Cardiopulmonary functions: A challenge for irradiation of lung and breast tumors

Dr Sofia Rivera

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Topics

- Lung toxicity after radiotherapy for breast or lung cancer
- Cardiac toxicity after radiotherapy for breast or lung cancer
- Are we improving it?
- How should we verify our prediction models?

Lung toxicity after radiotherapy

- **2 main toxicities: radiation pneumonitis and lung fibrosis**
- **Natural history in 5 phases:**
  - Immediate phase (hours todays)
  - Latent phase acute exudative/clinical RP phase (4–12 weeks post-RT)
  - Intermediate phase with resolution of exudate and deposition of fibroblast
  - final phase when fibrosis is established (usually 6–12 months post-RT)

Gokula et al. Radiation Oncology 2013

Lung toxicity after breast radiotherapy

- **Very heterogeneous literature (various techniques, doses and volumes)**
- **With 2D:**
  - Radiological RP: 27-40%
  - Clinical RP: 0-10%
- **With 3D: meta analysis from Gokula et al**
  - Radiological RP: 42% (95%CI=22-62%)
  - Clinical RP: 14% (95% CI = 8-21%)
- **With IMRT smaller high dose volumes but larger low dose volume**
- **Poor corelation between radiological and clinical RP and fibrosis**

McDonald Int J Radiat Oncol Biol Phys 1995
Gokula et al. Radiation Oncology 2013

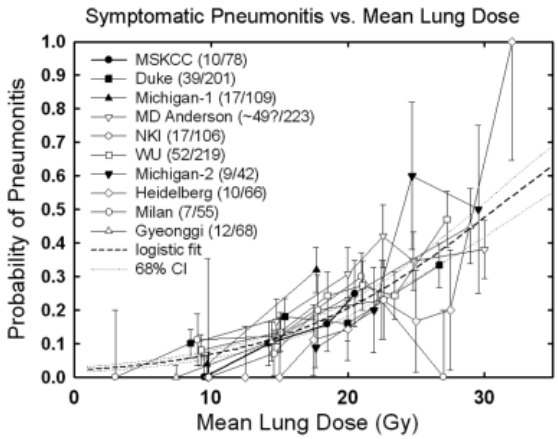
Lung toxicity after lung radiotherapy

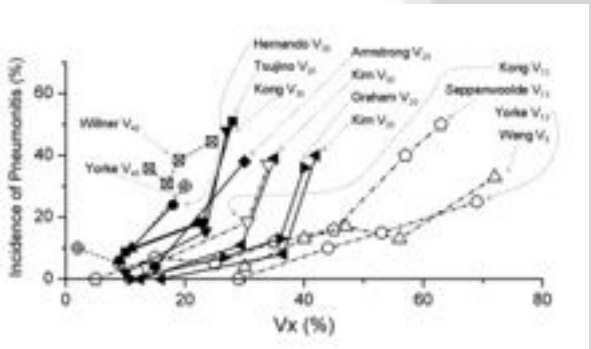
- **Symptomatic pneumonitis:**
  - ≈5–50% of patients irradiated for cancers of the lung
  - ≈5–10% of patients irradiated on mediastinal lymphatics,
- **Approximately 80% of RP is clinically manifest within 10 months of RT**
  - Dyspnea is non-specific
  - Toxicity grading systems often consider the medical interventions
  - Treatment-induced tumor shrinkage may improve overall lung function
  - The relevant grade of symptoms is controversial
- **The most widely used NTCP model for RP are the Lyman-Kutcher-Burman (LKB) model and the Mean lung dose**

Marks et al Int J Radiat Oncol Biol Phys. 2010

Lung toxicity after lung radiotherapy

- **QUANTEC:**
  - Risk of RP is correlated with MLD and Vx(%)
  - No Vx(%) threshold





Marks et al Int J Radiat Oncol Biol Phys. 2010

DVH-related parameters for breast RT

- **V20:**
  - V20Gy≤20% had a lower incidence of RP compared to V20Gy> 20% (12.5% vs 28.4% respectively*)
  - significance of ipsilateral V20Gy in clinical RP (p = 0.008) and radiological RP (p = 0.009)**
- **Mean lung dose (MLD)**
  - Correlated with incidence and grade of RP
  - For Perh Lind** the MLD was 7.5 Gy, 13.5 Gy and 16.0-16.6 Gy for no RP, mild RP and moderate RP respectively.
  - In Kahan's study*** the MLD of patients with no RP versus RP in this study was 12.2 Gy vs 15.0 Gy

*Wennberg et al Int J Radiat Oncol Biol Phys 2002
**Perh Lind et al. Breast Cancer Res Treat 2001
***Kahan et al Int. J. Radiation Oncology Biol. Phys. 2007

Concomitant and sequential treatments

- **Tamoxifen:**
  - Non hormonal effect: induction of TGF-ß
  - Significant association with the incidence of marked lung fibrosis (relative risk = 2.0; 95% confidence interval [CI] = 1.2-3.5; P = .01)*
  - OR of having RP is 1.20 (95% CI 0.57 – 2.51)**
  - Advised to start hormonotherapy after the completion of radiotherapy

*Bentzen et al J Natl Cancer Inst. 1996
**Gokula et al. Radiation Oncology 2013

Concomitant and sequential treatments

- **Chemotherapy:**
  - > Various drug and schedules
  - > Expected increased risk of RP not demonstrated with platinium or etoposide but demonstrated with gemcitabine and docetaxel

- **Targeted therapies**
  - > EGFR pathway
  - > Antiangiogenic
  - > mTOR pathway
  - > HSP90 inhibitors
  - > Aurora Kinases
  - > HER2 for breast

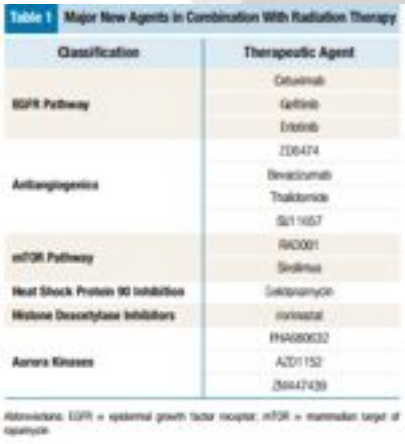


Table 1 Major New Agents in Combination With Radiation Therapy

Classification	Therapeutic Agent
EGFR Pathway	Cetuximab
	Gefitinib
	Erlotinib
Antiangiogenics	ZD6474
	Bevacizumab
	Thalidomide
	SU11657
mTOR Pathway	RAD001
	Sirolimus
Heat Shock Protein 90 Inhibition	Geldanamycin
Histone Deacetylase Inhibitors	vorinostat
Aurora Kinases	PHA680632
	AZD1152
	ZM447439

Abbreviations: EGFR = epidermal growth factor receptor; mTOR = mammalian target of rapamycin

Marks et al Int J Radiat Oncol Biol Phys. 2010
Provencio et al Clinical Lung Cancer 2010

⇢ Phase I combining RAD001and RT: Treatment overview

RAD001 *per os* 11 weeks

Arm A: 10, 20 or 50 mg **weekly**

Arm B: 2.5, 5 or 10 mg **daily**

W1 W2 W8 W11 W13 W14 W16 W17

Radiotherapy 6,5 weeks

66grays in 33 fractions, 2 Grays

Chemotherapy

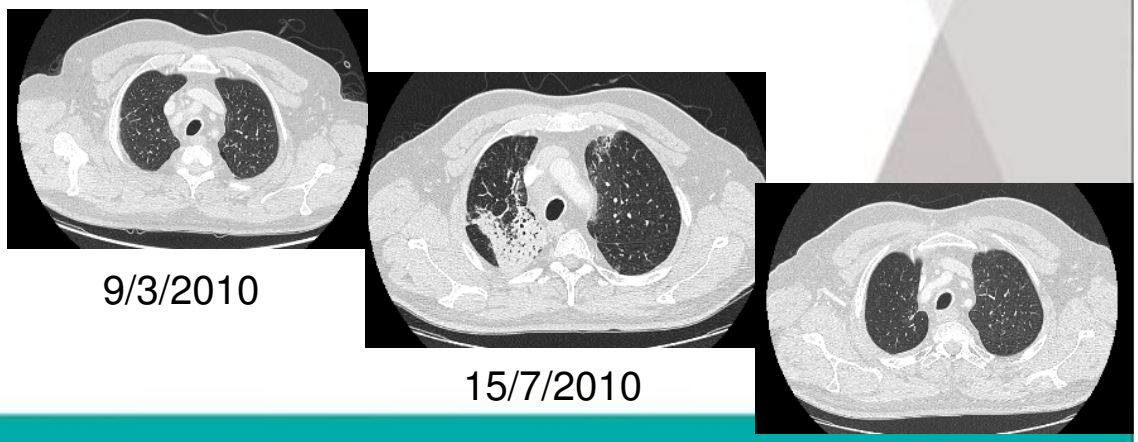
Cycle 1 (w13 + w14)
- d1 (w13): 25mg/m² navelbine +100mg/m² cisplatin
- d8 (w14): 25mg/m² navelbine

+ Antiemetics

Cycle 2 (w16 + w17)
- d1 (w16): 25mg/m² navelbine +100mg/m² cisplatin
- d8 (w17): 25mg/m² navelbine

mTOR inhibition during RT :

- Most pneumonitis where not symptomatic
- Most pneumonitis were transient and did completely recover particularly after the amendment excluding patients with emphysema



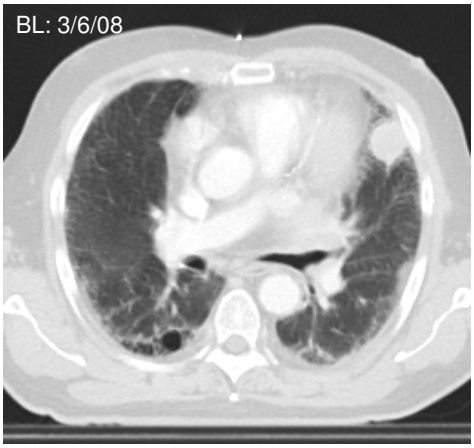
9/3/2010

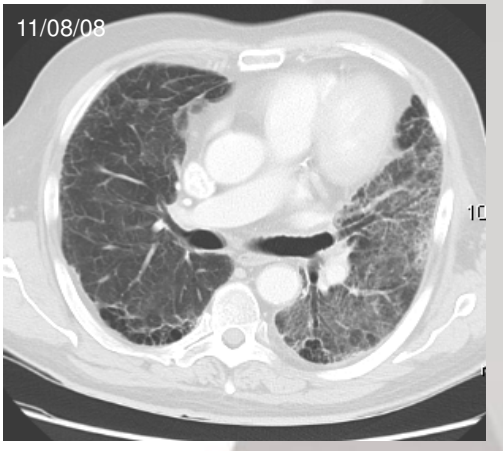
15/7/2010

7/3/2011

mTOR inhibition during RT :

- Pneumonitis grade V





Patients factors

- **Smoking:**
  - > Studied in a few trials, Gokula: OR of having RP
  - > in this smoking-group is 0.59 (95% CI = 0.26–1.34)
  - > Controversial data
  - > Potential anti-inflammatory effect

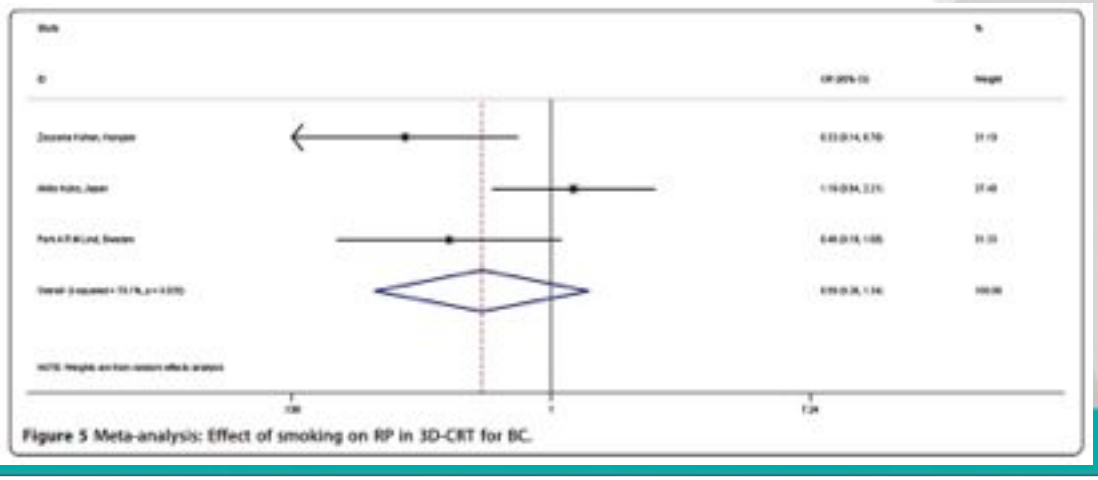
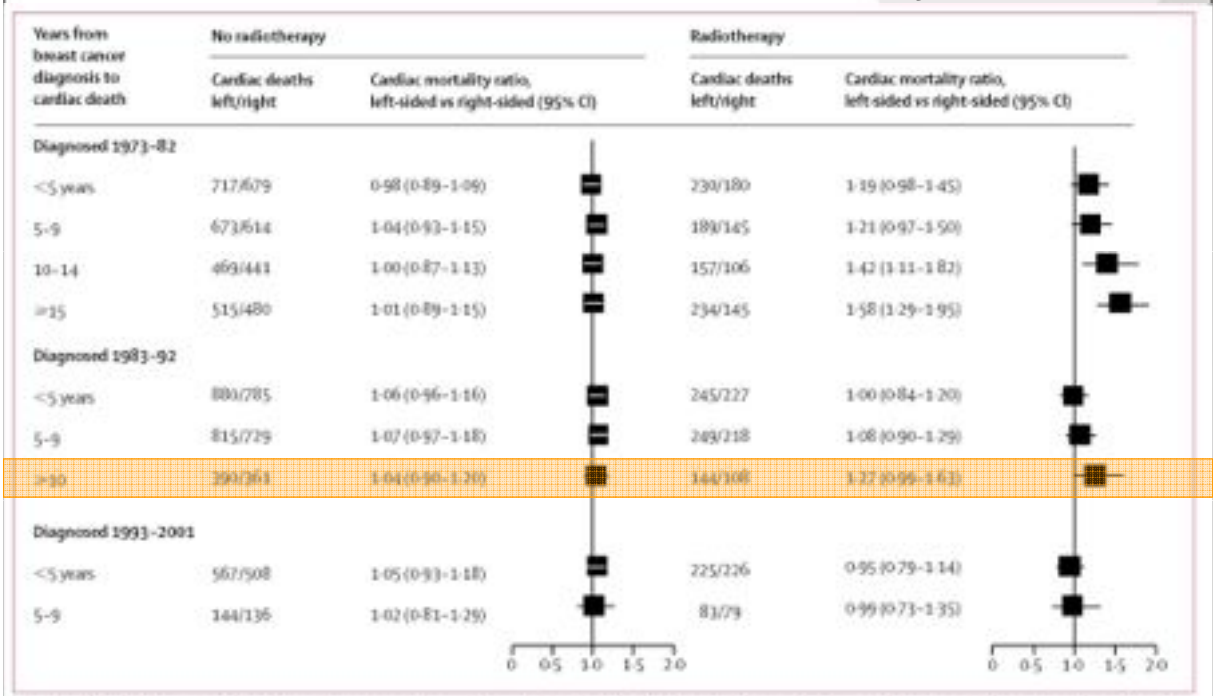


Figure 5 Meta-analysis: Effect of smoking on RP in 3D-CRT for BC.

Cardiac toxicity after breast RT

RR 1.27, increase in cardiac death risk (>10 years)



Years from breast cancer diagnosis to cardiac death	No radiotherapy		Radiotherapy	
	Cardiac deaths left/right	Cardiac mortality ratio, left-sided vs right-sided (95% CI)	Cardiac deaths left/right	Cardiac mortality ratio, left-sided vs right-sided (95% CI)
Diagnosed 1973–82				
<5 years	717/679	0·98 (0·89–1·09)	230/180	1·19 (0·98–1·45)
5–9	673/614	1·04 (0·93–1·15)	189/145	1·21 (0·97–1·50)
10–14	469/443	1·00 (0·87–1·13)	157/106	1·42 (1·11–1·82)
≥15	515/480	1·01 (0·89–1·15)	234/145	1·58 (1·29–1·95)
Diagnosed 1983–92				
<5 years	880/785	1·06 (0·96–1·16)	245/227	1·00 (0·84–1·20)
5–9	815/729	1·07 (0·97–1·18)	249/218	1·08 (0·90–1·29)
≥10	290/264	1·04 (0·90–1·20)	144/108	1·27 (0·99–1·63)
Diagnosed 1993–2001				
<5 years	567/508	1·05 (0·93–1·18)	225/226	0·95 (0·79–1·14)
5–9	144/136	1·02 (0·81–1·29)	81/79	0·99 (0·73–1·35)

0 0·5 1·0 1·5 2·0 0 0·5 1·0 1·5 2·0

Figure 2: Left-sided versus right-sided breast cancer: subsequent cardiac mortality ratios by radiotherapy status, period of diagnosis, and years from breast cancer diagnosis to cardiac death

Darby, Lancet Oncol 2005

Cardiac toxicity after breast irradiation

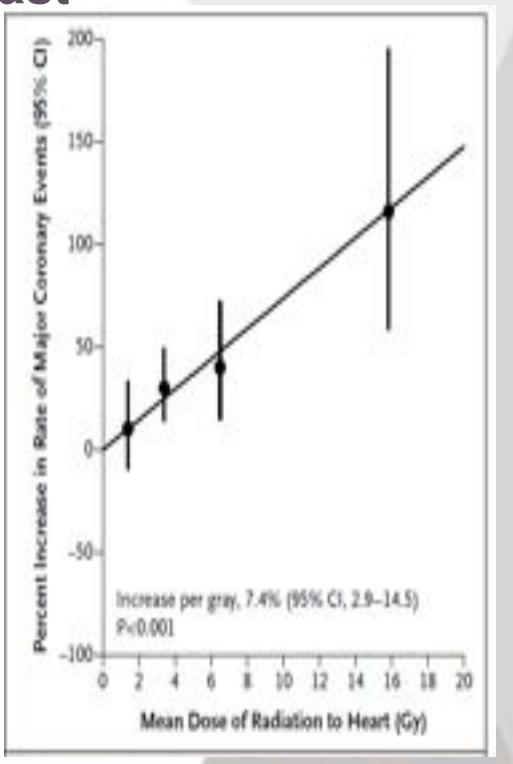
Table 3. Percentage Increase in the Rate of Major Coronary Events per Gray, According to Time since Radiotherapy.

Time since Radiotherapy*	No. of Case Patients	No. of Controls	Increase in Rate of Major Coronary Events (95% CI)†
			% increase/Gy
0 to 4 yr	206	328	16.3 (3.0 to 64.3)
5 to 9 yr	216	296	15.5 (2.5 to 63.3)
10 to 19 yr	323	388	1.2 (−2.2 to 8.5)
≥20 yr	218	193	8.2 (0.4 to 26.6)
0 to ≥20 yr	963	1205	7.4 (2.9 to 14.5)

Darby NEJM 2013

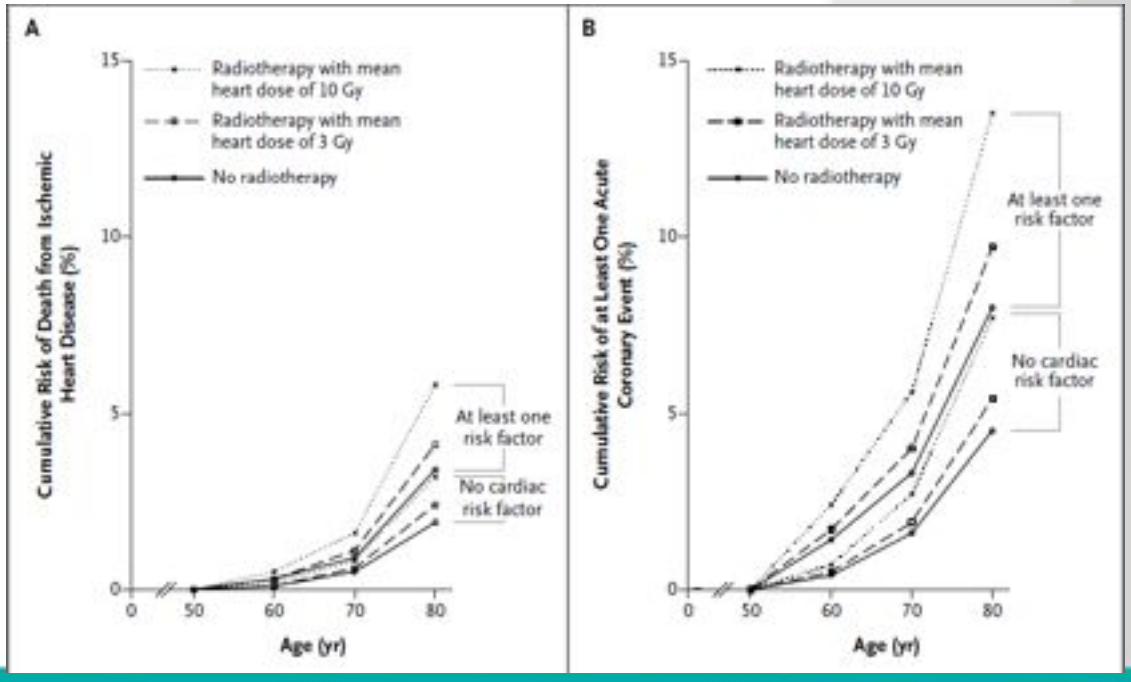
Cardiac toxicity after breast irradiation

- "The overall average of the mean doses to the whole heart was 4.9 Gy (range, 0.03 to 27.72). Rates of major coronary events increased linearly with the mean dose to the heart by **7.4% per gray** (95% confidence interval, 2.9 to 14.5; P<0.001), with **no apparent threshold**. The increase started within the first 5 years after radiotherapy and continued into the third decade after radiotherapy. The proportional increase in the rate of major coronary events per gray was similar in women with and women without cardiac risk factors at the time of radiotherapy"



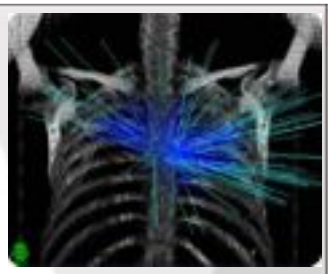
Darby NEJM 2013

Cardiac toxicity after breast irradiation Patients factors



Darby NEJM 2013

Reducing toxicities of lung RT

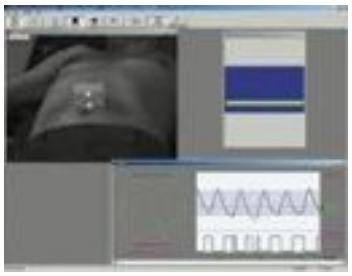


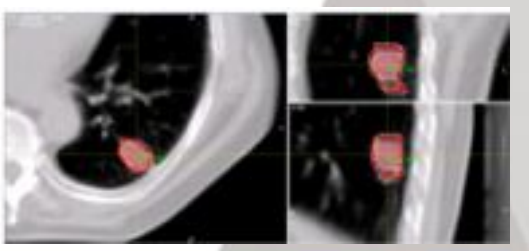
- **Hypofractionation in lung cancer RT:**
  - > Stereotactic body radiation therapy (SBRT)
  - > Few large fractions
  - > Small high-dose volumes, steep dose gradients, minimized dose to surrounding critical structures
  - > Numerous beams leading to large areas of lung receiving low-medium doses
  - > RP is relatively uncommon after SBRT, usually <10%
  - > Bronchial injury/stenosis, haemorrage unusual with normofractionation can be seen

Marks et al Int J Radiat Oncol Biol Phys. 2010

Reducing toxicities of lung RT

- **IMRT:**
  - > Most studies have shown a reduced rate of grade ≥3 RP with IMRT compared to conventional 3D for lung RT
  - > Postoperative IMRT for mesothelioma has been associated with a high rate of lethal pneumontis (8–46%)
  - > extreme care should be used to limit lung irradiation
- **Gatting:**





Marks et al Int J Radiat Oncol Biol Phys. 2010

Reducing toxicities of breast RT?

- **hypofractionation**

	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

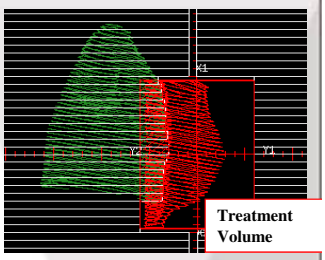
Reducing toxicities of breast RT?

- **Internal mammary chain irradiation: EORTC 22922**

Survival status	No IM-MS (N=2002)	IM-MS (N=2002)
Alive	1573 (78.6)	1620 (80.9)
Death	429 (21.4)	382 (19.1)
Breast cancer	*310*	*259*
Other cancer	*39*	*30*
Cardiovascular disease	*20*	*22*
Toxicity	*1*	*1*
Infection	*4*	*8*
Other chronic disease	*5*	*3*
Other cause	*23*	*25*
Unknown	*27*	*34*

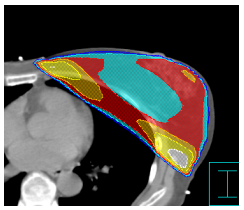
P.Poortmans ESMO 2013

Reducing toxicities of breast RT?

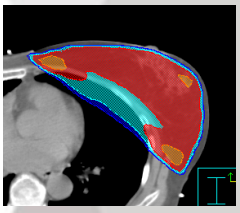


- **IMRT, VMAT, Tomotherapy:**
  - > Improved dose distribution : increased homogeneity
  - > Steep dose gradient
  - > Concave distribution

    →Better sparing of normal tissues



3D conventionnel

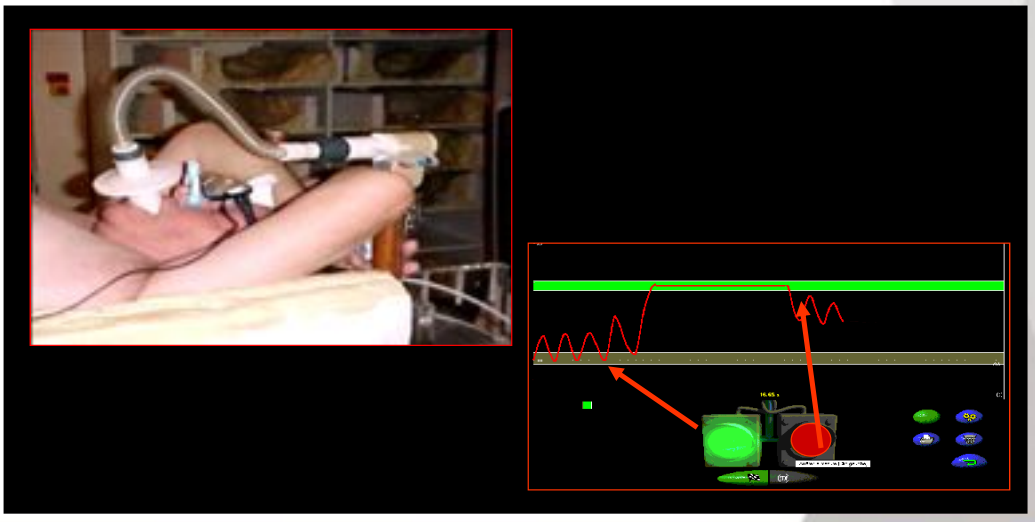


IMRT MLC lung block segment

- **No clinical consensus achieved**
  - > Movements, breast swelling
  - > Higher volumes with low dosis
  - > Benefit for bilateral, pectus excavatum, complicated lymph nodes irradiations, bilateral breast implants

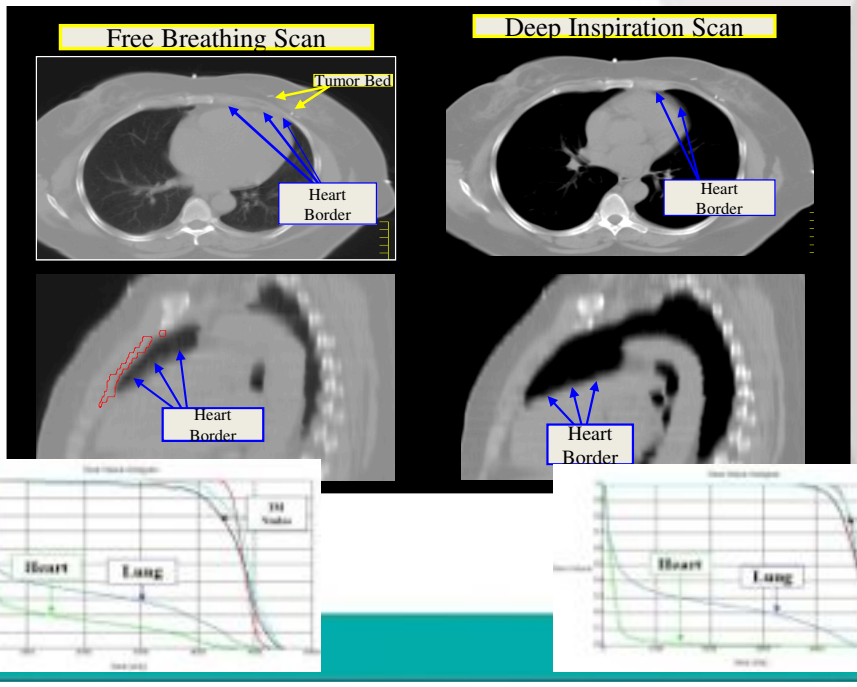
Reducing toxicities of breast RT

- Breath hold



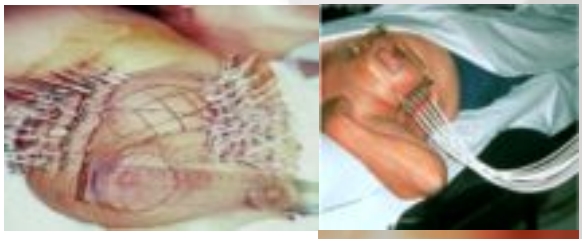
Reducing toxicities of breast RT

- Breath hold

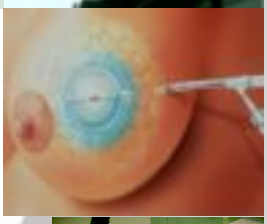


Reducing toxicities of breast RT: APBI

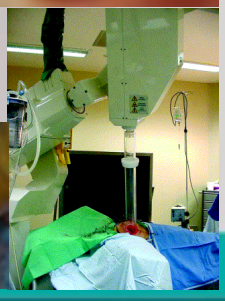
- **Interstitial Brachytherapy:**
  - Low dose-rate
  - High dose-rate



- **Intracavitary therapy:**
  - Orthovoltage photons (Intrabeam, UK)
  - Intraoperative electrons (Milan)
  - Brachytherapy (Mammosite)



- **External-beam therapy:**
  - 3D conformal photons/mixed beam
  - IMRT
  - Protons



Different 3D techniques for APBI

Baglan/ Vicini – William Beaumont hospital, IJROBP 2003

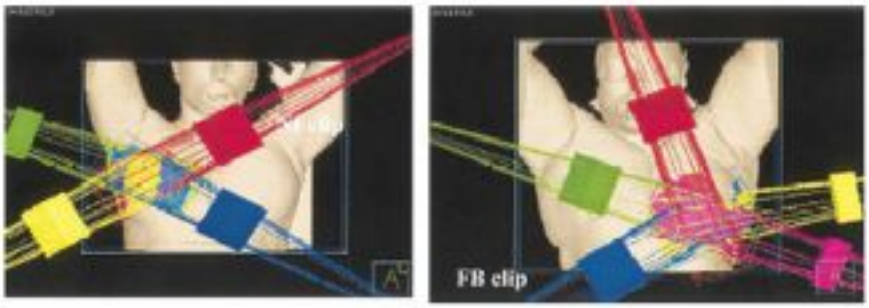


Fig. 1. Typical 4-field arrangement for right-sided lesions and 5-field arrangement for left-sided lesions.

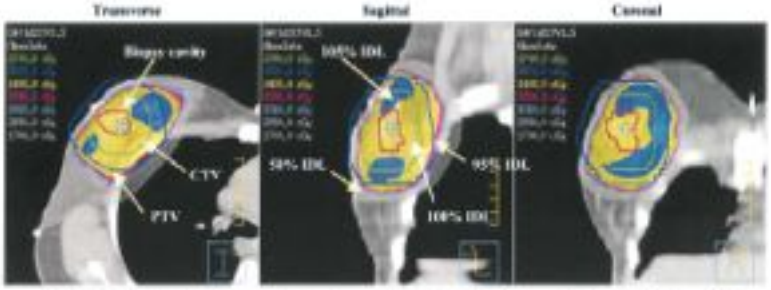
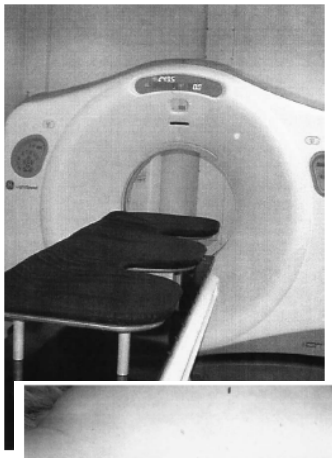
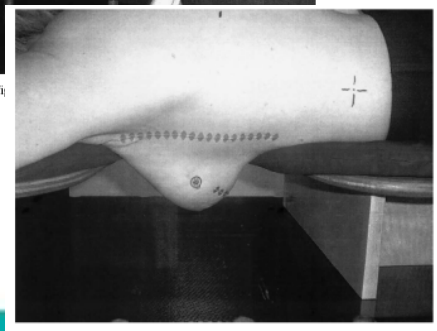


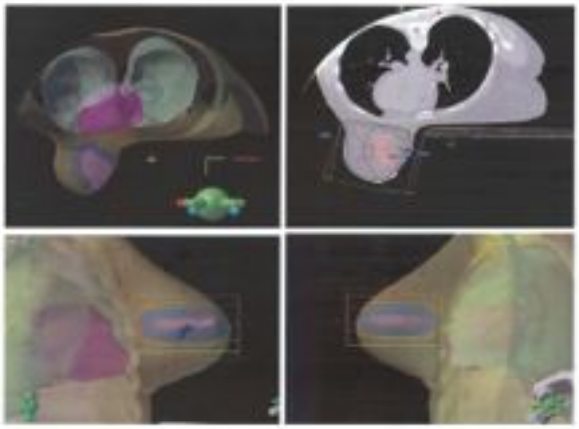
Fig. 3. Typical isodose distribution for a 4-field arrangement treating a right-sided lesion. The prescribed dose was 34 Gy.

Different 3D techniques for APBI

Formenti – NY University, IJROBP 2004

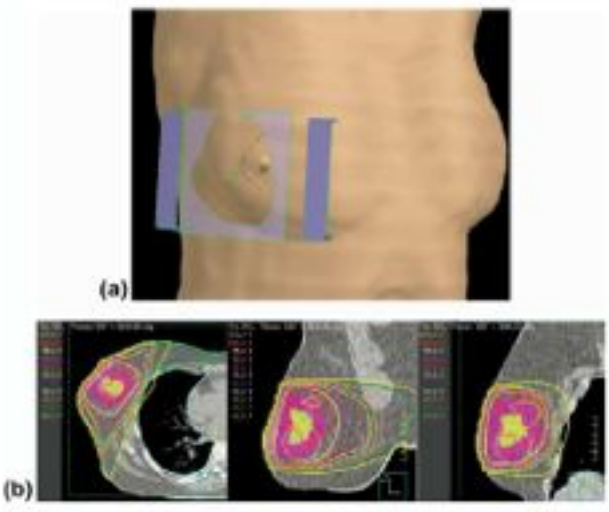






Different 3D techniques for APBI

Taghian - Massachusetts General Hospital, IJROBP 2006



Recent results in partial breast irradiation

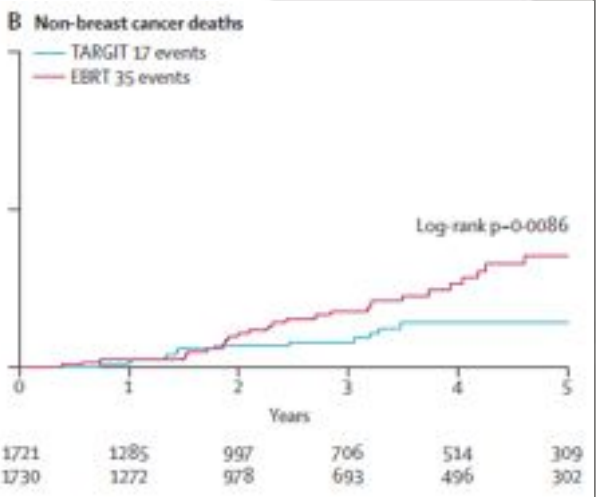
Trial	N	Arms	Median follow-up	Ipsilateral breast tumor recurrence	Cancer specific mortality	OS	Skin tox/ cosmetic
TARGIT-A Vaidya, Lancet 2014	3451	TARGIT vs WB EBRT	2years and 5months	**3.3%** (95% CI 2·1–5·1) for TARGIT vs **1.3%** (0·7–2·5) for EBRT p=0·042	2.6% [1·5–4.3] for TARGIT *vs* 1.9% [1·1–3.2] for EBRT; p=0.56	NS	**Grade 3-4 lower** for TARGIT p=0·029
ELIOT Veronesi, Lancet oncol 2013	1305	ELIOT vs WB EBRT	5,8 years	**4.4%** (95% CI 2.7–6.1) for ELIOT vs **0.4%** (0.0–1.0) for EBRT (HR 9.3 [95% CI 3.3–26.3])	NS	NS	**Fewer skin side-effects** in ELIOT p=0·0002
NIC, Hungary Polgar, Radiother Oncol 2013	258	PBI (brachy or electrons) vs WB EBRT	10.2 years	**5.9%** for PBI and **5.1%** for WBI (p = 0.77)	NS	NS	**Better cosmetic results** in PBI p<0.01
RAPID Olivotto, JCO 2013	2135	APBI 3D-CRT vs WB EBRT	36 months	-	-		**Worse results** in APBI

Reducing heart toxicity

	TARGIT	EBRT
Other cancers	8	16
Cardiovascular causes		
Cardiac*	2	8
Stroke	0	2
Ischaemic bowel	0	1
Other†	7	8
Total	17	35

5-year risk 1·4% for TARGIT versus 3·5% for EBRT; log-rank p=0·0086. TARGIT=targeted intraoperative radiotherapy. EBRT=external beam radiotherapy. *Included one "sudden death at home" in EBRT group. †TARGIT: two diabetes, one renal failure, one liver failure, one sepsis, one Alzheimer's disease, one unknown; EBRT: one myelopathy, one perforated bowel, one pneumonia, one old age, four unknown.

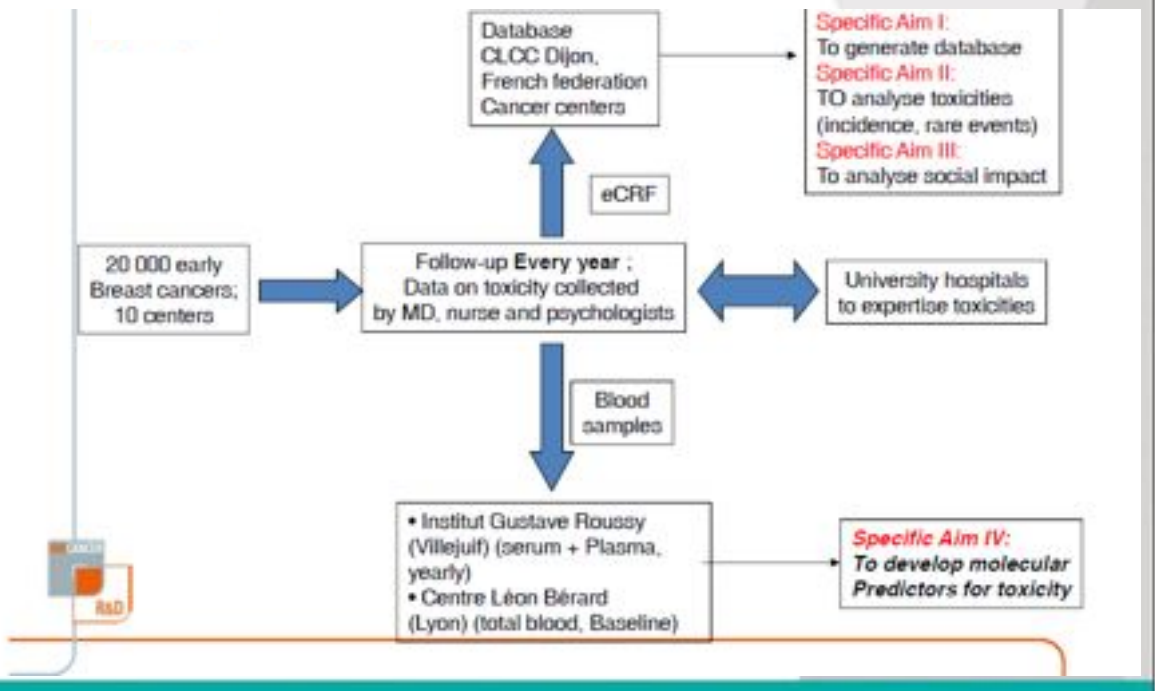
Table 2: Causes of death other than breast cancer in all patients



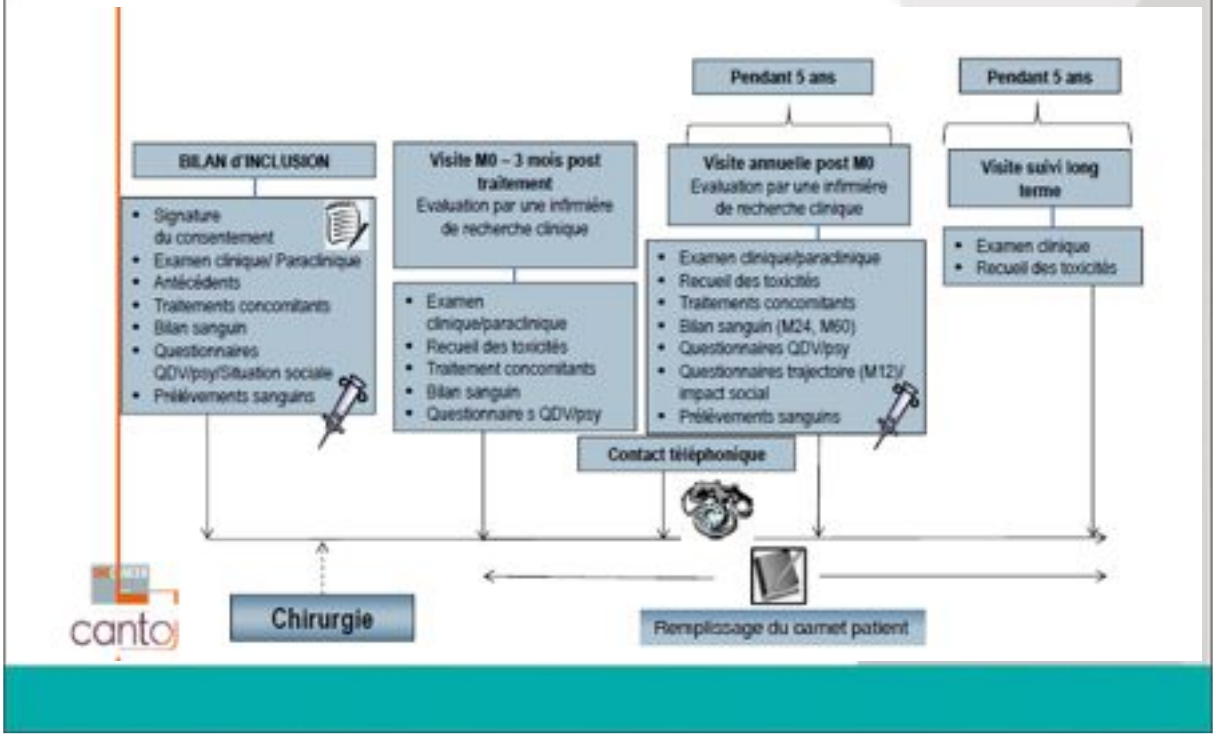
How to validate our predictive models for toxicities: need for prospective cohorts

- **CANTO:**
  - Aim: identify and avoid risk factors for toxicity of localised breast cancer
  - National multicentric prospective cohort study (22 centers)
  - 20 000 participants expected
  - cT0-T3,N0-N3,M0 histologically proven
  - Blod collection
  - Patient questionnaires
  - Medical and para-medical follow up

A need for prospective cohorts: CANTO

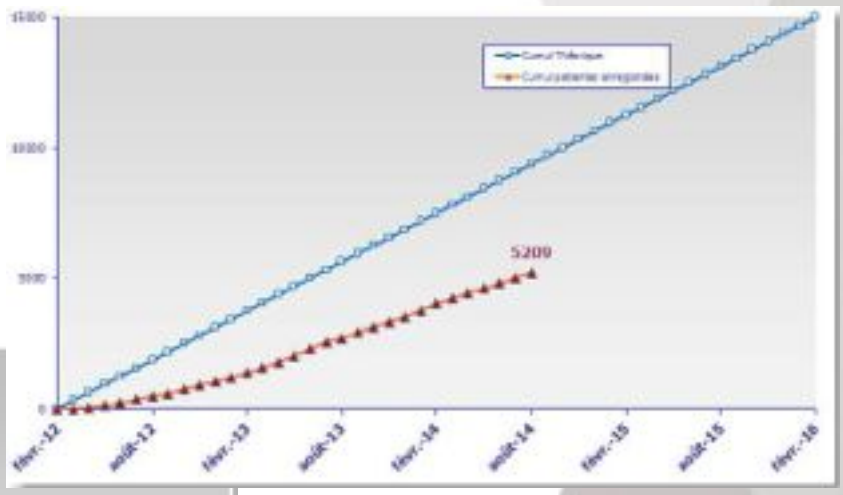


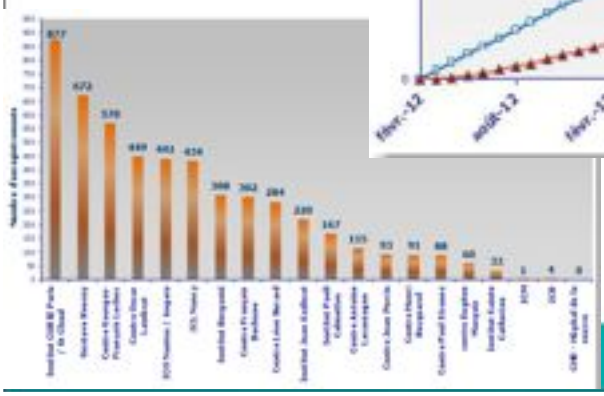
A need for prospective cohorts: CANTO



A need for prospective cohorts: CANTO

Patients recruitment





Conclusions

What should we recommend?

- **Control patients related factors**
- **Caution with associated treatments**
- **ALARA**
  - > Heart and lung toxicity is related to dose and volume
  - > The threshold question remains open
- **Need for a prospective population based validation of toxicities prediction models**

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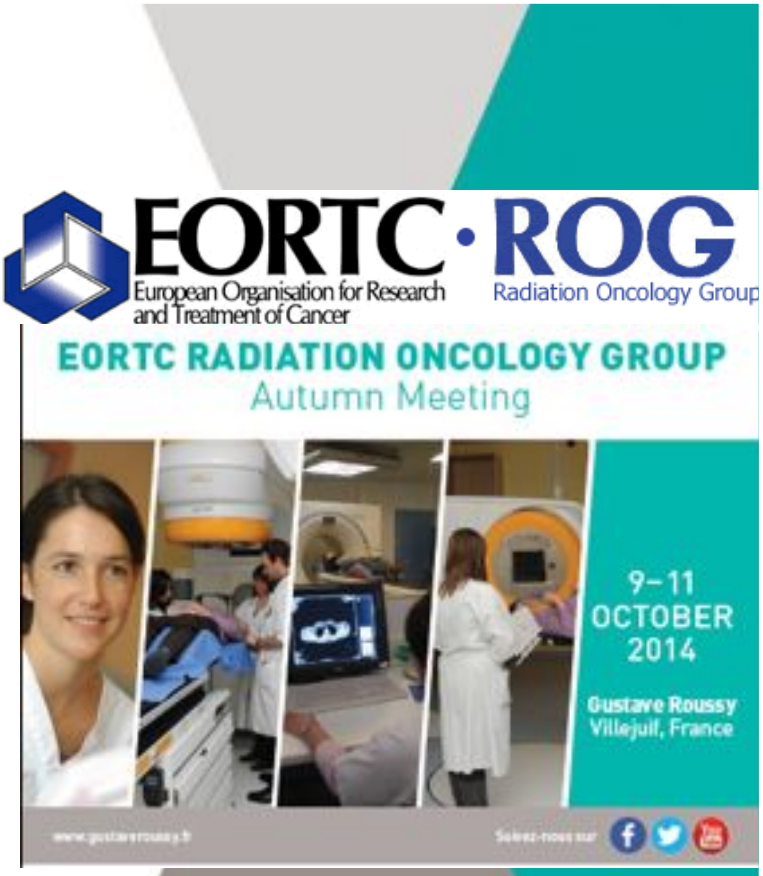
Our patients from who we learn and for who we need to improve



http://www.gustaveroussy.fr/index.php?p_id=5789