

# Radioterapia ipofrazionata ad intensità modulata con boost simultaneo integrato per l'irradiazione adiuvante della mammella utilizzando campi statici di tomoterapia (TomoDirect): studio prospettico di fase II

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# Tumor bed boost

## Boosting the tumor bed raises local control

**20-50% relative reduction in local failure**

### **EORTC 22881/10882 'boost vs no boost trial'**

- ✓ Boost provided a benefit in terms of local failure (6.2% vs 10.2% at 10 yrs;  $p < 0.0001$ ), especially in younger pts (< 40 yrs)
- ✓ Boost pts had worse cosmetic results in terms of 10-year severe fibrosis (4.4% vs 1.6%) (photographic assessment with a subjective panel and objective measurements)

### **Lyon Trial**

- ✓ Boost provided benefit in terms of local failure (3.6% vs 4.5% at 5 yrs;  $p < 0.05$ )
- ✓ Boost had a higher rate of G1-G2 telangiectasia (12.4% vs 5.9%) but no difference in cosmetic self- and physician-scoring results.

*Graham P and Fourquet A, Clin Oncol 2006*

## How to integrate hypofractionated WBRT and tumor bed boost ?

- **Canadian trial was a no boost trial**
- **UK trials delivered conventionally fractionated boost dose sequential to WBRT, according to institution discretion**

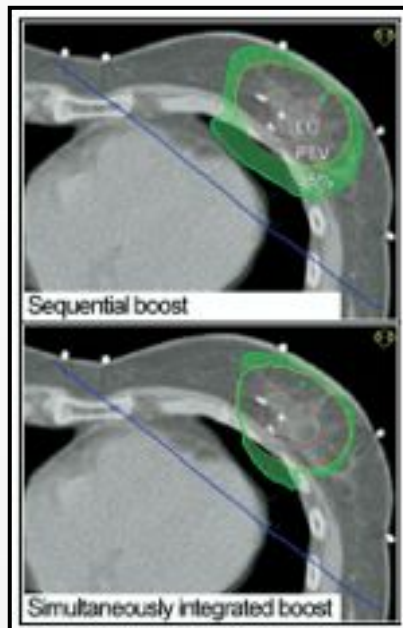
**None of the 3 UK RCTs explored the use of the boost dose to the TB within treatment protocol**

**No definitive conclusions can be drawn**

## Whole breast RT: phase III trials on boost integration

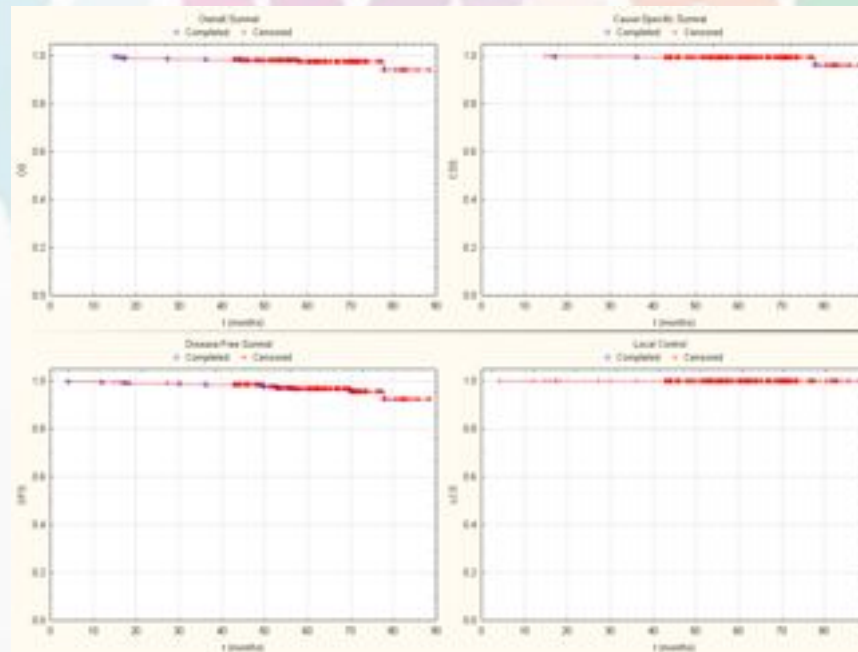
Study	Country	Primary end-point	Target population	Dose and fractionation (experimental arm)		
				Whole breast	Index quadrant	Tumor bed
RTOG 1005	USA	In-breast relapse	2300 pts	40.05 Gy/ 15 fr (2.67 Gy daily)	/	48 Gy/15 fr (3.2 Gy daily)
IMPORT-HIGH	UK	Palpable induration	2568 pts	36 Gy/15 fr (2.4 Gy daily)	40.05 Gy/ 15 fr (2.67 Gy daily)	I: 48 Gy/15 fr (3.2 Gy daily) II: 53 Gy/15 fr (3.53 Gy daily)
IMRT MC-2	Germany	Cosmesis	502 pts	50.4 Gy/28 fr (1.8 Gy daily)	/	64.4 Gy/28 fr (2.3 Gy daily)
UZH trial	Belgium	Pulmonary-Heart function Arm mobility and lymphedema	123 pts	42 Gy/15 fr (2.8 Gy daily)	/	51/15 fr (3.4 Gy daily)

## THREE-DIMENSIONAL CONFORMAL SIMULTANEOUSLY INTEGRATED BOOST TECHNIQUE FOR BREAST-CONSERVING RADIO THERAPY



- ✓ 30 L-sided breast cancer pts
- ✓ WBRT + sequential boost (50 Gy/25 fr + 16 Gy 8 fr) vs concomitant boost (WBRT: 50.68 Gy/28 fr; 1.81 Gy daily; TB: 64.4 Gy/28 fr; 2.3 Gy daily)
  - Mean volume  $\geq 107\%$  breast dose reduced by 20%
  - Mean volume outside TB receiving  $> 95\%$  of the boost dose reduced by 54.4%
  - MHD and MLD reduced by 10%

# LINAC-based concomitant boost to the tumor bed



- 5yr-OS: 97.6%
- 5yr-CSS: 99.4
- 5yr-DFS: 96.6%
- 5yr-LC: 100%

Over 1.000 pts treated; long-term results on 375 pts

- 45 Gy/20 fr 2.25 Gy/daily - WBRT
- 50 Gy/20 fr 2.5 Gy/daily – Tumor bed (Direct Photon Field and then FIF)

*Cante et al, Breast J 2011; Med Oncol 2013 and 2014*



## **Intensity-modulated adjuvant whole breast radiation delivered with static angle tomotherapy (TomoDirect): a prospective case series**

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Giuseppe Girelli · Gianmauro Numico · Maria Rosa La Porta · Santi Tofani · Umberto Ricardi

**WBRT: 50 Gy/25 fr (2 Gy daily) over 5 weeks delivered with TomoDirect**

**Sequential boost of 10 Gy/5 fr (2 Gy daily) for R0 resection or 16 Gy/8 fr (2 Gy daily) for R1 resection delivered with Helical Tomotherapy**

**120 patients**

## **Intensity-modulated and hypofractionated simultaneous integrated boost adjuvant breast radiation employing static ports of tomotherapy (TomoDirect): a prospective phase II trial**

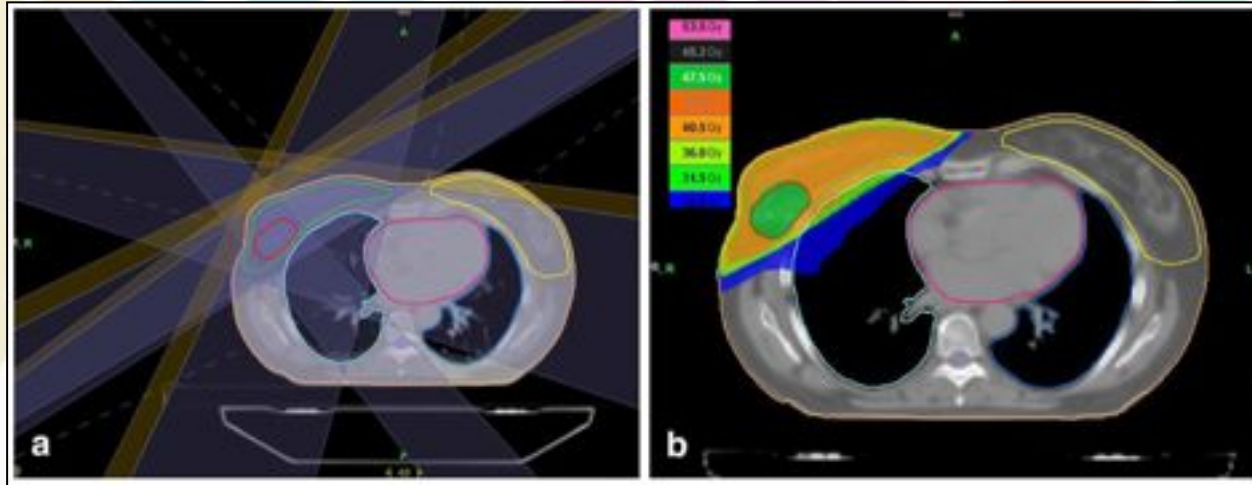
- 2010-2012**
- 82 patients**
- After BCS, pT1-T2, pN0-N1, M0 margins >2mm**
- Excluded prior thoracic RT, synchronous second primary tumor and pregnancy**
- 45 Gy/20 fr over 4 weeks (2.25 Gy daily) as WBRT**
- Simultaneous 0.25 Gy to the surgical bed**
- 50 Gy/20 fr over 4 weeks**



# Trial design

- ❑ One-armed optimal two-stage Simon's design
- ❑ Historical data of success ( $p_0$ ): 85% G0-G1 acute skin toxicity (G2-G3: 15%) with TD + helical tomotherapy
- ❑ Threshold for successful trial ( $p_1$ ): set to 94% of G0-G1 acute skin toxicity (G2-G3: 6%)
  - $\alpha$  error (one-sided type I error): 5%
  - $\beta$  error (type II error; power 80%): 20%
  - $H_0$ : no difference in acute skin toxicity
- ❑ First stage: 18/21 (86%) patients should have scored as G0-G1 acute skin toxicity
- ❑ Second stage: another 61 pts accrued; at least 74/82 (90.2%) is the threshold for  $H_0$  rejection and definition of SIB-TD as 'promising'

## Technical issues



- 4 beams conformed to the WB-PTV: 2 canonical tangential beams, 1 anterior-posterior (AP) and 1 latero-lateral (LL) with a  $\pm 15^\circ$  gantry angle range
- 1 or 2 small beams conformed to the TB-PTV to improve homogeneity and conformality; oblique incidence to reduce dose spread around TB-PTV
- FW: 2.5 cm; Pitch: 0.25 cm/projection; planning MF: 2-2.5
- A 10 mm ring was used around WB-PTV and TB-PTV to reduce overdosage (skin and breast tissue)
- Helping structures around WB-PTV used to avoid hotspots
- OARs as avoidance structures

	Mean	SD
<b>PTV</b>		
<b>WB</b>		
<u><math>D_{98}</math> (Gy)</u>	42.8	2.1
$D_2$ (Gy)	47.3	1.2
<u><math>V_{95}</math> (%)</u>	98.1	11.3
$V_{105}$ (%)	1.9	0.9
<b>Boost</b>		
<u><math>D_{98}</math> (Gy)</u>	48.1	1.9
$D_2$ (Gy)	50.9	5.6
$V_{95}$ (%)	99.5	1.1
$V_{105}$ (%)	0	0
<b>WB (excluding boost)</b>		
$V_{105}$ (%)	2.4	0.9
$V_{110}$ (%)	0.01	0
<b>OARs</b>		
<b>Ipsilateral lung</b>		
$V_5$ (%)	26.2	4.5
$V_{10}$ (%)	15.6	3.4
<u><math>V_{20}</math> (%)</u>	9.6	3.1
$D_{max}$ (Gy)	45	2.9
<u>MLD (Gy)</u>	6.4	1.5
<b>Contralateral lung</b>		
<u><math>D_{max}</math> (Gy)</u>	2.1	1.1
<b>Heart (left-sided tumors)</b>		
$V_5$ (%)	12.8	8.6
$V_{10}$ (%)	2.7	1.1
<u><math>V_{20}</math> (%)</u>	1.3	0.5
<u><math>V_{25}</math> (%)</u>	1.1	0.3
MHD (Gy)	2.1	1.2
$D_{max}$ (Gy)	25.1	19.1
<b>Contralateral breast</b>		
<u><math>D_{max}</math> (Gy)</u>	2.9	1.3

## Dosimetric results

Volume of WB-PTV minus TB-PTV receiving 105% of prescription dose was 2.4%

No volume gets 110%-115%

V20 ipsilateral lung 9.6%

MLD ipsilateral lung 6 Gy

Dmax contralateral lung 2 Gy

V25 heart 3%, MHD 2 Gy in left sided tumors

Dmax contralateral breast < 3Gy

## Results

**Mean follow-up 12 months (range 6-24)**

**Majority of patients older than 50**

**Mean BMI 25.2**

**79% received concomitant hormonal therapy**

**25% adjuvant CT**

**17% Trastuzumab**

**No local relapse**

## Results: acute skin toxicity

Skin toxicity	Grade	Patients	%
No change over baseline	0	33	41
Follicular, faint or dull erythema/epilation/dry desquamation/decreased sweating	1	43	53
Tender or bright erythema, patchy moist desquamation/moderate edema	2	5	6
Confluent, moist desquamation other than skin folds, pitting edema	3	1	<1
Ulceration, hemorrhage, necrosis	4	0	0

## Results: late skin toxicity and cosmesis

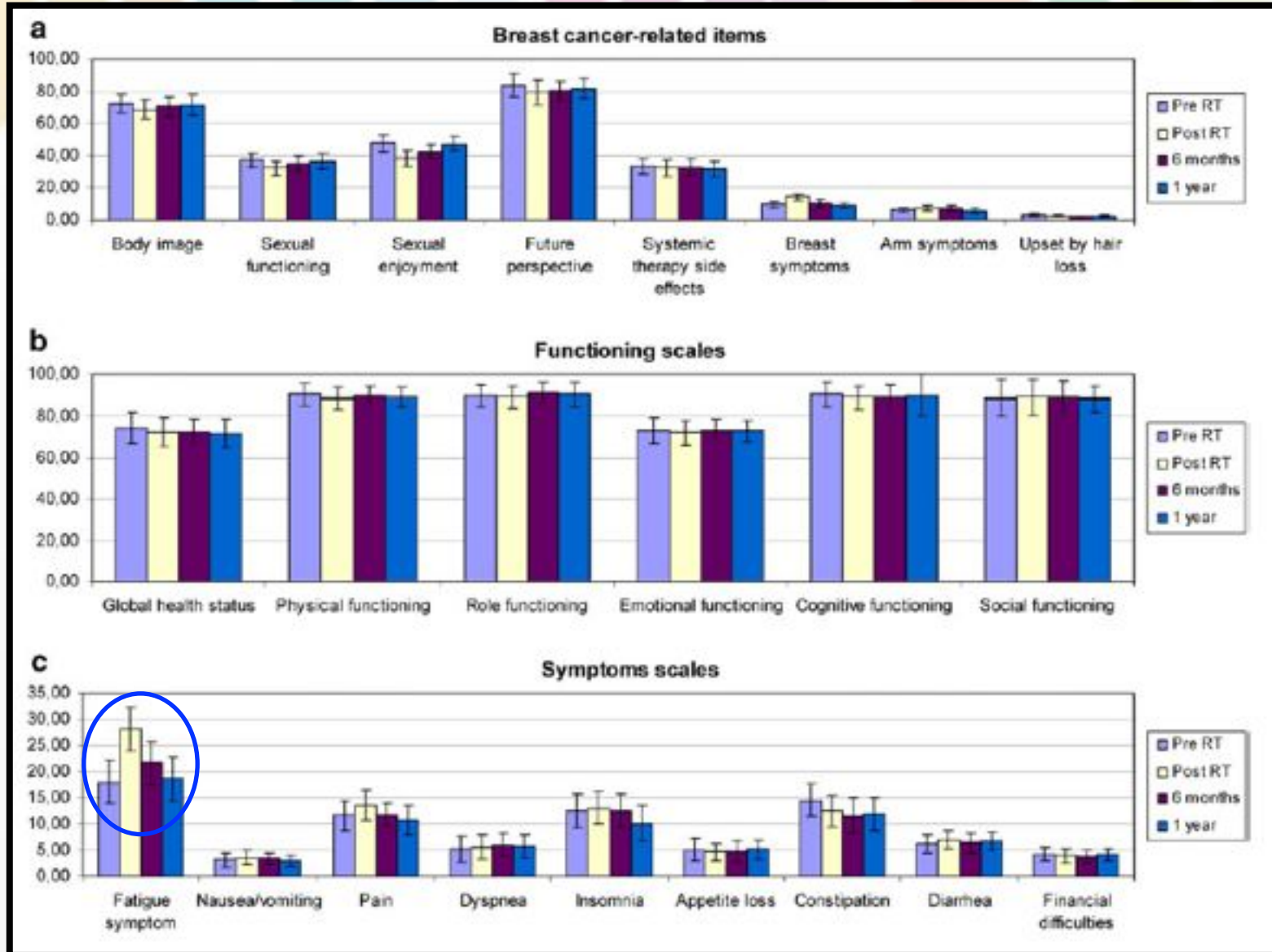
Parameters	Grade (%)			
	G1	G2	G3	G4
Induration–fibrosis	4 (5)	1 (1)	0	–
Atrophy	3 (4)	0	–	–
Telangiectasia	1 (1)	0	0	–
Hyperpigmentation	10 (12)	2 (2)	–	–
Striae	2 (2)	0	–	–
Ulceration	–	0	0	0
Cosmesis				
Definition	Poor	Fair	Good	Excellent
	3 (4)	4 (5)	18 (22)	57 (69)

**No events > G2**

**Good cosmetic results**



# QoL – EORTC QLQ-C30 and BR-23



## Conclusions

- ✓ **IMRT and hypofractionated WBRT using a SIB to the TB and delivered with TD provides mild toxicity, promising cosmesis and good QoL**
- ✓ **The reduction of excessive dose outside TB decreases acute skin toxicity rate**
- ✓ **A longer follow-up is needed**





San Remo - Panorama.