BREAST P1: Multicenter European Randomized Phase III trial comparing protons *vs.* optimal photon radiotherapy in breast cancer with an indication for regional lymph node irradiation in terms of cardiac and other long term toxicities

Youlia M. Kirova, M.D.,

Head of Breast Cancer Research and Treatment in the Department of Radiation Oncology,

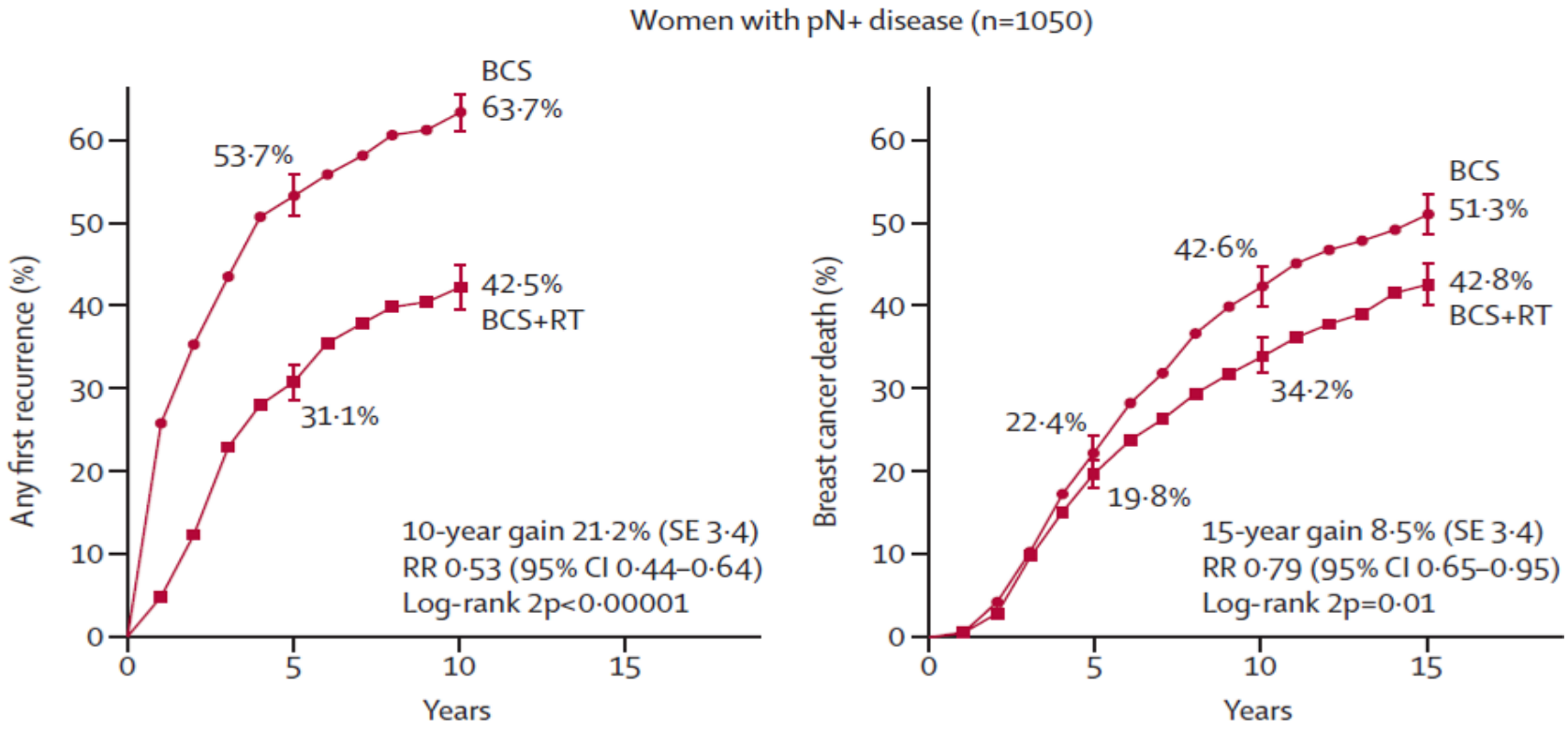
Institut Curie, Paris, France

youlia.kirova@curie.fr

Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

Lancet 2011; 378: 1707–16



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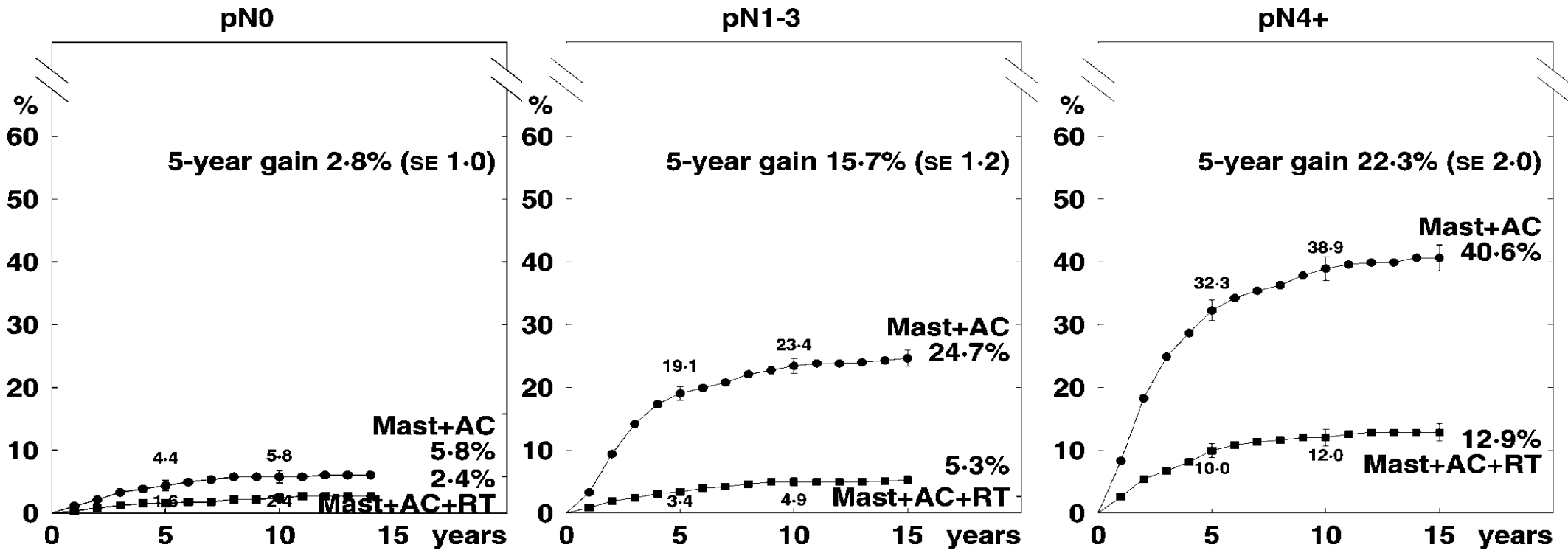
Mastectomie+ CA + RT vs. Mast+CA

Isolated local recurrence by pathological nodal status (pN)



49 events in 1277 women

399 events in 3316 women

487 events in 2813 women

Courtesy S. Darby,

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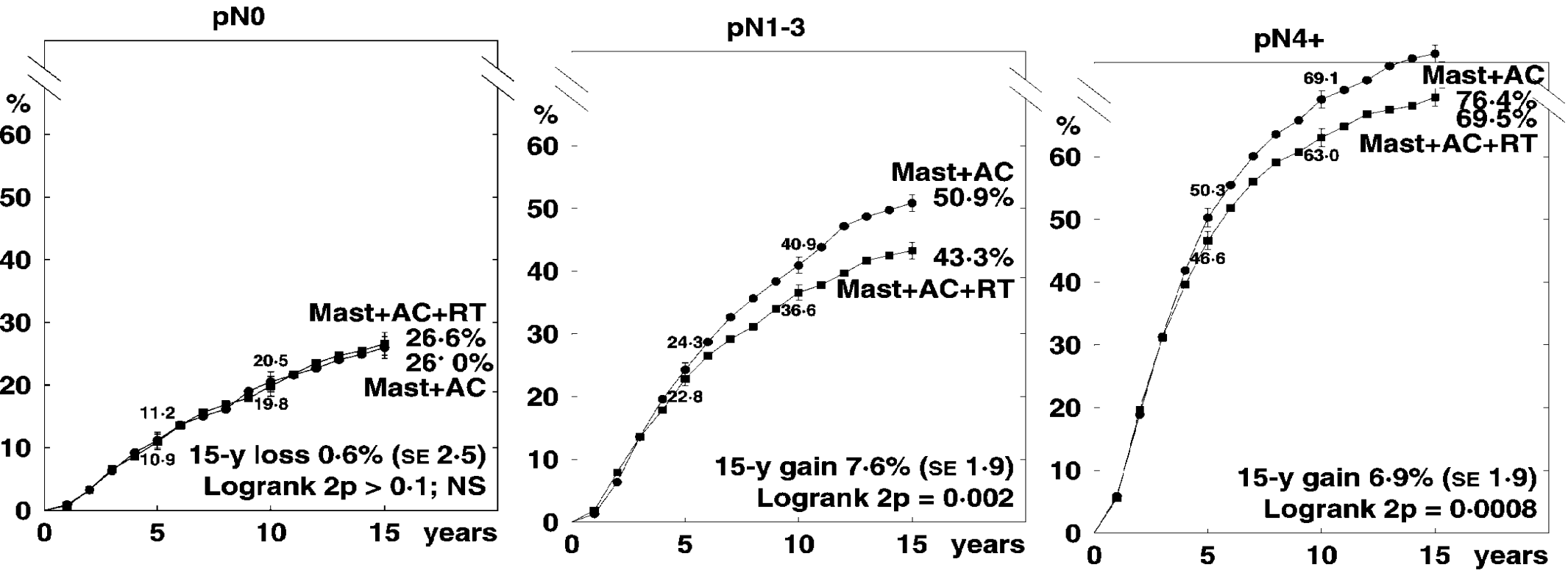
Mastectomie + CA + RT vs. Mast + CA

Breast cancer mortality by pathological nodal status (pN)



414 events in 1354 women 1552 events in 3344 women 1986 events in 2876 women

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No consensus on RT to pN1-3

- Old data
- Outdated surgical techniques
- Outdated systemic therapy
- Today´s patients do much better

But we have new data on modern treated patients

MA 20

- 2000-2007: 1832 pts
- Breast-conserving surgery + Whole Breast Irradiation
- **Randomisation**

Breast RT **50 Gy/25f**

vs. Breast RT & nodes **45 Gy/25f**

IMN

Supra and infraclavicular ± inferior axilla

Whelan T et al. N Engl J Med, 2015

MA 20.

Results
Median follow-up: 9.5 years

Table 2. Disease Recurrence or Death.

Event	WBI (N=916)	WBI+RNI (N=916)
	no. of patients with event (%)	
Isolated locoregional recurrence	62 (6.8)	39 (4.3)
Local (in breast) only	38 (4.1)	33 (3.6)
Regional only	23 (2.5)*	5 (0.5)†
Local and regional	1 (0.1)*	1 (0.1)†
Distant recurrence	151 (16.5)	118 (12.9)
First or concurrent with locoregional recurrence	118 (12.9)	100 (10.9)
After locoregional recurrence	33 (3.6)	18 (2.0)
Any recurrence or contralateral breast cancer	195 (21.3)	154 (16.8)
Any recurrence	175 (19.1)	134 (14.6)
Contralateral breast cancer	20 (2.2)	20 (2.2)
Death	168 (18.3)	155 (16.9)
Breast cancer	113 (12.3)	93 (10.2)
Other cancer	26 (2.8)	32 (3.5)
Cardiovascular cause	11 (1.2)	11 (1.2)
Other cause	12 (1.3)	8 (0.9)
Unknown	6 (0.7)	11 (1.2)

Whelan T et al. *N Engl J Med*, 2015

EORTC 22922/10925

- 1996-2004
- 4004 patients
- Breast-conserving surgery (76%) or Mastectomy
- Randomisation
  - Breast/CW RT 50 Gy/25f
  - vs Breast/CW + IM-MS RT

Poortmans P. et al. *N Engl J Med*, 2015

EORTC RT Trial. Patients distribution

	No IM-MS (N=2002)	IM-MS (N=2002)
Median age (yrs.)	54	54
	%	%
Breast-conserving surgery	76.1	76.2
pT1	60.1	60.2
pN0	44.5	44.4
pN+ 1-3	43.3	42.9
pN+ > 3	12.2	12.6
ER+ve	73	74
Chemotherapy	55.1	54.6
Endocrine treatment	60	59.6

Poortmans P. et al. *N Engl J Med,* 2015

EORTC

Table 2. Events in the Intention-to-Treat Population.

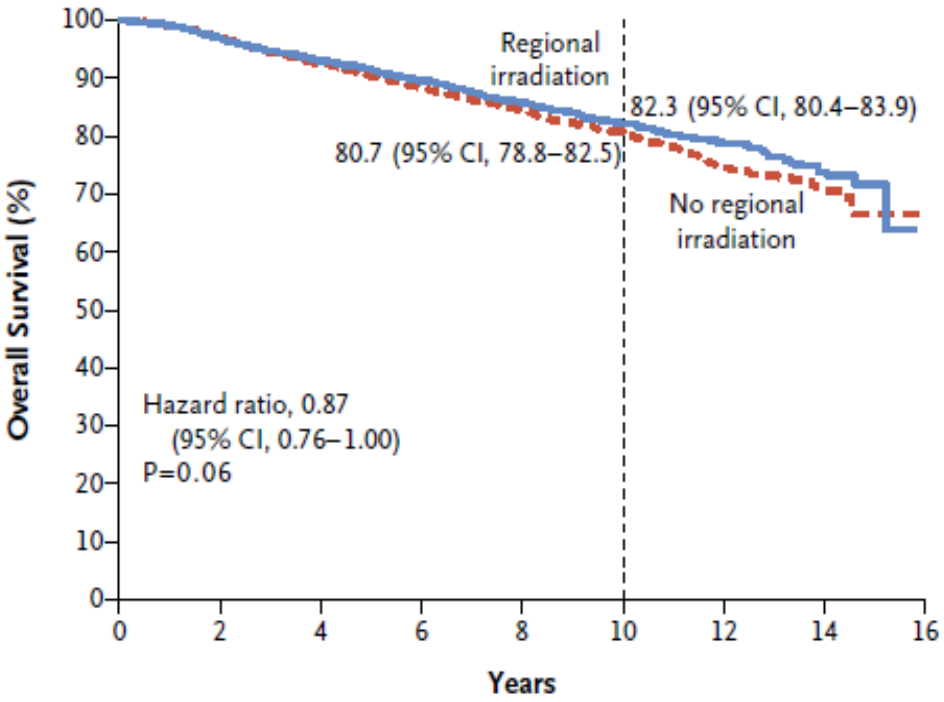
Event	Control Group (N = 2002)	Nodal-Irradiation Group (N = 2002)	Total (N=4004)
		no. of patients (%)	
Recurrence			
Local	107 (5.3)	112 (5.6)	219 (5.5)
Regional*	85 (4.2)	54 (2.7)	139 (3.5)
Axillary	38 (1.9)	27 (1.3)	65 (1.6)
Medial supraclavicular	41 (2.0)	30 (1.5)	71 (1.8)
Internal mammary	16 (0.8)	4 (0.2)	20 (0.5)
Distant disease	392 (19.6)	319 (15.9)	711 (17.8)
Second cancer			
Any	222 (11.1)	191 (9.5)	413 (10.3)
Ipsilateral or contralateral breast cancer	105 (5.2)	97 (4.8)	202 (5.0)

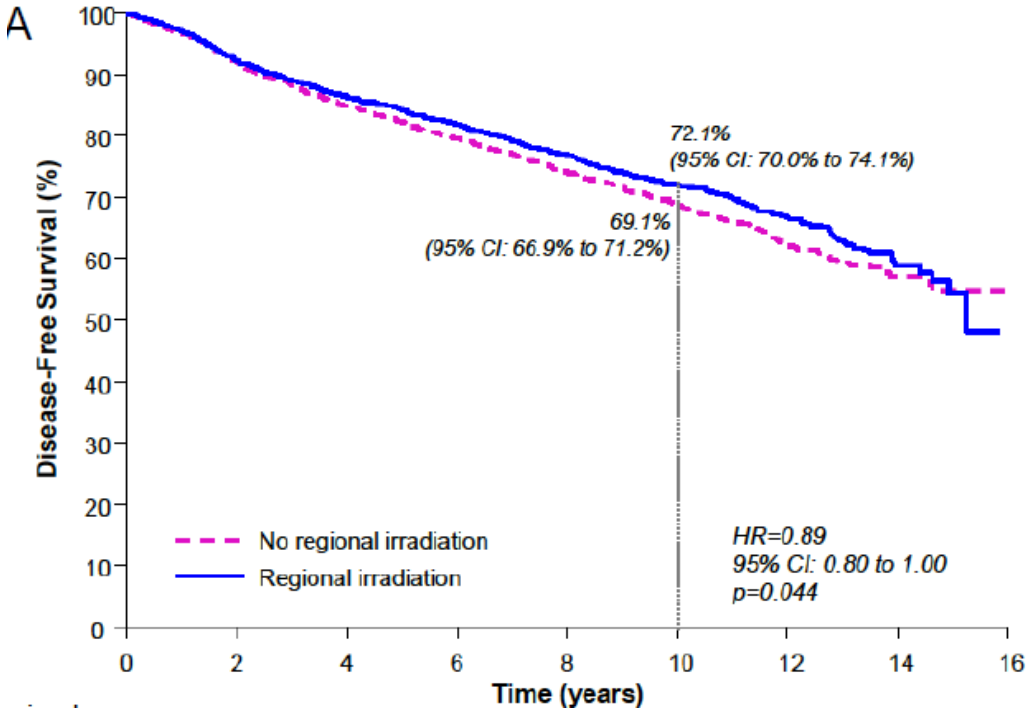
* Multiple locations of regional recurrence may have been observed.

Cardiac toxicity 6.5% in LN irradiation group, NS

Poortmans P. et al. *N Engl J Med*, 2015

EORTC RT Trial: OS, DFS





Poortmans P. et al. *N Engl J Med*, 2015

But one of the

most discussed…

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 14, 2013 VOL. 368 NO. 11

Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer

Sarah C. Darby, Ph.D., Marianne Ewertz, D.M.Sc., Paul McGale, Ph.D., Anna M. Bennet, Ph.D., Ulla Blom-Goldman, M.D., Dorthe Brønnum, R.N., Candace Correa, M.D., David Cutter, F.R.C.R., Giovanna Gagliardi, Ph.D., Bruna Gigante, Ph.D., Maj-Britt Jensen, M.Sc., Andrew Nisbet, Ph.D., Richard Peto, F.R.S., Kazem Rahimi, D.M., Carolyn Taylor, D.Phil., and Per Hall, Ph.D.

Case-control study

Population-based case-control study of major coronary events (MCEs)

- **Population: Women irradiated for breast cancer**
  (Denmark: 1977-2006, Stockholm: 1958-2002)
- **963 Major Coronary Events (MCEs)**
- **1205 controls also irradiated for breast cancer**
  (matched for country, age, calendar period & time since cancer diagnosis)
- **Information from oncology records**
  (tumor characteristics, medical history, treatment)
- **Cardiology records sought for all cases to verify diagnoses**

NEJM 2013; 368:987-98

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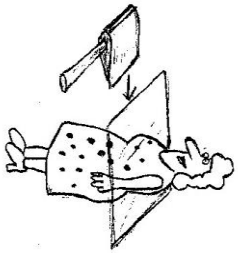

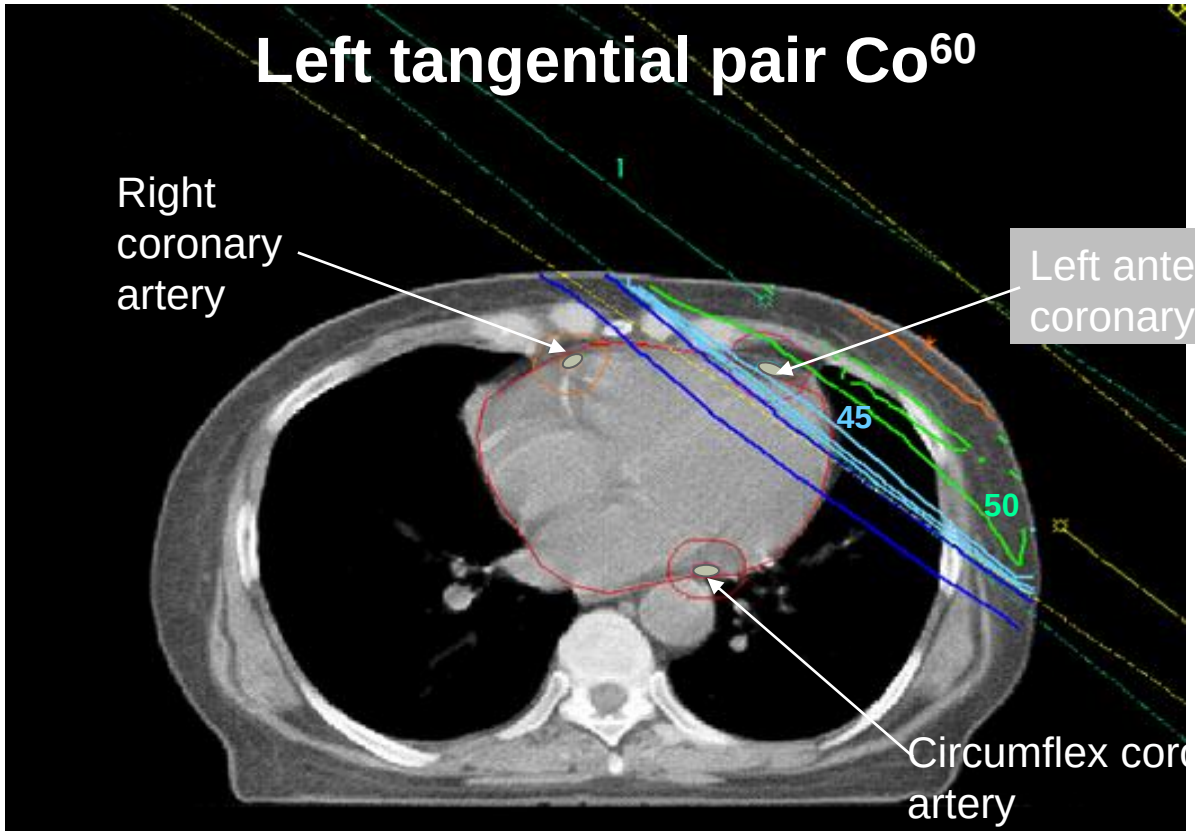

- Detailed dose-plan for each woman reconstructed on modern planning system
- 97 x 2 different regimens reconstructed using CT-scan for patient with typical anatomy
- Physical dose to whole heart estimated from dose-volume histogram
- Mean heart dose in study subjects: 4.9 Gy

Taylor *et al,* Rad Onc 2011

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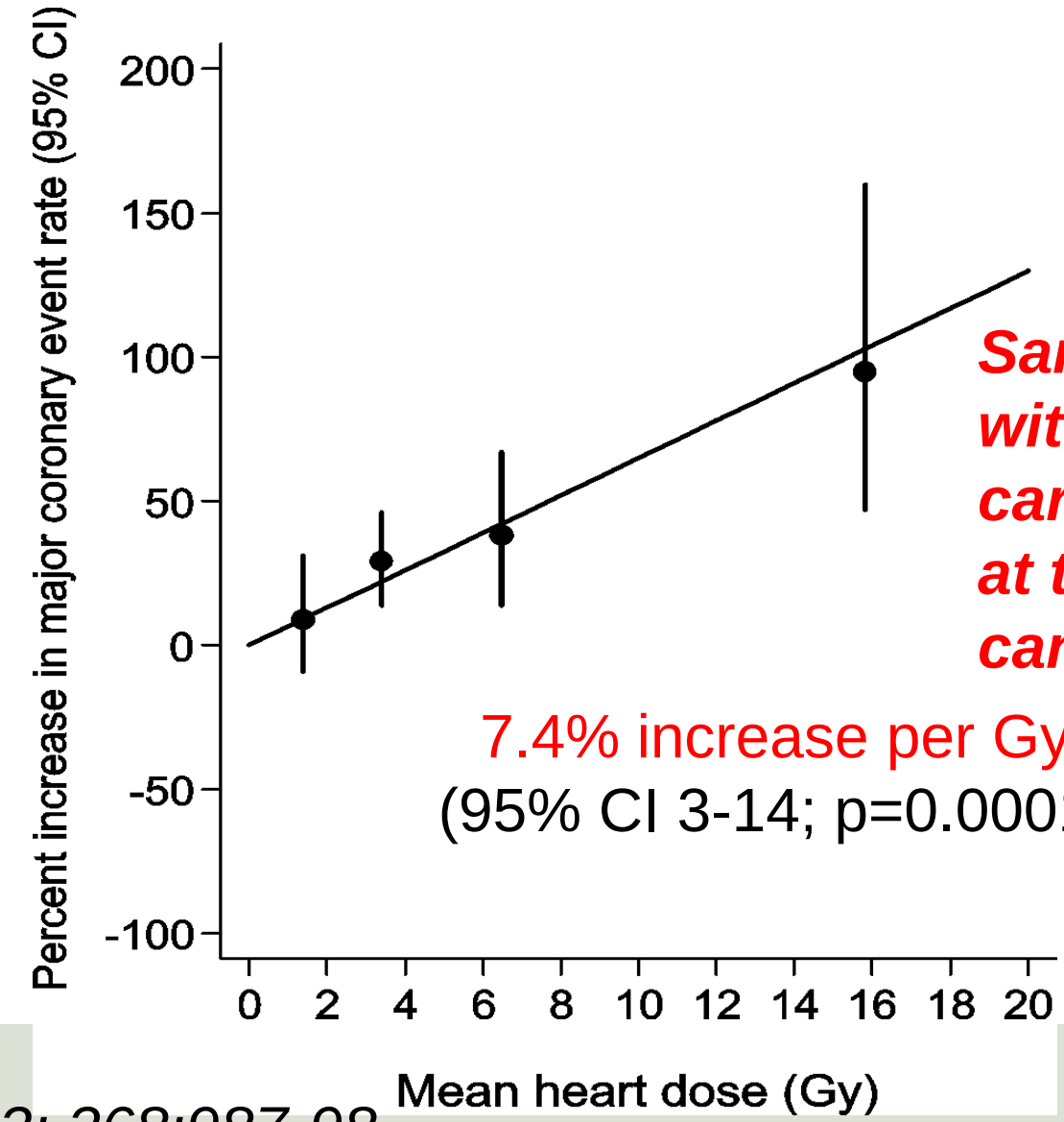
Radiation Associated Cardiac Events (RACE)
Dose-response relationship for major coronary events



Same slope for women with and without cardiac risk factors at time of breast cancer diagnosis

7.4% increase per Gy
(95% CI 3-14; p=0.0001)

NEJM 2013; 368:987-98

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Improved Outcome in RT comes at the Cost of Higher Cardiac Toxicity

Relative risk (RR) of cardiac death after RT for left versus right breast cancer (laterality)

Laterality after dx, RR (95% CI)		
Diagnosis	<10 y	10 - 14 y
1973-1982	1.2 (1.04-1.38)	1.52 (1.11-1.82)
1983-1992	1.04 (0.91-1.18)	1.27 (0.99-1.63)
1993-2001	0.96 (0.82-1.12)	NA

Bird, Swain Clin Cancer Res. 2008;14(1):14-24.

- RCTs conducted over the last 30 years demonstrated beneficial local control and survival after BCT/mastectomy RT.
- With dose-sparing modern approaches, the absolute benefits of radiation may be increased

…not so simple because the cardiac toxicity is multifactorial

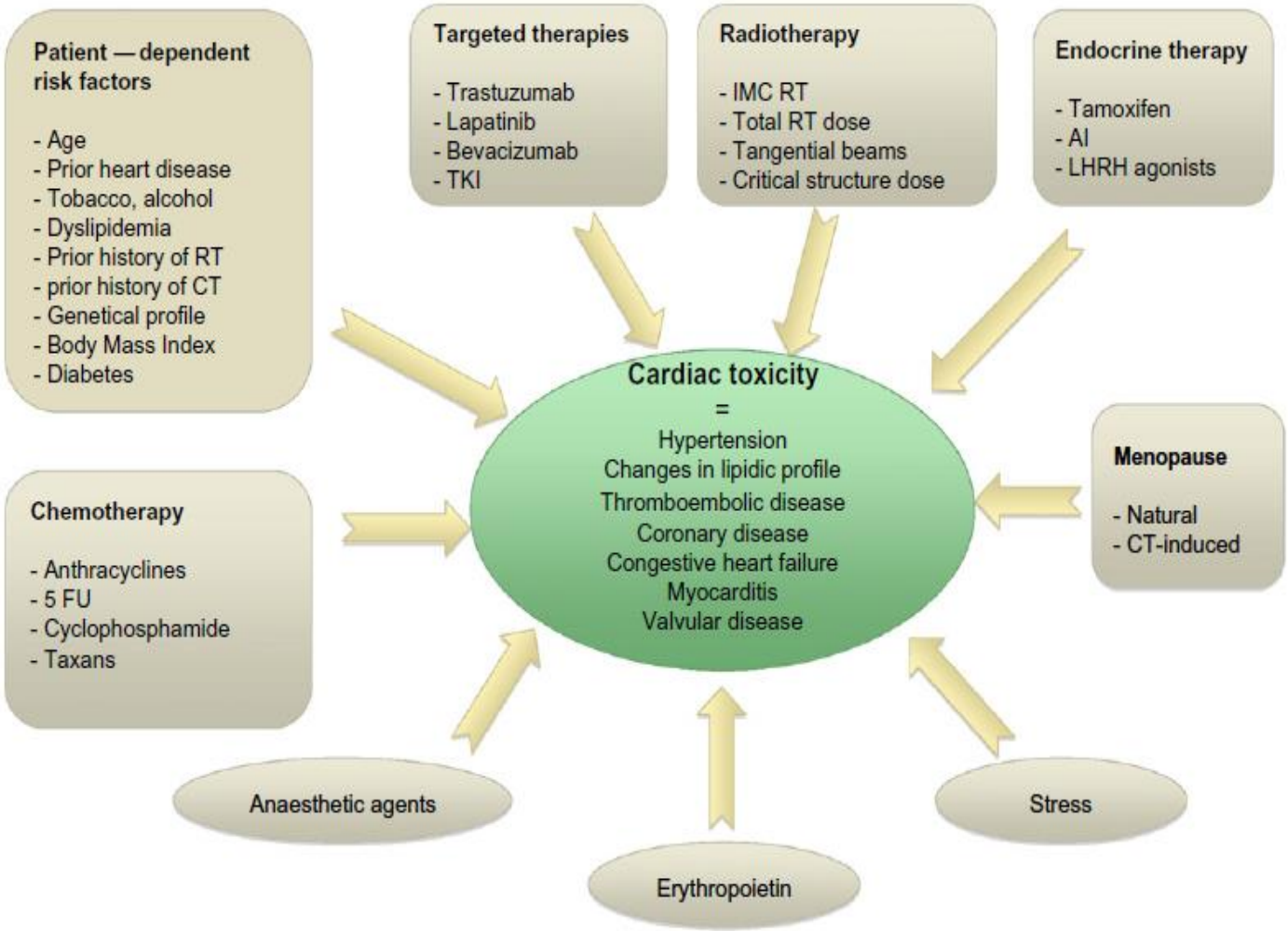

Fig. 1. List of factors that may potentially lead to cardiac hazard in breast cancer patients.

Please cite this article in press as: Chargari C et al. Cardiac toxicity in breast cancer patients: From a fractional point of view to a global assessment. *Cancer Treat Rev* (2010), doi:10.1016/j.ctrv.2010.08.007

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BREAST P1: Main objective

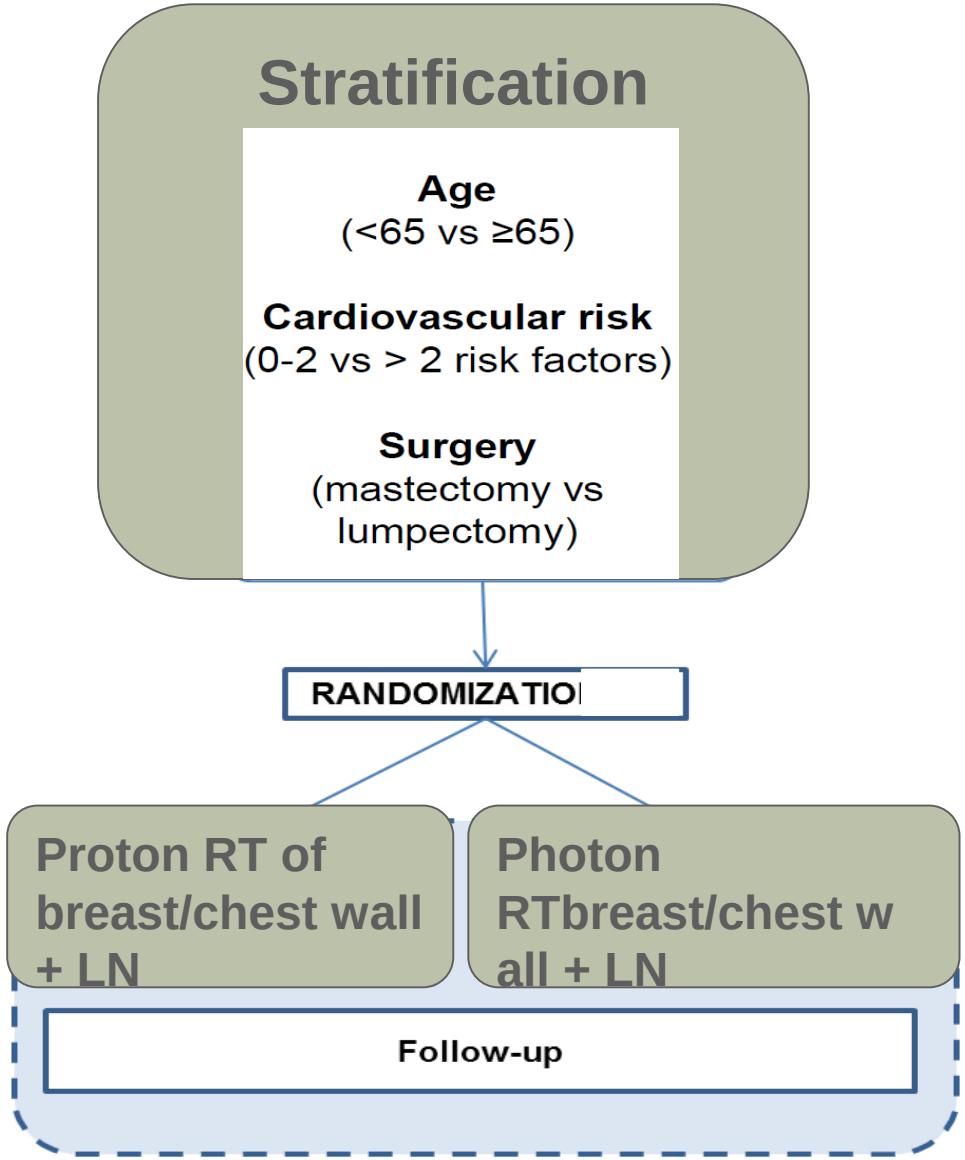
- To assess the superiority of the proton locoregional radiotherapy to currently used photon-electrons 3D conformal or IMRT radiotherapy in term of cardiac toxicity at 10 years.

BREAST P1: SECONDARY OBJECTIVES

- To show that the proton locoregional radiotherapy is not inferior to currently used photon-electrons 3D conformal or IMRT radiotherapy in early breast cancer with an indication for irradiation of regional lymph nodes in terms of local-regional recurrence
- to assess loco-regional events: acute and late toxicities (radiodermatitis, arm motion and function, cosmetic result, lung events)
- to assess cancer related-events: locoregional relapse-free survival, distant disease-free survival, overall survival, causes of death,
- to assess the contralateral breast cancer incidence, as well as the incidence of other second malignancies
- to assess and compare health related quality of life between arms
- to conduct a cost-utility analysis
- Translational research

Woman ≥ 18 years who had radical surgery for invasive

breast cancer pT1-3, pN0-N3, M0 with either mastectomy or breast conservation.



REQUIRED NUMBER OF PATIENTS TO BE SCREENED / INCLUDED:

We estimated that among patients treated with normofractionated radiotherapy in EORTC IMN vs no IMN study, the cardiac disease rates were 6.5% at 10 years after radiation therapy. If we want to show 50% decrease of this cardiac toxicity using protons with 87% power, 1310 patients in total are needed. The interim analysis will be performed at 5 years with a type I error equal to 0.1%, allowing a type I error equal to 4.9% at the final analysis.

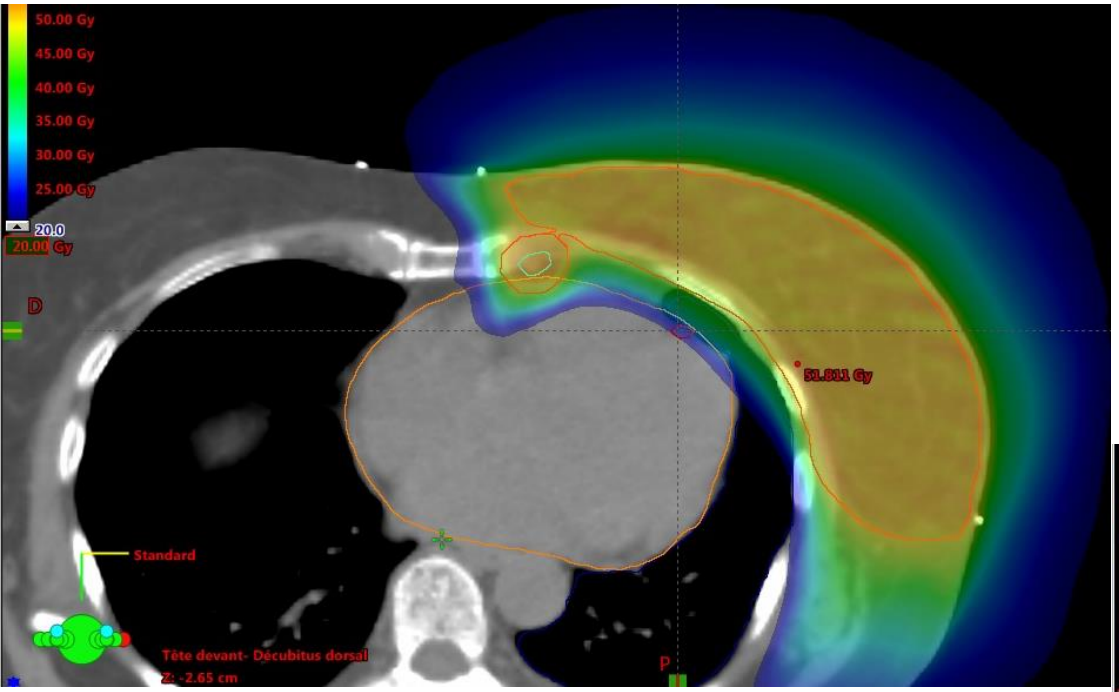
With this total of 1310 patients, there is 80% power for a 5-year non-inferiority not higher than 3 % for local-regional recurrence assuming local-regional recurrence in the photon arm of 5% at 5 years with a type one error equal to 5% (unilateral).

Statistics

Concerning the non-inferiority analysis, the alternative hypothesis is that the hazard rate of arm A is not worse than arm B. The analysis will be performed using the Deheuvels procedure at 0.05 unilateral significance level stratified for the factors used to stratify the randomization, according to the per-protocol population. A supplementary analysis on the ITT population will be performed.

Standard statistical methods as Kaplan-Meier analyses, Cox proportional cause-specific hazards regression will be used to compare the time-to-event variables between the 2 treatment arms and estimate hazard ratios adjusted for the stratification factors (using DATECAN definitions of breast-cancer related endpoints) at a one-sided 0.05 significance level. A multivariate model will also be constructed using relevant prognostic variables on the different time-to-event endpoints.

Dosimetric work: best photons vs protons

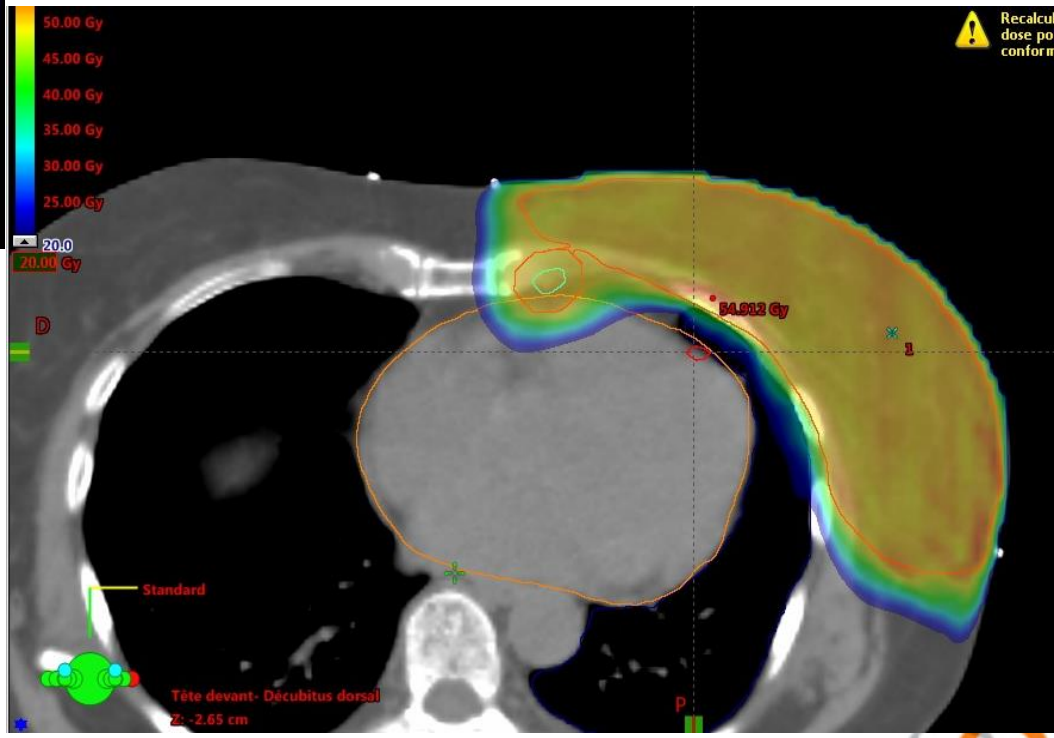


Photons using IMRT by Tomotherapy

-Homogeneous dose distribution

-Optimal couverage but higher dose to heart, corronaries and lung

-Low but increased dose to contralateral breast



Photons using 2 fields

-Homogeneous dose distribution

-Optimal couverage and lower dose to heart and corronaries

-No dose delivered to contralateral breast (young high risk patients+++)

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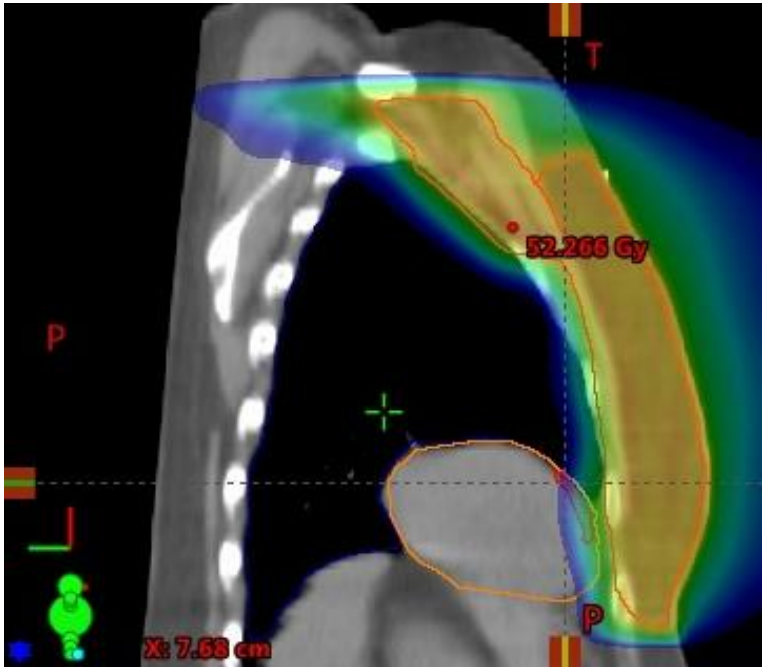
Dosimetric work: best photons vs protons



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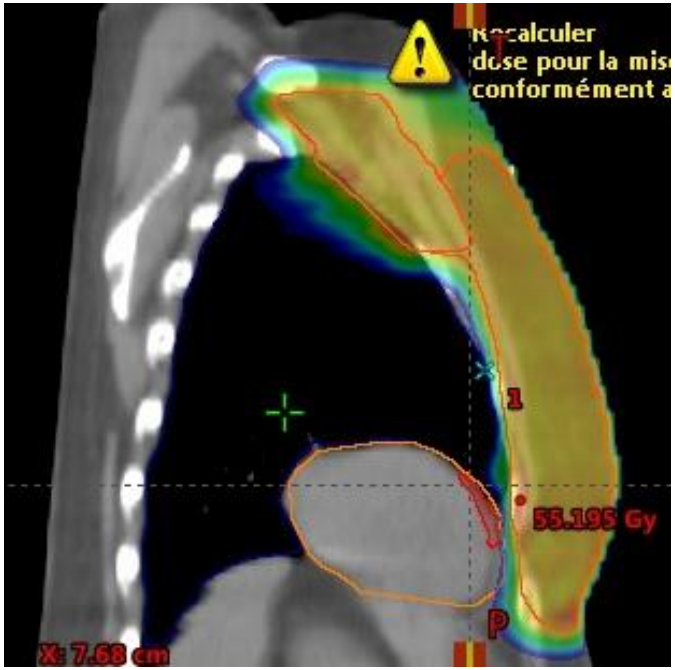

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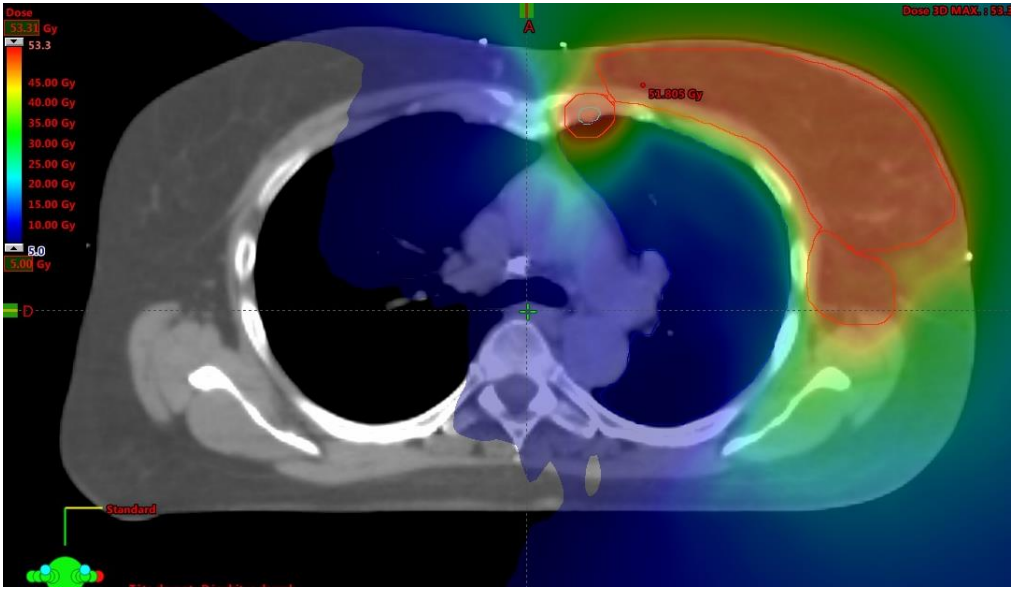

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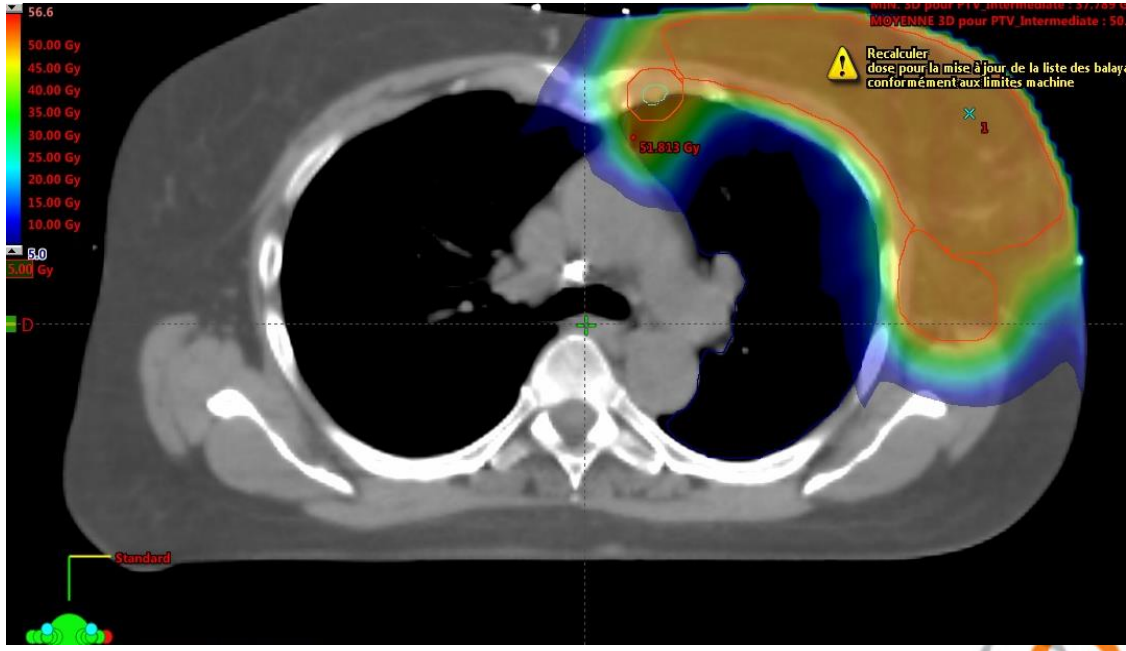

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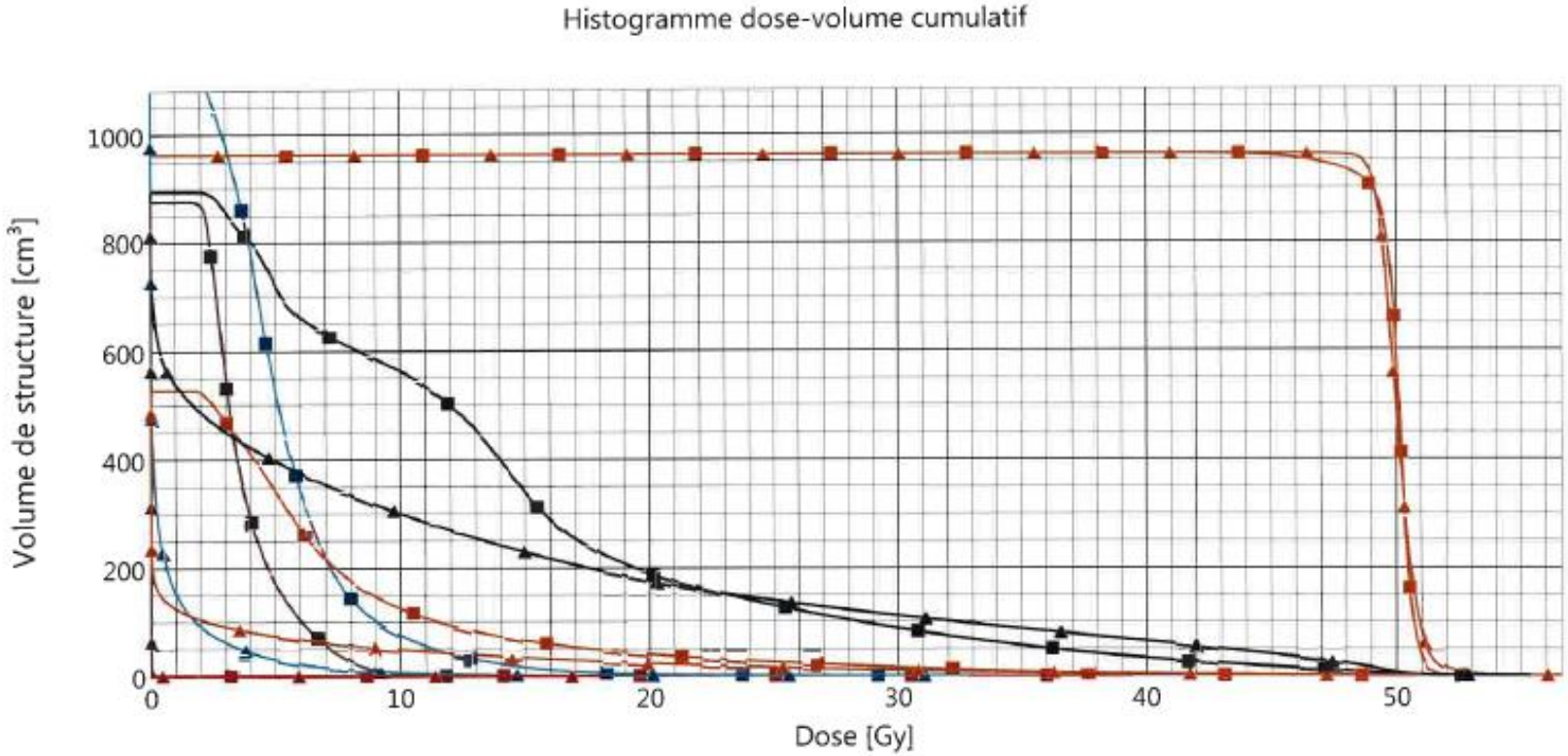

HDV	Structure	État de la structure	Recouvrement [%/%]	Volume	Dose min.	Dose max.	Dose moyenne	Dose modale	Dose médiane	Écart type
	PTV Sein G	Approuvée	100.0 / 100.0	962.8 cm³	40.9 Gy	52.7 Gy	50.0 Gy	50.2 Gy	50.1 Gy	0.8 Gy
	POUMON D	Approuvée	100.0 / 100.1	1173.4 cm³	1.1 Gy	32.8 Gy	5.3 Gy	4.1 Gy	4.7 Gy	2.9 Gy
	POUMON G	Approuvée	100.0 / 100.1	894.3 cm³	1.8 Gy	52.7 Gy	14.6 Gy	4.9 Gy	13.2 Gy	10.4 Gy
	SEIN D	Approuvée	100.0 / 100.0	875.9 cm³	1.5 Gy	14.1 Gy	3.9 Gy	2.7 Gy	3.3 Gy	1.6 Gy
	COEUR	Approuvée	100.0 / 100.0	527.2 cm³	1.7 Gy	51.1 Gy	8.5 Gy	5.2 Gy	6.1 Gy	7.2 Gy
	CORONAIRE G	Approuvée	100.0 / 104.4	1.1 cm³	5.5 Gy	39.5 Gy	22.1 Gy	7.3 Gy	25.7 Gy	11.9 Gy
	PTV Sein G	Approuvée	100.0 / 100.0	962.8 cm³	37.8 Gy	56.6 Gy	50.1 Gy	50.0 Gy	50.0 Gy	0.7 Gy
	POUMON D	Approuvée	100.0 / 100.1	1173.4 cm³	0.0 Gy	32.9 Gy	0.5 Gy	0.0 Gy	0.0 Gy	1.6 Gy
	POUMON G	Approuvée	100.0 / 100.1	894.3 cm³	0.0 Gy	55.3 Gy	10.2 Gy	0.0 Gy	3.2 Gy	14.0 Gy
	SEIN D	Approuvée	100.0 / 100.0	875.9 cm³	0.0 Gy	0.4 Gy	0.0 Gy	0.0 Gy	0.0 Gy	0.0 Gy
	COEUR	Approuvée	100.0 / 100.0	527.2 cm³	0.0 Gy	51.0 Gy	2.8 Gy	0.0 Gy	0.0 Gy	7.3 Gy
	CORONAIRE G	Approuvée	100.0 / 104.4	1.1 cm³	0.0 Gy	18.2 Gy	4.4 Gy	0.0 Gy	3.8 Gy	4.0 Gy

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TRIAL DURATIONS

Inclusion period : 3-5 years

Treatment period: :5-7 weeks

Follow-up: 10 years

Duration until primary endpoint evaluation: Inclusion period : 5 years

Estimated time of interim analysis: when the 5 years median follow-up will be reached

Estimated time of final analysis: when the 10 years median follow-up will be reached

Overall trial duration (including follow-up): about 13 years with the hypothesis of an uniform inclusion rate.

Thank you for your attention

Writing Committee

Youlia Kirova,
Farid Goudjil,
Rémi Dendale
Alexia Savignoni,
Emmanuelle Fourme,
Philip Poortmans,
Alain Fourquet

Questions, discussion and collaboration projects?

youlia.kirova@curie.fr

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