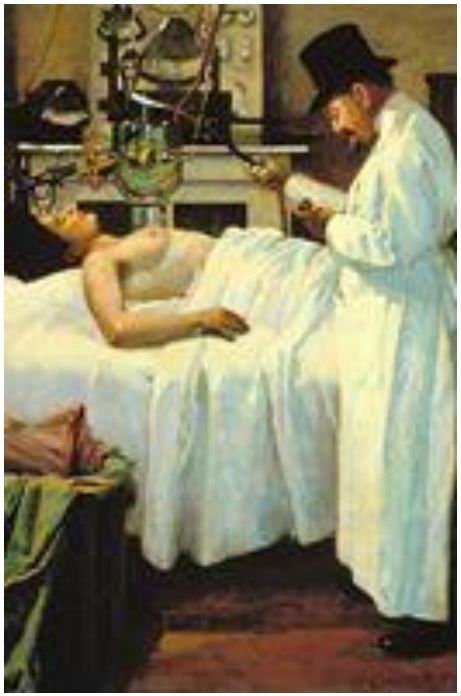


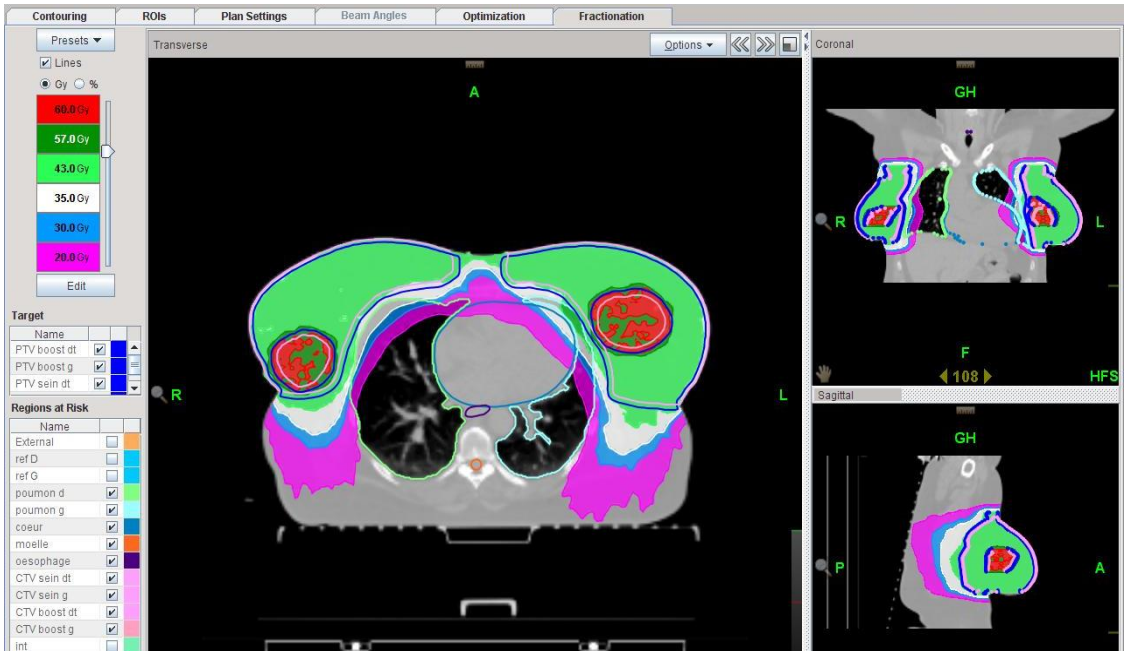
Lederman « The early history of radiotherapy 1895-1931 »

IJROBP 1981

Premiers essais du traitement du cancer par les rayons X

Dr Georges CHICOTOT (1845-1923)





Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials

EBCTCG (Early Breast Cancer Trialists' Collaborative Group)*

Lancet 2014; 383: 2127–35

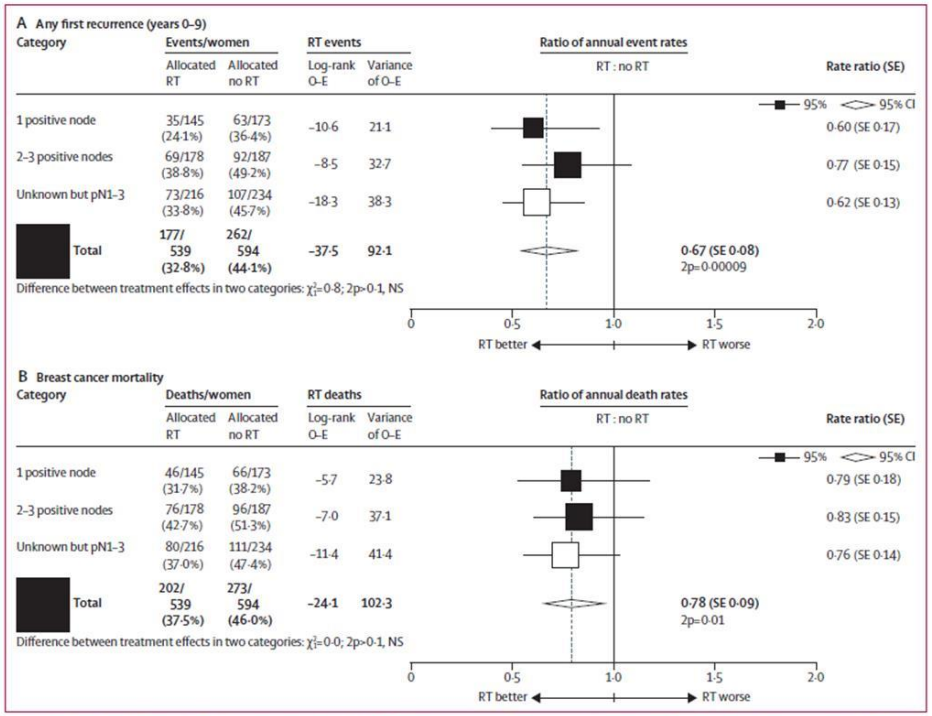


Figure 6: **Effect of radiotherapy (RT) after mastectomy and axillary dissection on overall recurrence during years 0–9 and on breast cancer mortality for the entire follow-up in 1133 women with one to three pathologically positive nodes (pN1–3) in trials in which systemic therapy was given to both randomised treatment groups, by number of positive nodes**

See also appendix pp 23–26. NS=not significant. SE=standard error.

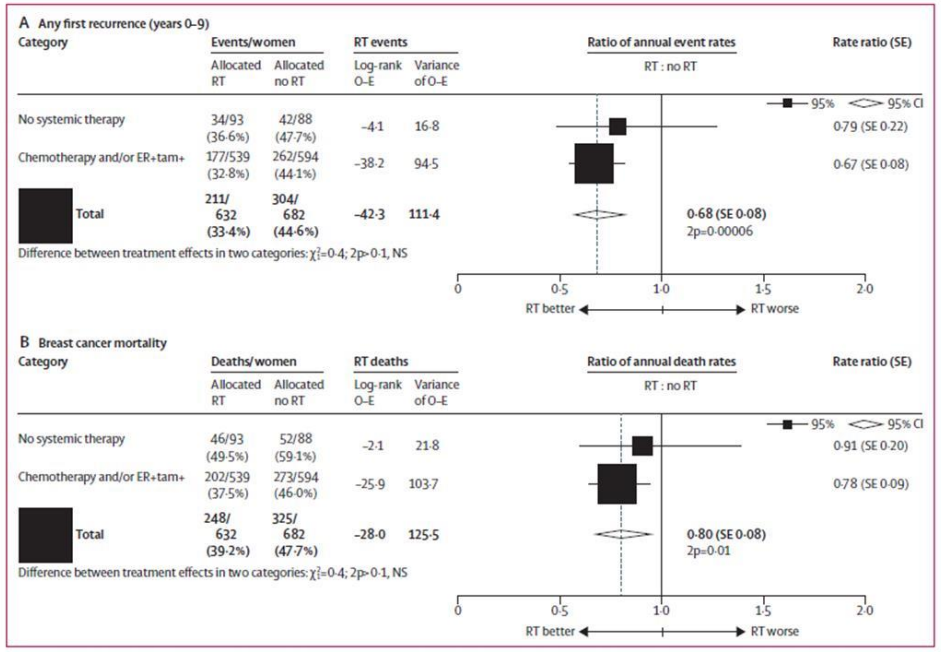


Figure 4: **Effect of radiotherapy (RT) after mastectomy and axillary dissection on overall recurrence during years 0–9 and on breast cancer mortality for the entire follow-up in 1314 women with one to three pathologically positive nodes, according to whether or not they were in trials in which systemic therapy was given to both randomised treatment groups**

Chemotherapy was usually cyclophosphamide, methotrexate, and fluorouracil. ER-negative women in trials in which tamoxifen was given to both groups are included in the "no systemic" category. ER=oestrogen receptor. tam=tamoxifen. NS=not significant. SE=standard error.

Standards et questions

- **Standards > 2 Gy / fraction**
- **Questions:**
  - **Boost/no boost**
  - **Technique: RCMI ?**
  - **SIB ?**
  - **Ganglions ?**
  - **TT adjuvants ?**

Standards et questions

- **Standards > 2 Gy / fraction**
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  - **TT adjuvants ?**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

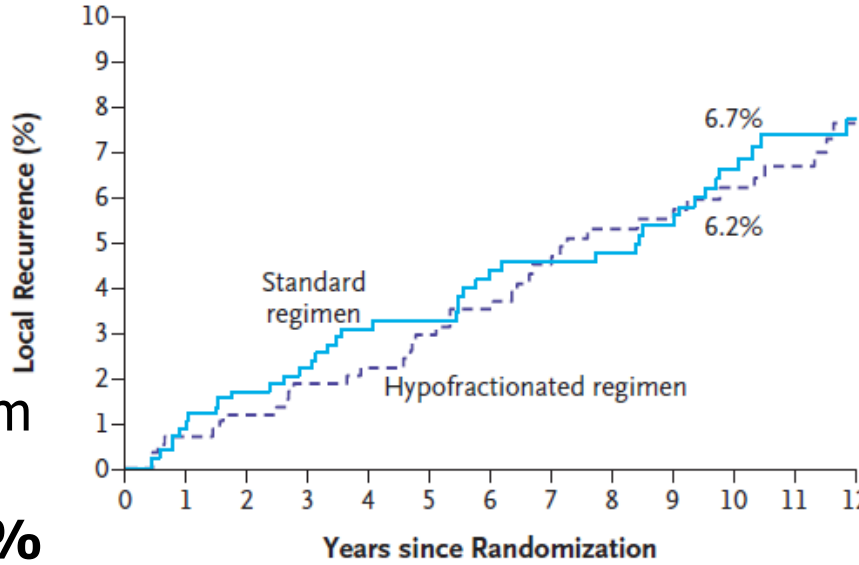
N Engl J Med 2010;362:513-20.

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.,

1200 patientes Suivi médian 12 ans

Bras standard: 50 Gy en 25 fr 5 sem
Bras hypofractionné: 42.5 Gy en 16 fr 3 sem



Récidive locale 10 ans: 6.7 % et 6.2 %

Résultat esthétique bon ou excellent: 71 % et 70 %

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

Lancet Oncol 2013; 14: 1086–94

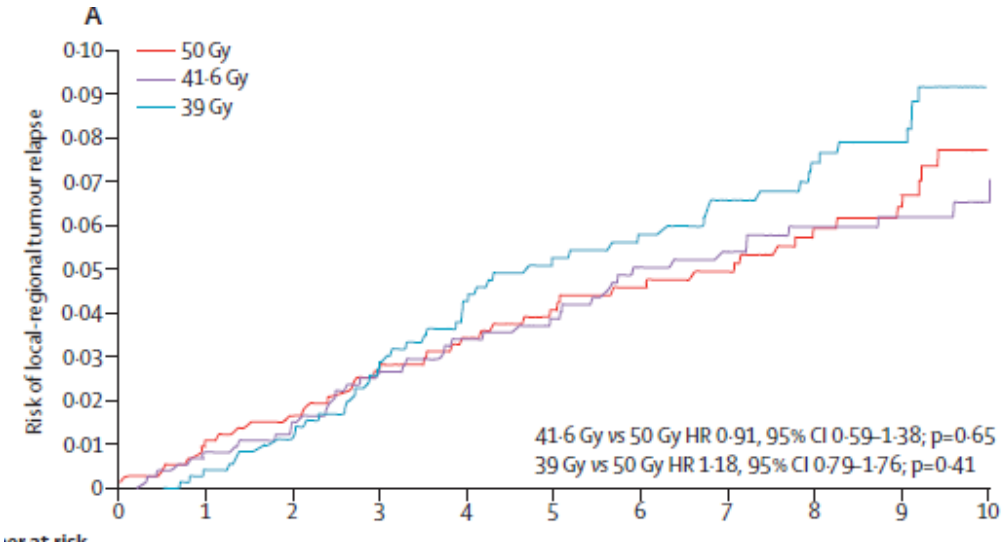
Joanne S Haviland, J Roger Owen, John A Dewar, Rajiv K Agrawal, Jane Barrett, Peter J Barrett-Lee, H Jane Dobbs, Penelope Hopwood,

START A

2200 patientes Age médian 57 ans Suivi médian 10 ans

50 Gy 25 fr vs 41.6 Gy vs 39 Gy 13 fr 5 semaines

61 % boost 10 Gy



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

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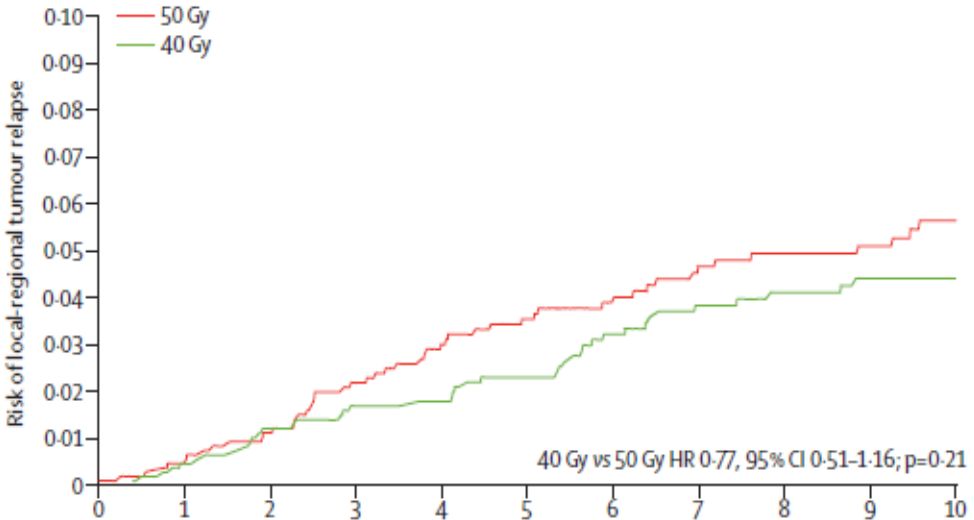
Joanne S Haviland, J Roger Owen, John A Dewar, Rajiv K Agrawal, Jane Barrett, Peter J Barrett-Lee, H Jane Dobbs, Penelope Hopwood,

START B

2200 patientes Age médian 57 ans Suivi médian 10 ans

50 Gy 25 fr 5 semaines vs 40 Gy en 15 fr **3 semaines**

<u>43 % boost 10 Gy</u>



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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

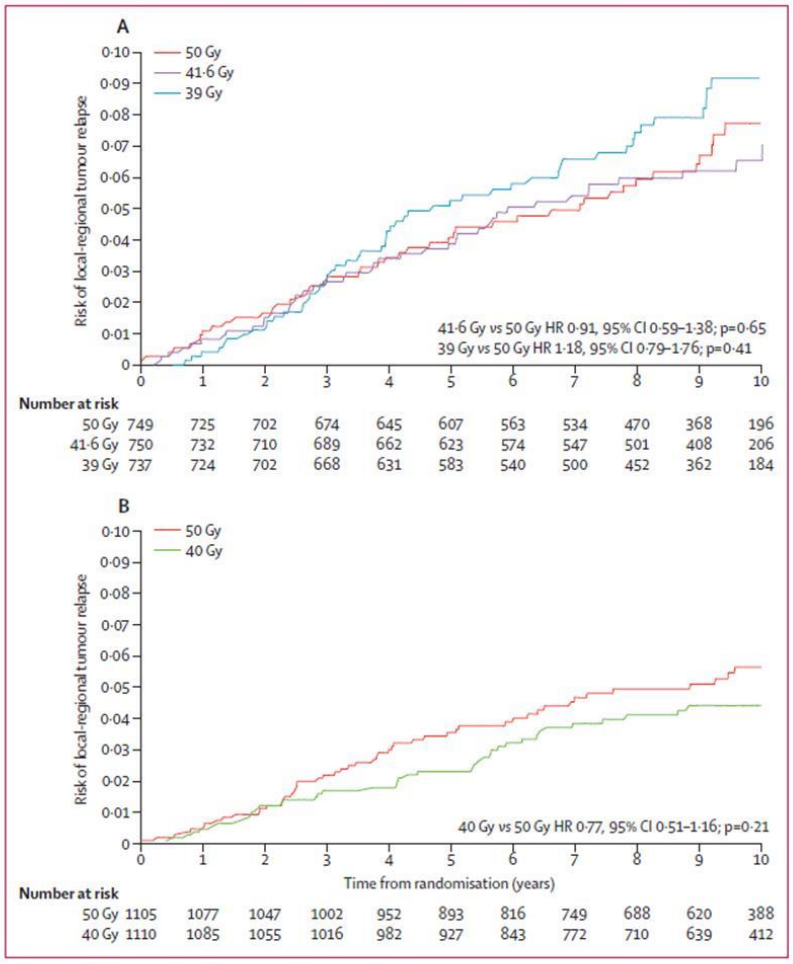

Figure 1: **Cumulative risk of local-regional tumour relapse**
In START-A (A) and START-B (B).

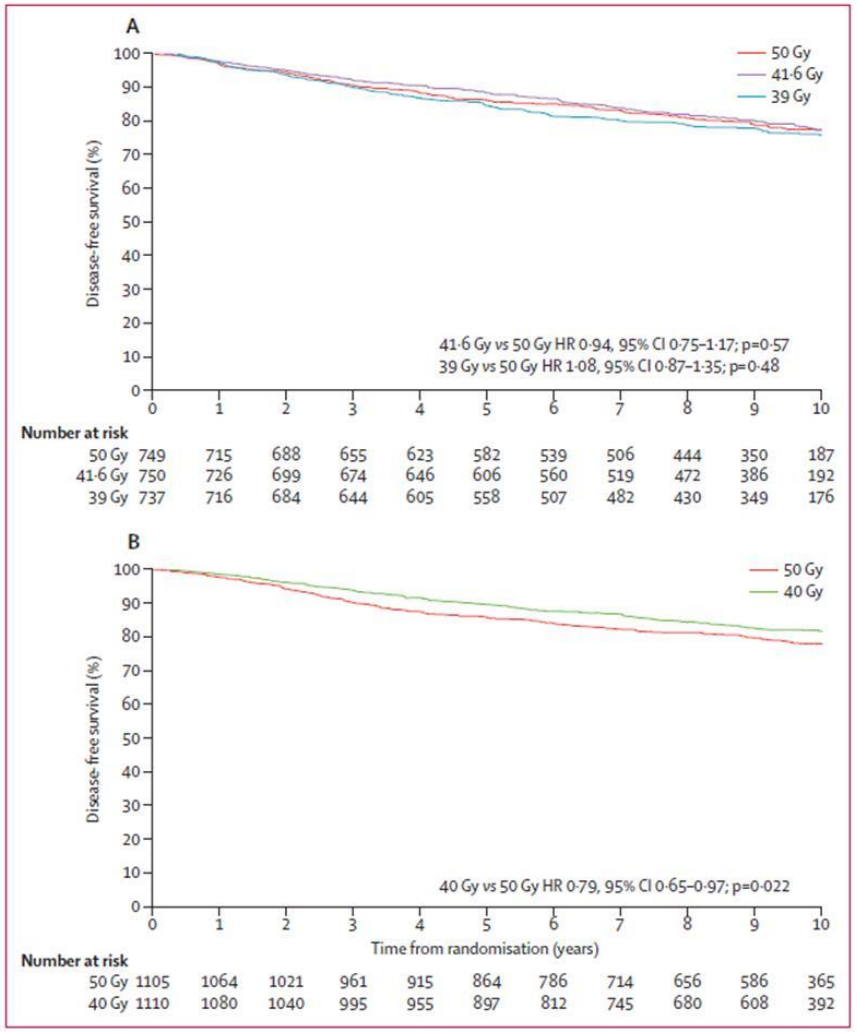

Figure 2: **Kaplan-Meier analysis of disease-free survival**
In START-A (A) and START-B (B).

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

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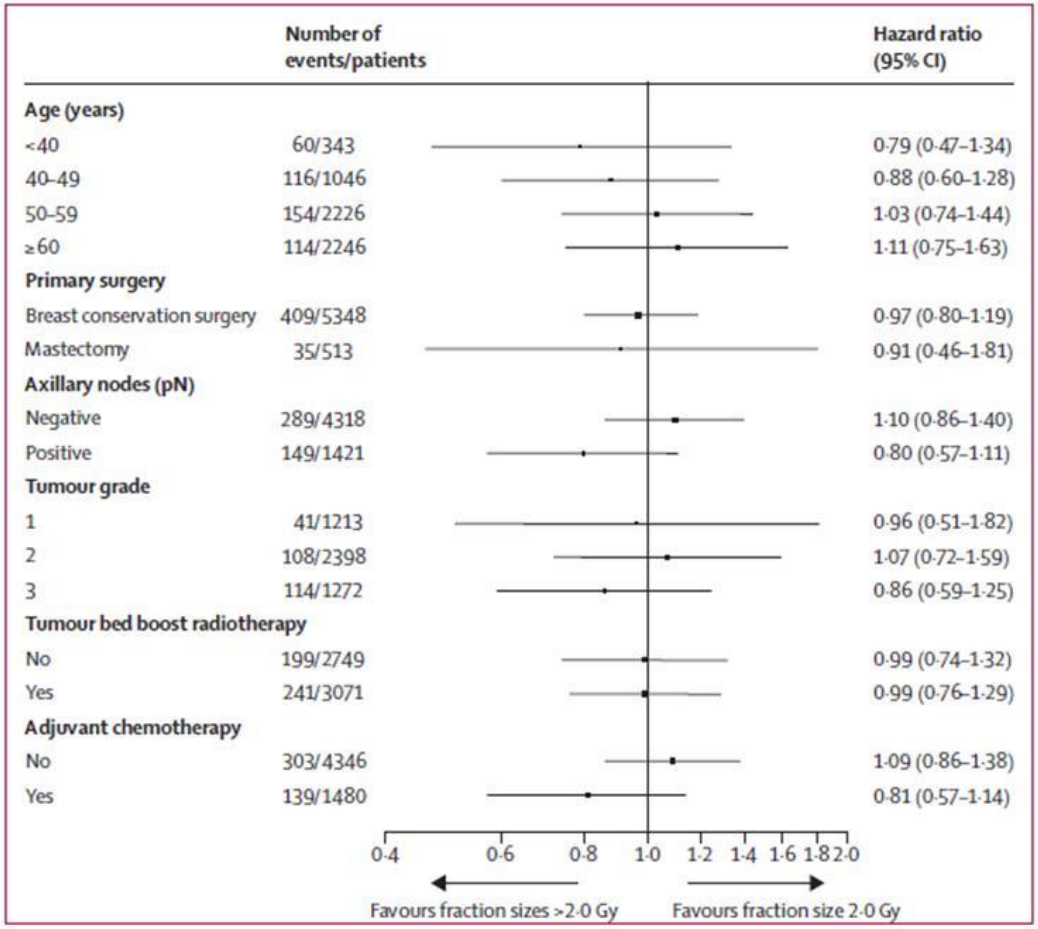


Figure 4: **Meta-analysis of local-regional relapse comparing hypofractionated regimens versus 50 Gy in 25 fractions**

Includes 5861 patients from the START pilot trial, START-A, and START-B.

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

Lancet Oncol 2013; 14: 1086–94

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†

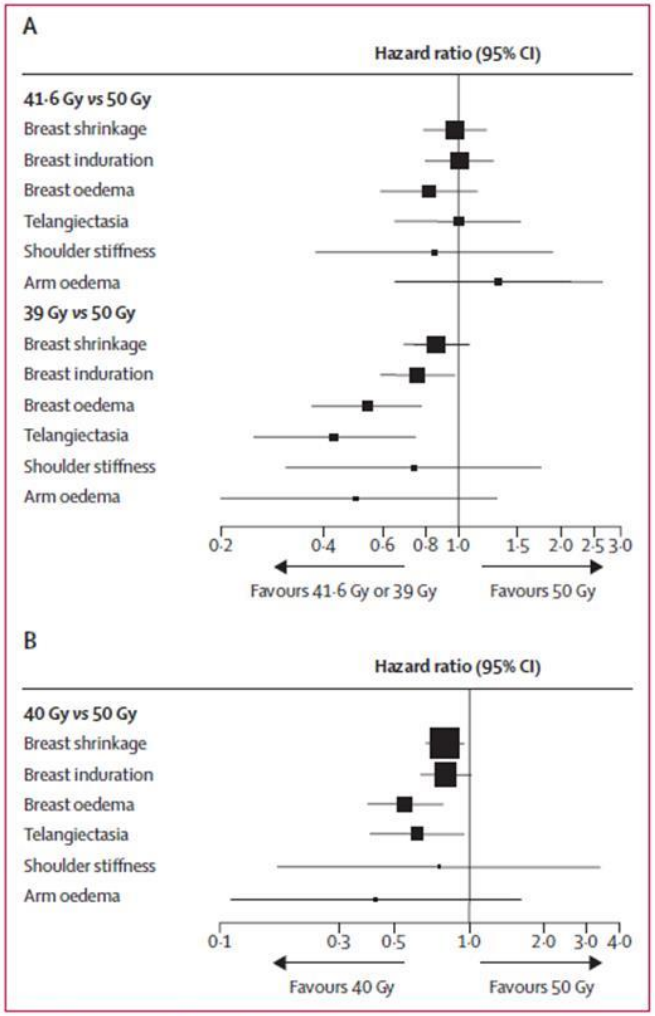


Figure 3: **Late normal tissue effects**
In START-A (A) and START-B (B). Assessed as moderate or marked by physicians.

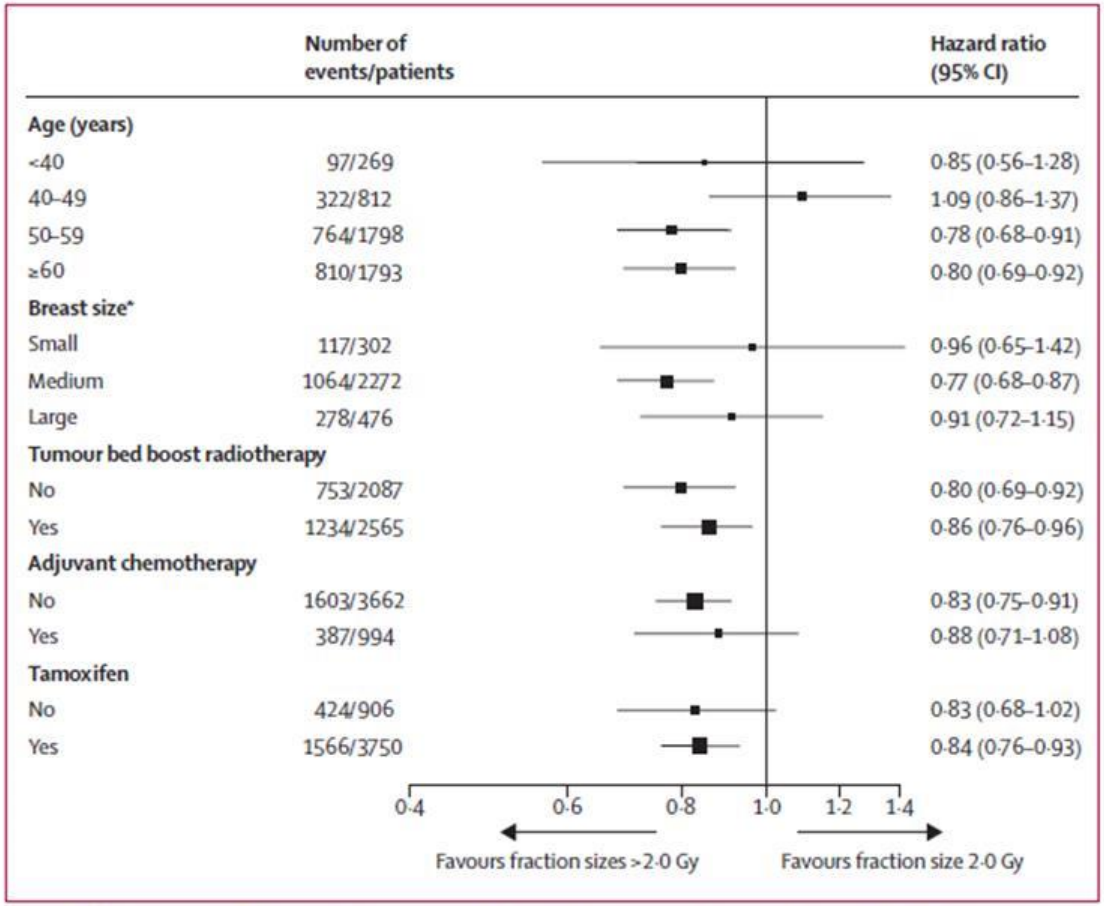


Figure 5: **Meta-analysis of any moderate or marked physician-assessed normal tissue effects in the breast comparing hypofractionated regimens versus 50 Gy in 25 fractions**
Includes 4672 patients from START pilot trial, START-A, and START-B. *Assessed from baseline photographs.

Radiotherapy and Oncology 108 (2013) 293–298

Normal tissue complication probability (NTCP) parameters for breast fibrosis: Pooled results from two randomised trials

Mukesh B. Mukesh [a,*], Emma Harris [b], Sandra Collette [c], Charlotte E. Coles [a], Harry Bartelink [d], Jenny Wilkinson [a], Philip M. Evans [e], Peter Graham [f], Jo Haviland [g], Philip Poortmans [h], John Yarnold [i], Raj Jena [a]

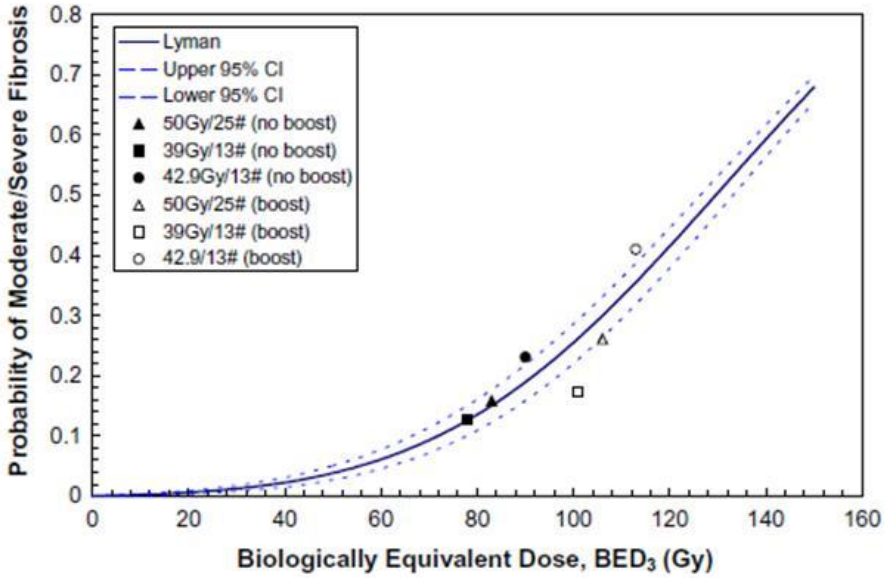


Fig. 1. Lyman Kutcher Burman model – the probability of moderate–severe breast fibrosis versus biological equivalent dose using α/β of 3 Gy (BED_3). The solid line is based on the best fit parameters (BED_3 = 132 Gy and m = 0.35) and the dashed lines are upper and lower 95% CI. The summative toxicity data of the three dose fractionations ± boost at five years from the START pilot trial are plotted.

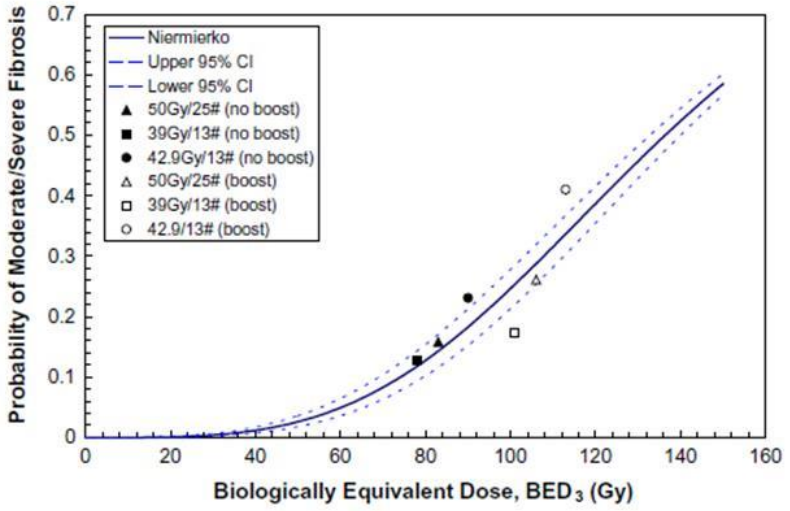


Fig. 2. Niemierko model – the probability of moderate–severe breast fibrosis versus biological equivalent dose using α/β of 3 Gy (BED_3). The solid line is based on the best fit parameters (BED_3 = 136.4 Gy and $\gamma 50$ = 0.9) and the dashed lines are upper and lower 95% CI. The summative toxicity data of the three dose fractionations ± boost at five years from the START pilot trial are plotted.

- **Attendonc nous d'autres données ?**
- **CLINICALTRIALS.GOV 10/2014**

Radiotherapy breast: 1207
Hypofractionation: 24

Pas une question ou résolu ?

Standards et questions

- Standards > 2 Gy / fraction
- **Questions:**
  - **Boost/no boost**
  - **Technique: RCMI ?**
  - **SIB ?**
  - **Ganglions ?**
  - **TT adjuvants ?**

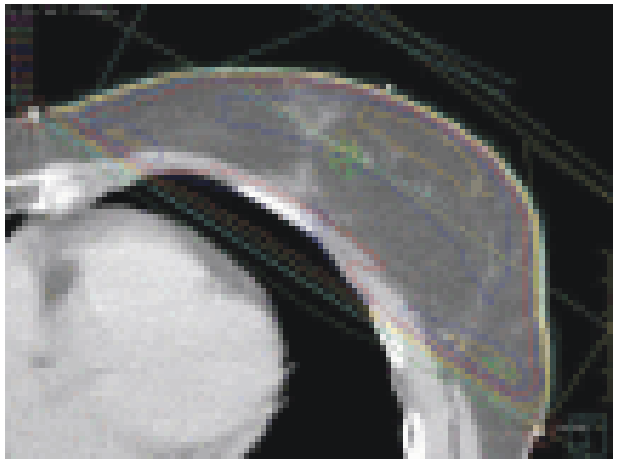
Quel boost ?

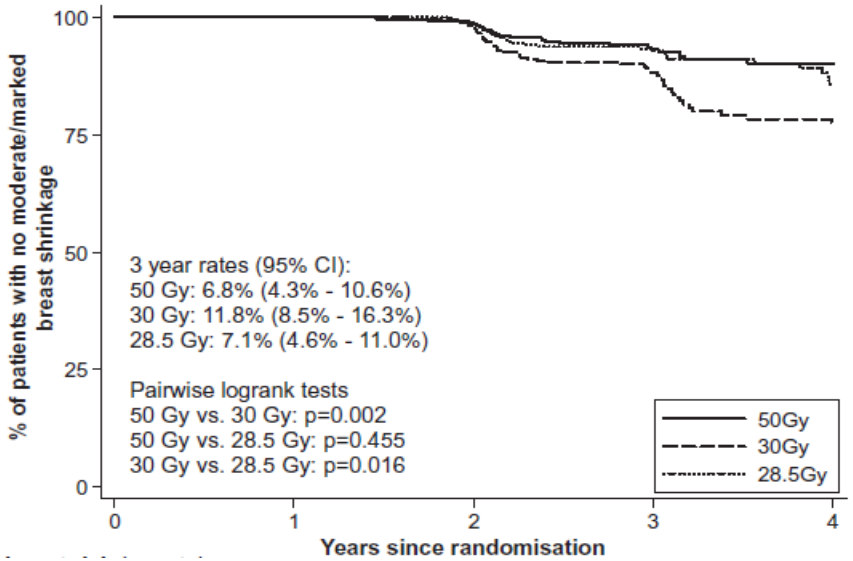
- **RTOG 1005** whole-breast irradiation (WBI) including a concomitant boost in 15 fractions non-inferior in local control to a regimen of standard WBI with a sequential boost for early-stage breast cancer patients

- **2364 au 11/10/2014**
  - **A.** pStage I, II Breast Cancer AND at least one of the following:
    - Age < 50 years or N+ or marges +
  - **B.** pStage 0 breast cancer with nuclear grade 3 DCIS and patient age <50 years or
  - **C.** ypStage post therapy

50 (25/5) Gy + sequential boost
Versus`
40 (15/3) Gy + concomitant boost

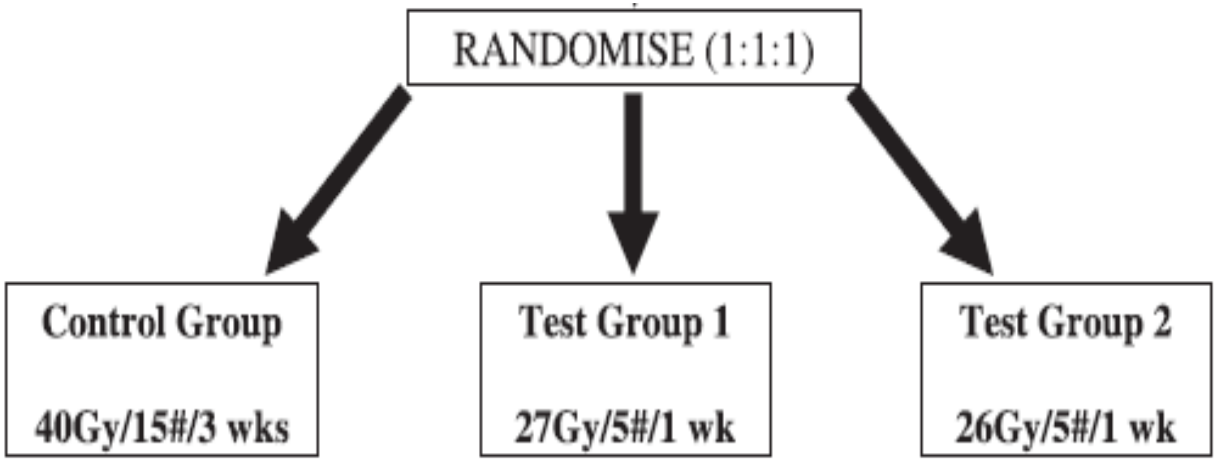
Quel fractionnement ?





FAST trial: 5 weeks

EARLY : 50 ans, 3cm, N-



FAST-Forward

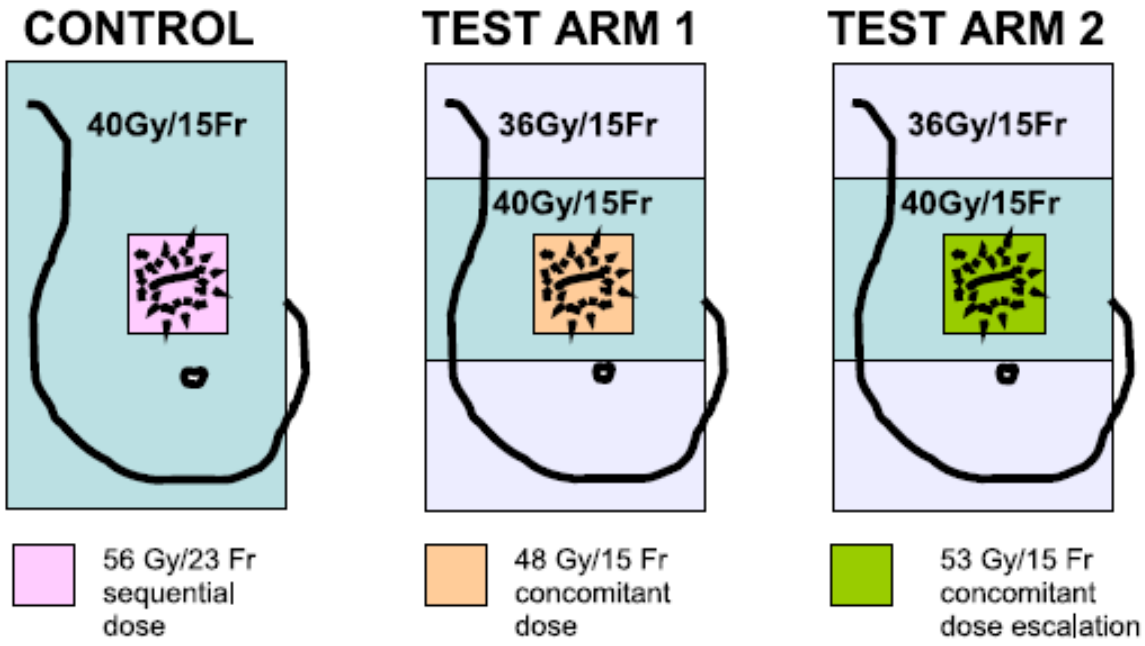
a randomised clinical trial to identify a 5-fraction schedule of curative radiotherapy **delivered in 1 week** that is at least as effective and safe as the UK standard 15-fraction regimen

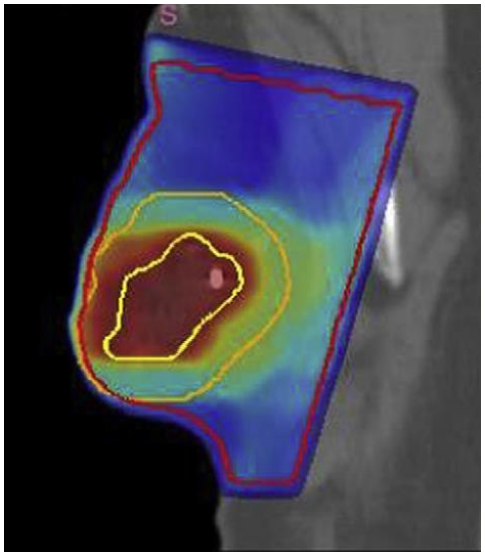
- 4000 patients. pT1-3 pN0-1 M0 disease
- **Control: 40.05 Gy in 15 Fr of 2.67 Gy**
- **Test 1: 27.0 Gy in 5 Fr of 5.4 Gy**
- **Test 2: 26.0 Gy in 5 Fr of 5.2 Gy**
- A sequential tumour bed boost may be added after breast conservation surgery (10 Gy or 16 Gy in 2.0 Gy Fr)
- Closure Date 01/03/2016
- Global Recruitment to Date : **102%**

Hypo. et Boost: hauts risques

IMPORT HIGH: RCMI

- N = 2568 Age 18-49 years
- Tumor size > 2.0 cm after primary surgery or any size treated by primary medical therapy
- Grade III disease
- Axillary node positive





Radiotherapy and Oncology 100 (2011) 236–240

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

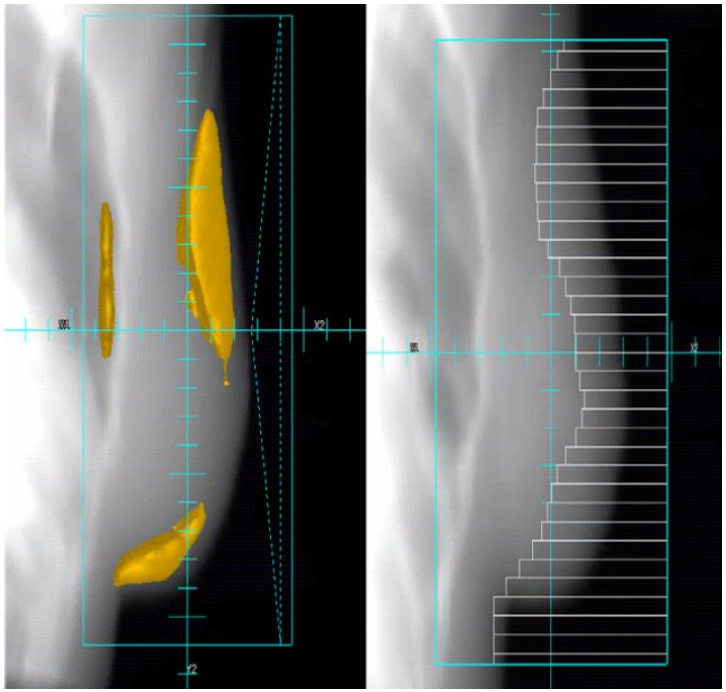
Large breast size as a risk factor for late adverse effects of breast radiotherapy: Is residual dose inhomogeneity, despite 3D treatment planning and delivery, the main explanation?

Christy Goldsmith [a,*], Joanne Haviland [b], Yat Tsang [c], Mark Sydenham [b], John Yarnold [d], on behalf of the FAST Trialists' Group

Essai FAST RT 3D ± RCMI

Volume mammaire corrélé avec V > 100 %

MAIS facteur pronostique indépendant en analyse multivariée des modifications esthétiques à 2 ans



Phase III randomised trial

Hypofractionated whole breast irradiation for patients with large breasts: A randomized trial comparing prone and supine positions

Thomas Mulliez [a,*], Liv Veldeman [a], Annick van Greveling [a], Bruno Speleers [a], Simin Sadeghi [a], Dieter Berwouts [a], Frederik Decoster [a], Tom Vercauteren [a], Werner De Gersem [a], Rudy Van den Broecke [b], Wilfried De Neve [a]

Radiotherapy and Oncology 108 (2013) 203–208

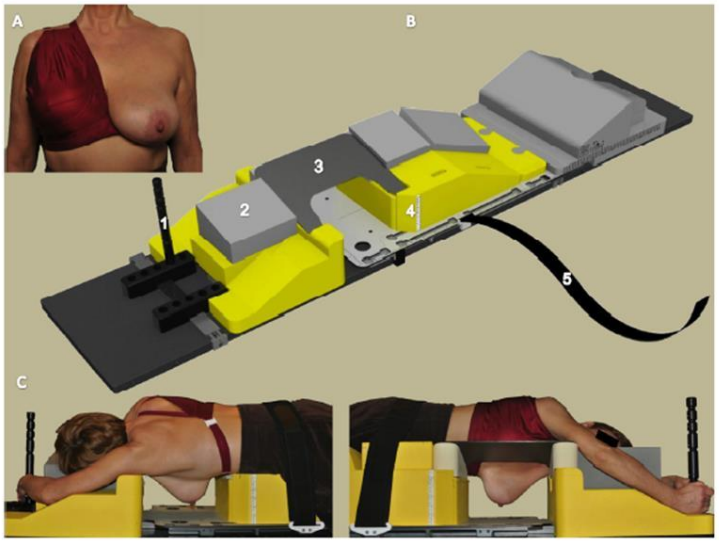


Fig. 1. Patient set-up devices for prone CT-simulation and treatment: (A) Unilateral breast holder to retract the contra-lateral breast away from the tr breast board: 1: hand grip; 2: head rest; 3: carbon fiber wedge support of the contra-lateral breast; 4: numeric scale (at both sides of the caudal part using the in-room laser system; 5: safety belt. (C) Ipsilateral (left panel) and contralateral (right panel) views of a patient positioned on the breast l

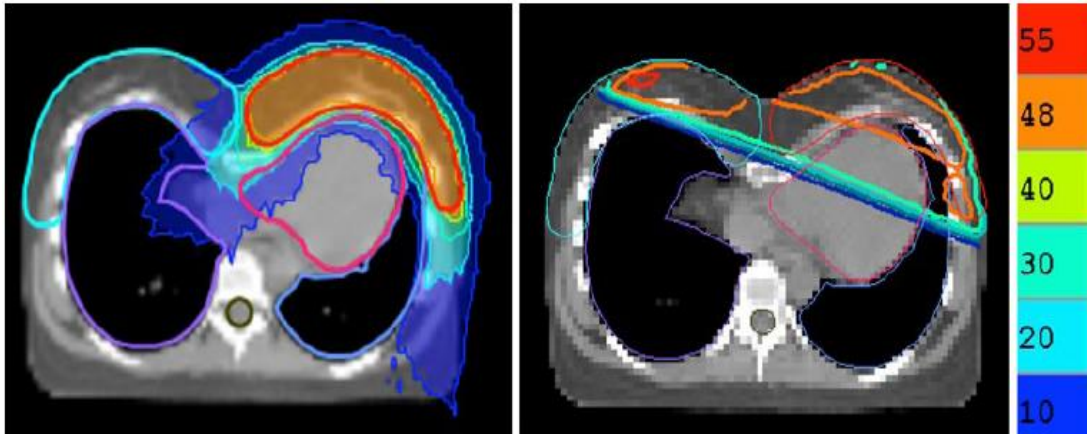
Large breasts ?

Table 2
Dose-volume statistics.

Organ	Dose-volume	Treatment group		*p*-value
		Supine	Prone	
PTV_{optim}	Coverage (%)	92.7 ± 4.9	96.2 ± 2.2	**<0.001**
	Homogeneity	0.87 ± 0.04	0.90 ± 0.04	**<0.001**
	V_{105} (cc)	30.9 ± 40.4	8.9 ± 17.7	**<0.001**
	V_{107} (cc)	7.6 ± 12.6	0.9 ± 2.7	**<0.001**
Heart	D_{mean} (Gy)	2.0 ± 1.1	1.5 ± 0.6	0.08
	D_{max} (Gy)	12.1 ± 9.5	9.7 ± 6.5	0.25
	V_5 (%)	5.9 ± 5.5	3.8 ± 3.9	0.09
	V_{20} (%)	1.4 ± 2.3	0.7 ± 0.9	0.12
LAD	D_{mean} (Gy)	9.3 ± 6.5	5.4 ± 3.7	**0.007**
	D_{max} (Gy)	23.0 ± 11.7	19.5 ± 11.1	0.25
Ipsilateral lung	D_{mean} (Gy)	3.8 ± 1.1	1.1 ± 0.9	**<0.001**
	D_{max} (Gy)	26.6 ± 6.5	8.6 ± 8.9	**<0.001**
	V_5 (%)	16.9 ± 5.7	2.9 ± 3.7	**<0.001**
	V_{20} (%)	5.5 ± 3.3	0.9 ± 2.1	**<0.001**

Mean ± standard deviation for dose coverage index (Coverage), dose homogeneity (Homogeneity) and volume receiving ⩾105% (V_{105}) and ⩾107% (V_{107}) of the prescription dose in the planning target volume for optimization (PTV_{optim}); heart, left anterior descending coronary artery (LAD), ipsilateral lung mean dose (D_{mean}), maximum dose (D_{max}) and partial volume receiving ⩾5 Gy (V_5) and ⩾20 Gy (V_{20}). Dose–volume data for heart and LAD were analyzed for patients treated to the left breast. Statistically significant results (p <0.05) are highlighted.

Place de la RCMI ?



- **Donovan et al. 2007**
  - IMRT vs standard in higher risk patients
  - Breast appearance altered in long term in more standard patients

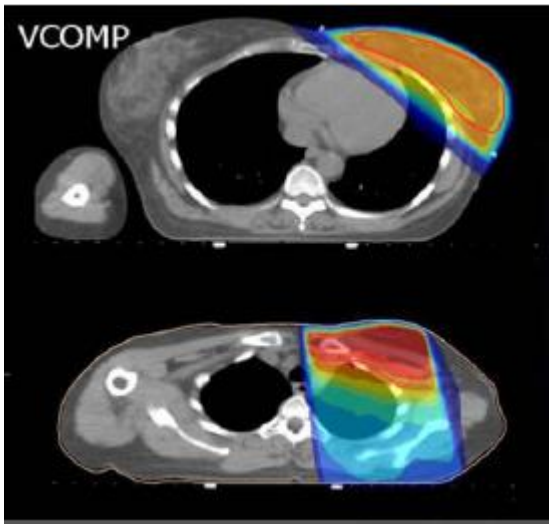
  Pignol et al. 2008
  - Dose distribution within the breast better with IMRT
  - IMRT reduced risk of moist desquamation to inframammary fold compared to standard wedge technique

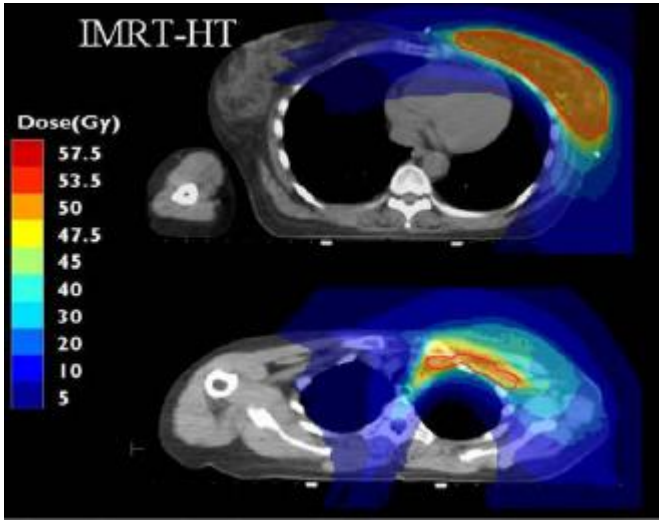
- **McDonald et al. 2008**
  - Acute skin toxicity lessened by IMRT

- **Shah et al. 2012**
  - WB IMRT reduced Grade 2+ acute radiation dermatitis and induration relative to Hyp IMRT, standard RT
  - WB IMRT reduced chronic edema relative to standard RT
  - Both WB and Hyp IMRT trend toward better cosmesis than standard

Ganglions: Sus clav. et CMI

- Caudrelier et al. 2009
  - Standard 3- or 4-field vs RCMI
  - Target homogeneity improved
  - Often lower doses to OARs



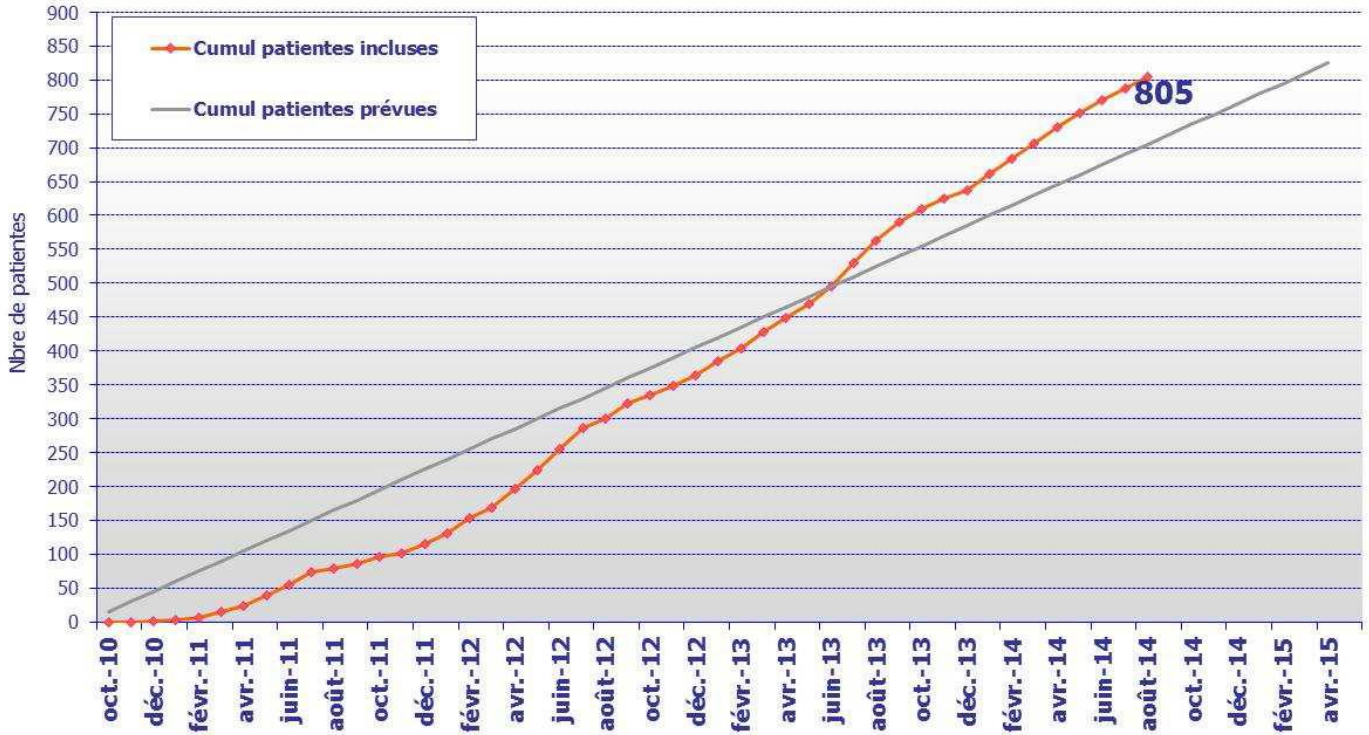


Normal Tissue	HT-IMRT (mean ± SD)	Standard VCOMP (mean ± SD)
Ipsilateral lung		
Mean dose	8.3 Gy ± 2.8 Gy	17.4 Gy ± 2.8 Gy
$V5_{Gy}$	35.4% ± 4.0%	48.5% ± 13.4%
$V20_{Gy}$	9.2% ± 3.8%	31.2% ± 5.3%
$V30_{Gy}$	5.1% ± 2.9%	28.7% ± 5.8%
$V45_{Gy}$	0.7% ± 0.9%	21.8% ± 5.7%
Contralateral lung		
Mean dose	6.2 Gy ± 2.2 Gy	2.5 Gy ± 0.3 Gy
$V5_{Gy}$	38.1% ± 10.6%	0.4% ± 0.4%
$V20_{Gy}$	1.8% ± 4.9%	0.01% ± 0.01%
Heart		
Mean dose	7.0 Gy ± 2.9 Gy	5.5 Gy ± 1.4 Gy
$V5_{Gy}$	38.3% ± 17.2%	41.0% ± 22.8%
$V30_{Gy}$	1.5% ± 1.9%	3.2% ± 2.2%
$V45_{Gy}$	0.002% ± 0.0006%	1.6% ± 1.4%
Contralateral breast		
Mean dose	4.8 Gy ± 1.6 Gy	3.1 Gy ± 1.3 Gy
$V5_{Gy}$	31.0% ± 20.0%	4.4% ± 9.9%
$V10_{Gy}$	7.3% ± 5.1%	2.8% ± 0.9%
Unspecified tissue		
Vol. D ⩾50 Gy	230cc ± 63cc	1057cc ± 674cc
$V10_{Gy}$	4236cc ± 1037cc	2482cc ± 1003cc

WBI versus APBI ?

SHARE & IRMA

An Italo-French study
3000 patients



Design de l'essai

Carcinome invasif, pN0 ou pN0(i+), M0
et chirurgie conservatrice avec pose de clips chirurgicaux

Critères d'inclusion et de non inclusion vérifiés
Signature du consentement éclairé, puis randomisation

La radiothérapie doit être effectuée entre 4 et 12 semaines après la chirurgie

Bras A : (en 6,5sem)
Dose Standard
RT de la glande mammaire

Dose totale :
50 Gy en 25 fr (1/j)
+ (Boost) 16 Gy en 8 fr

OU: (en 3 sem)
Dose Hypofractionnée
RT de la glande mammaire

Dose totale :
40 Gy en 15 fr (1/j)
ou 42,5 Gy en 16 fr

Bras C : (en 1sem)
IPAS
RT du lit de tumorectomie

Dose totale :
40 Gy en 10 fr
(2 séances de 4Gy/j)

N’oublions pas les facteurs liés à la patiente

et aux traitements !

(analyse multivariée)

Volume mammaire

Age

BMI

Diabète

Tabagisme (pigmentation)

Radiosensibilité

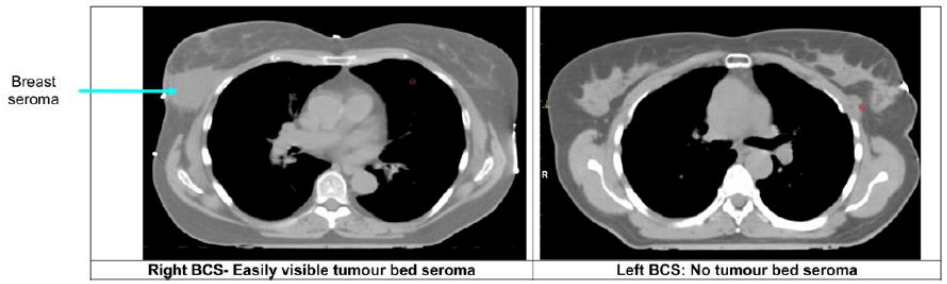
Résultat chirurgical

Sérome

Infection post opératoire

Chimio ?

TAM ?



Mukesj Eur J Surg Oncol 2012, Barnett Clin Oncol 2011…

Le débat n'est plus le fractionnement > 2 Gy…

mais comment encore progresser sur la technique et les indications…

pour aller vers une personnalisation de la radiothérapie des cancers du sein ?