Radiotherapy: smaller volumes for shorter times. Why? How? When?

APBI: 3D CRT

B. Meduri, F. Bertoni

Brescia Meetings in Radiation Oncology

September 30th, 2011

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Modena
Policlinico

Epidemiology

•Breast cancer has the highest incidence among all cancer types in females

• 60% of diagnosed breast cancer is early stage (screening programs)

There is a need for proper clinical management of early stage breast cancer

Hayat MJ, *Oncologist* 2007;12 (1): 20–37

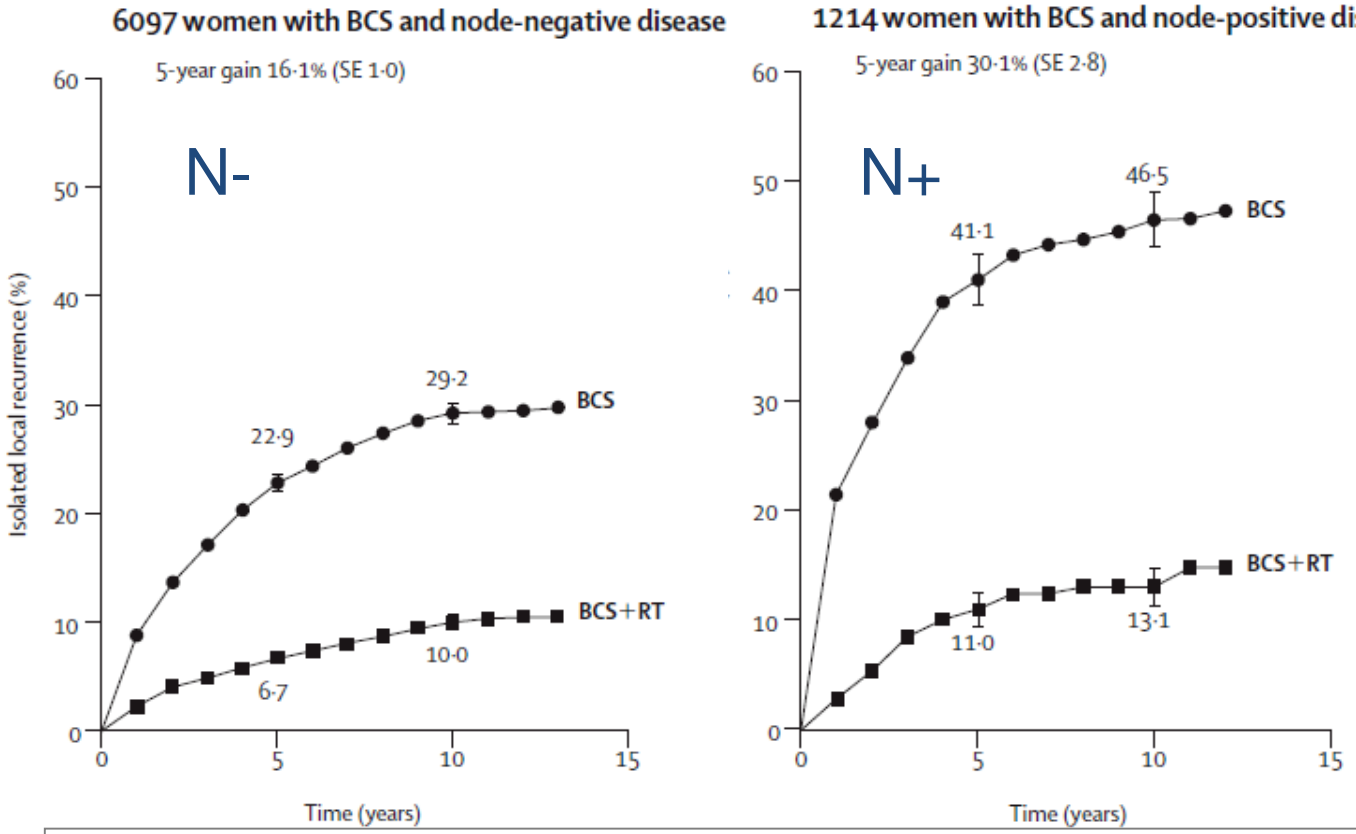
Early stage cancer

- Is radiotherapy the standard treatment after breast conservative surgery (BCS) in early stage cancer?

Yes!

BCS ± RT

Isolated local recurrence



5-year risk:

No-RT: 25.9 %

RT: 7.3 %

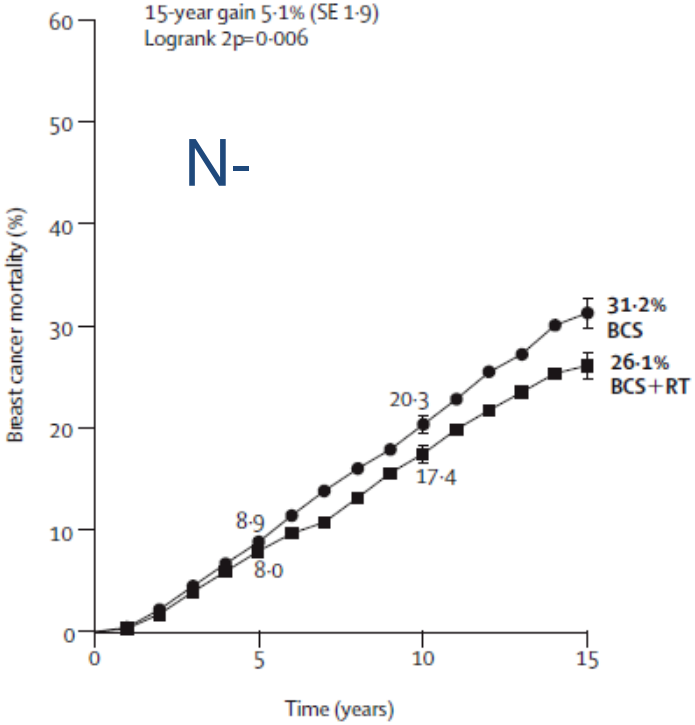
Absolute reduction of 19%

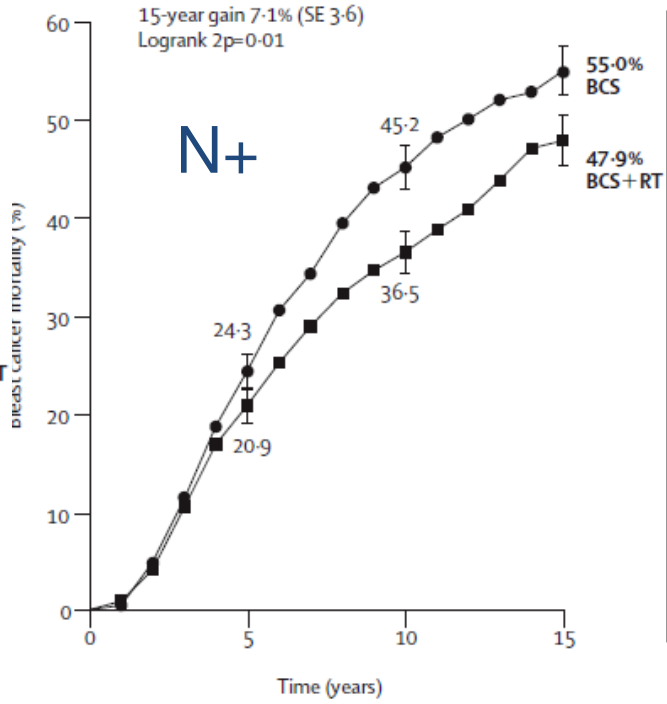
Reduction in **local recurrence** produced by allocation to radiotherapy is substantial and highly significant (p=0.00001) in every separate trial.

Clarke M, *Lancet* 2005;366:2087–106

BCS ± RT

Breast cancer mortality





15-year risk of death cancer specific:

No-RT: 35.9 %

RT: 30.5 %

Absolute reduction of 5.4%

The proportional risk reduction for **breast cancer mortality** is much less extreme than that for local recurrence but highly significant (p=0.0002)

Clarke M, *Lancet* 2005;366:2087–106

BCS ± RT

Nowadays, *whole breast irradiation* is the procedure of choice

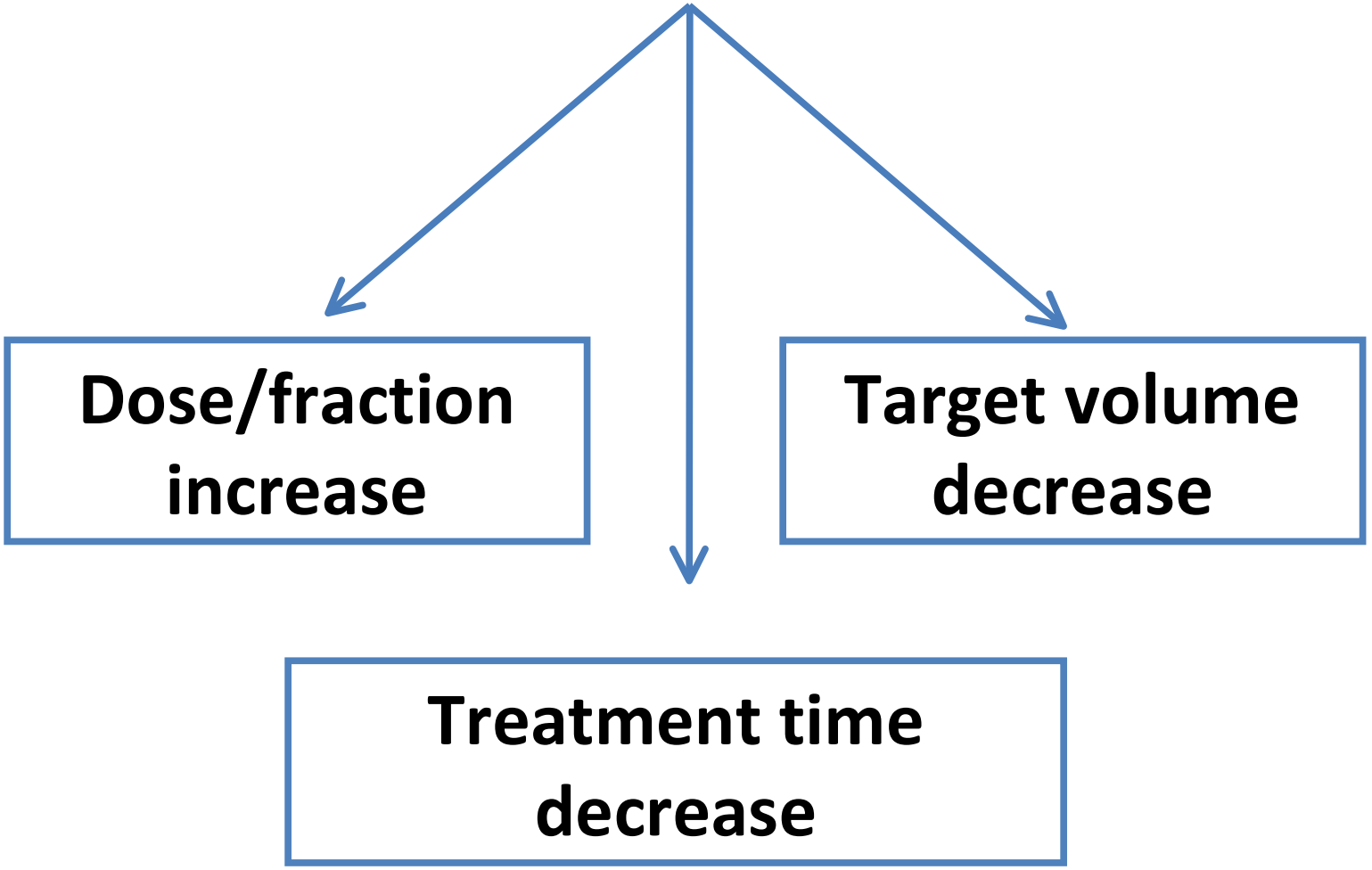
But….

•Women don't receive BCT because of age, logistical issues, cost, type of hospital

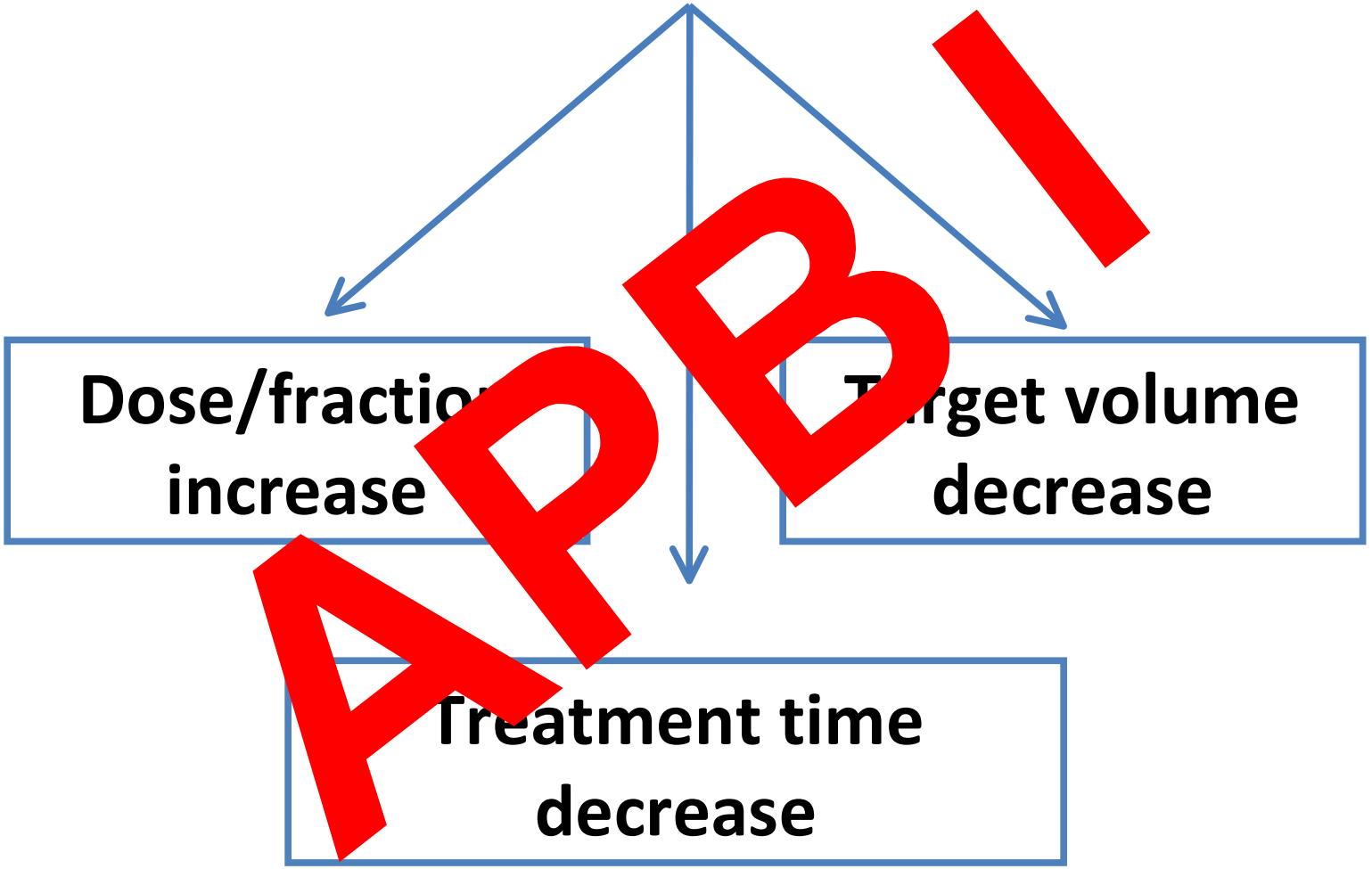
•Another criticism of BCT relates to consumption of resources (breast irradiation may constitute more than 25% of a radiation department workload and not all countries have adequate resources)

Njeh CF *Radiat Oncol* 2010; 5:90

Early stage cancer



Early stage cancer



APBI: Theoretical advantages

- Reducing treatment time, could improve compliance
- Decreasing dose to normal tissue, could reduce toxicity
- Less consumption of resources

Without compromising efficacy (??)

Waiting for ongoing phase III study

But...

- Can WBI rates of local control be achieved with radiation therapy delivered only to the tumor bed?
- Is accelerated partial breast irradiation (APBI) an acceptable option?

APBI: Rationale

Ongoing phase III trials are based on:

- 76–90% of local recurrence occurs close to the *tumor bed*
- Ipsilateral breast recurrences in areas other than the tumor bed ("*elsewhere relapse*") occurred in 3–4% of the cases

Table 2. Site of LR After BCT With and Without XRT

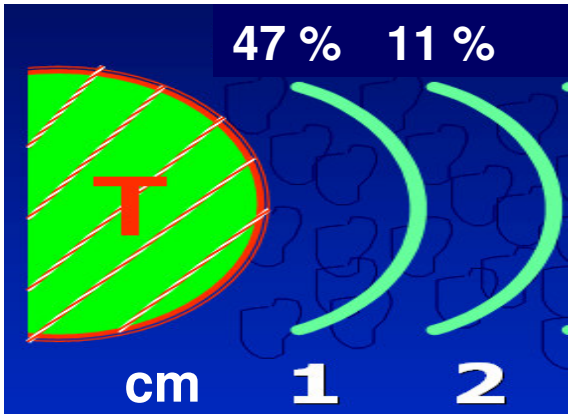
Study	No. of Patients	LR (%)	
		Tumor Bed	Elsewhere
With XRT			
Yale University[51]	1,152	44	6
M.D. Anderson Cancer Center[52]	1,339	62	3.6
Institute Curie[53]	519	46	5.8
Switzerland[54]	1,593	79	2.4
University of Pennsylvania[55]	1,093	74	1.7
Princess Margaret, Ontario, Canada[56]	416	83	0.9
JCRT, Boston[57]	974	79	2.8
Paris, France[58]	528	59	4.2
Milan, Italy [59]	299	85	0.6
Without XRT			
Princess Margaret, Ontario, Canada[56]	421	86	3.5
Milan, Italy[59]	280	86	2.9
Total No. of Patients	9,396		
Average LR, %		71	3.1

Abbreviations: LR, local recurrence; BCT, breast-conservation therapy; XRT, radiation therapy.

- Elsewhere relapse are similar to the recurrences of contra-lateral breast cancer (NSABP B-06 trial - Fisher ER, Cancer 2001; 91:1679–87.)

SandersME, J Clin Oncol 2007; 25:996–1002

APBI: Rationale

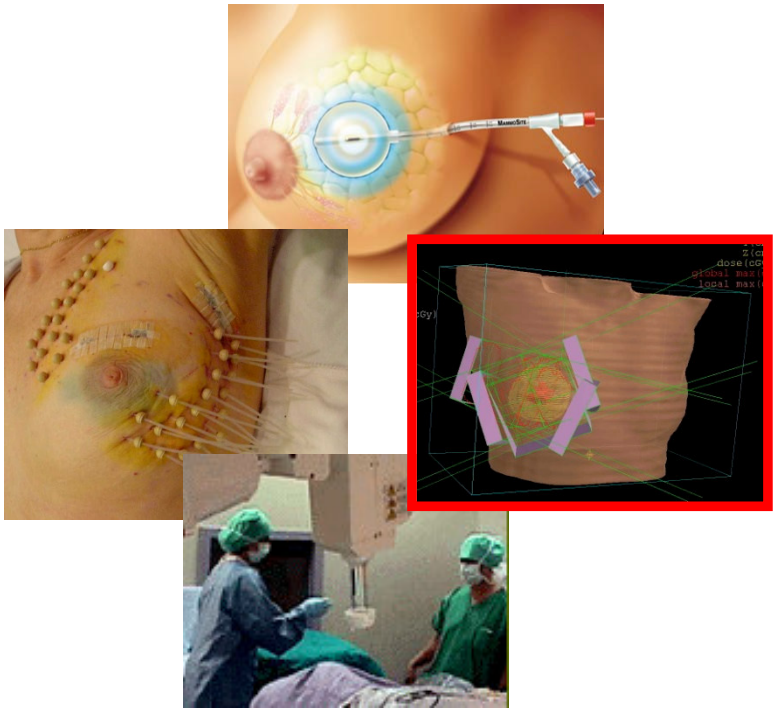


- Pathology studies: 47% of cases had disease that extended more than 1 cm beyond the grossly evident tumor, with 11% having residual foci outside of a 2-cm margin (Faverly D, Semin Diagn Pathol 11:193-198, 1994)
- Radiation-induced lung injury and increase in lung cancer incidence and mortality after WBI are well documented (Darby SC, Lancet Oncol 2005;6:557–65)

For selected patients WBI could be an

over-treatment

APBI techniques: 3D-CRT

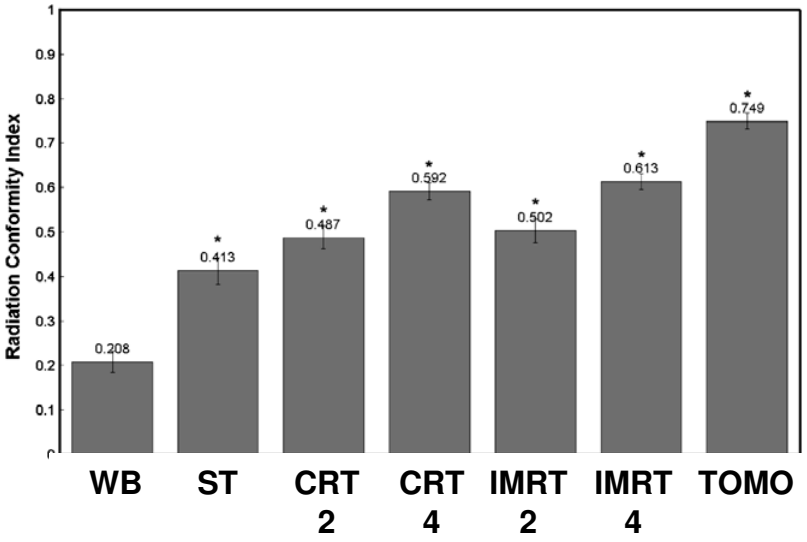


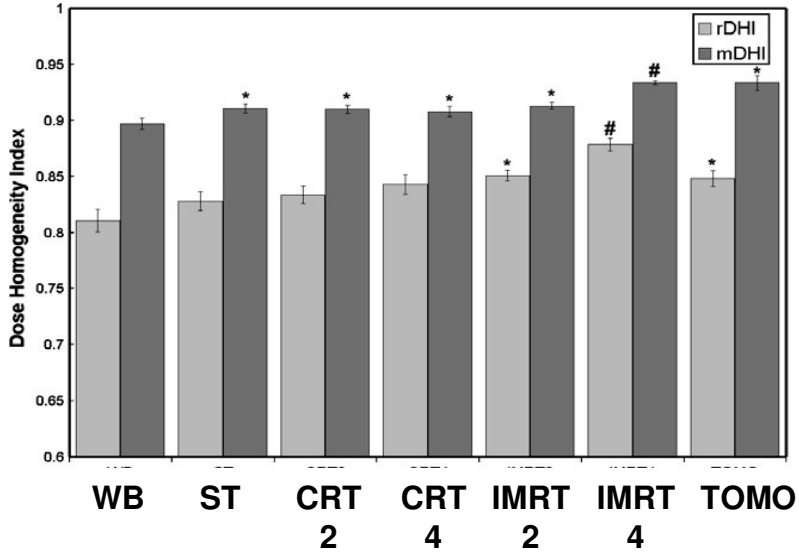
APBI: 3D -CRT

- Potential advantages over the other techniques:
  - Non-invasive (reduce the potential risk of surgical procedure complications)
  - The treatment can wait until completion of pathological analysis (resection margin, pathological prognostic factors)
  - Widespread availability
  - Cheaper than other techniques (especially if an extra surgical procedure are needed)
  - Treatment results with ERT may be more uniform between radiation oncologists (the outcome depends less on the experience of operators
  - Better dose homogeneity (may result in a better cosmetic outcome)

APBI: 3D –CRT

Treatment planning studies comparing whole breast irradiation therapy against conformal, IMRT and tomotherapy for accelereted partial breast irradiation





•The four-field IMRT plan produced the best dosimetric results

If intra-fraction motion cannot be appropriately addressed

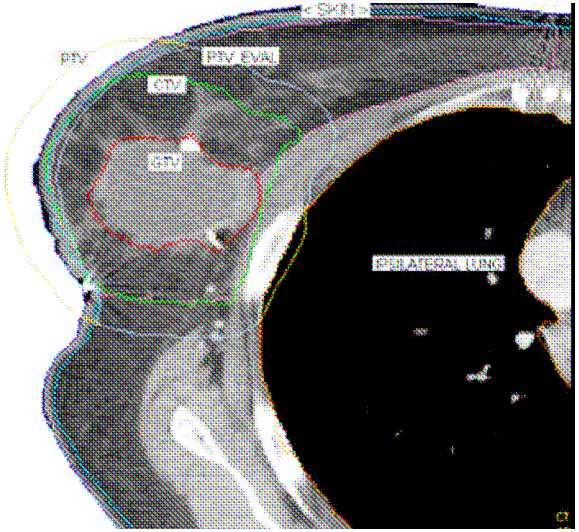
a four-field 3D conformal plan is superior.

Oliver M, Radiother Oncol 2007;82:317–23

3D –CRT Technique

- The most widely used 3D-CRT approach was initially described by investigators at the William Beaumont Hospital

  - GTV: seroma cavity and surgical clips
  - CTV: GTV with a 1.5 cm margin limited by 0.5 cm from the skin and chest wall
  - PTV: CTV with 1 cm uniform 3D expansion



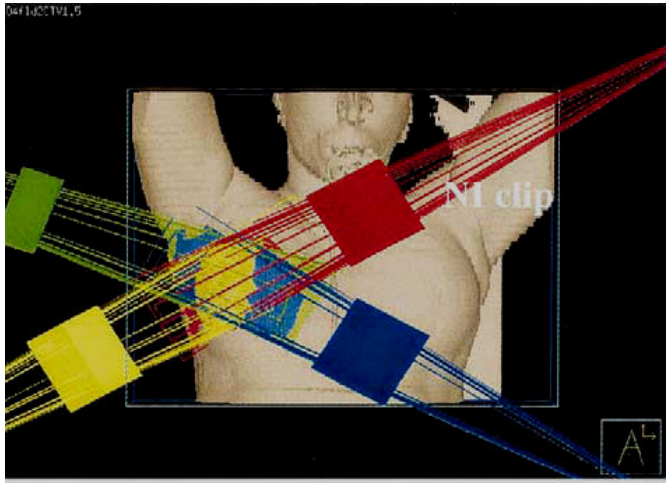
Baglan KL, Int J Radiat Oncol Biol Phys 2003; 55:302–11

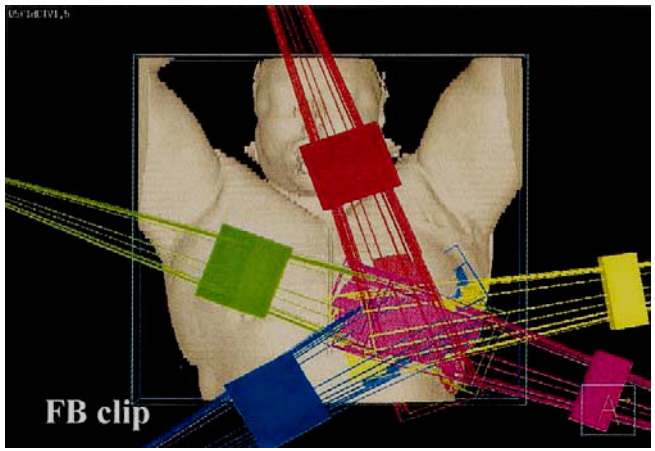
3D –CRT Technique

- 3-5 non-coplanar beams

- Dose:

3.85 Gy twice daily to a total dose of 38.5 Gy delivered within 1 week





Baglan KL, Int J Radiat Oncol Biol Phys 2003; 55:302–11

3D APBI: critical issues

- Patient setup:
  - Patient position
  - Setup errors and organ motion
- Target delineation
- Dose fractionation
- Patient selection

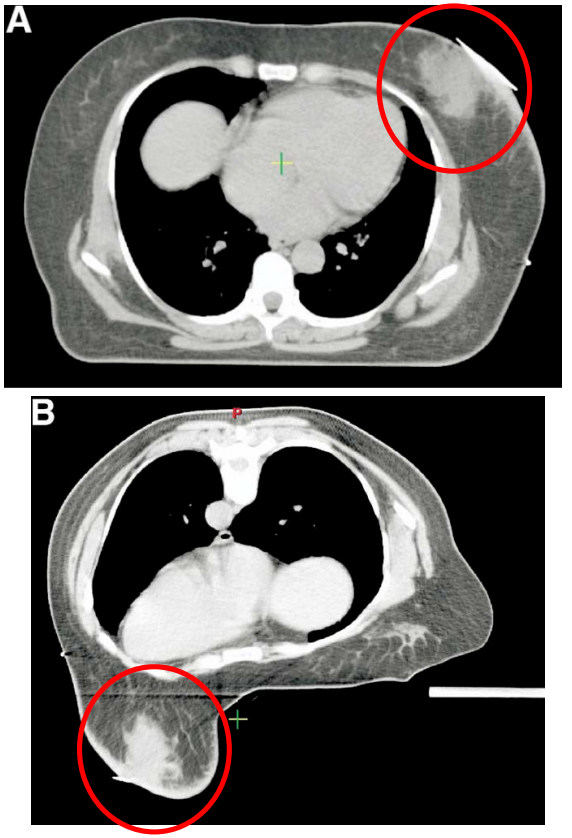
3D APBI: critical issues

- **Patient setup:**
  - **Patient position**
  - Setup errors and organ motion
- Target delineation
- Dose fractionation
- Patient selection

Patient position

- Stantard patient setup: supine, on a carbon fiber breast board, both arms above the head

- Prone position:
  - advantages for selected patients as large pendulous breasts: spare lung and heart, minimize target tissue movement
  - Requires a special immobilization device, uncomfortable for patients



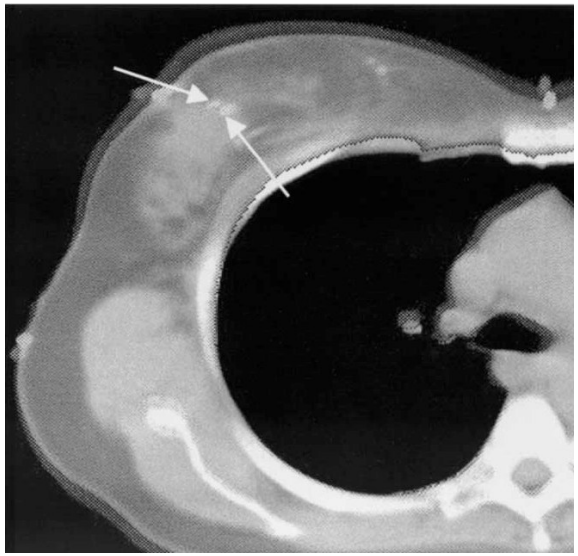
Formenti SC,Int J Radiat Oncol Biol Phys 2004;60:493–504 Merchant TE, Int J Radiat Oncol Biol Phys 1994;30:197–203

3D APBI: critical issues

- **Patient setup:**
  - Patient position
  - **Setup errors and organ motion**
- Target delineation
- Dose fractionation
- Patient selection

Setup errors - organ motion

- The concept CTV-PTV margin uncommon for WBI
- APBI requires the use of this concept
  - Average positional difference between normal inhalation e normal exhalation: 6 mm
  - Adding a CTV-PTV “breathing only” margin of 5mm, 98%-100% CTV is covered by 95% isodose
  - 5 mm for additional components of setup error



A margin of 10 mm seems to provide coverage for most patients

Baglan KL, Int J Radiat Oncol Biol Phys 2003; 55:302–11

3D APBI: critical issues

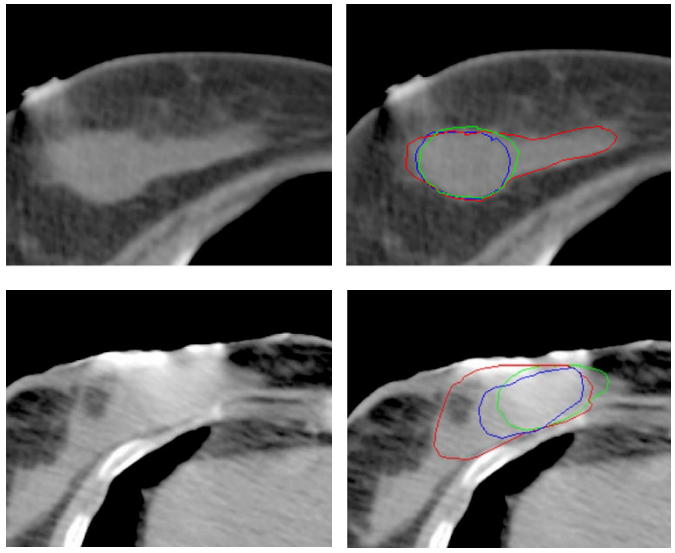
- Patient setup:
  - Patient position
  - Setup errors and organ motion
- **Target delineation**
- Dose fractionation
- Patient selection

Target delineation

GTV: lumpectomy cavity or seroma volume

- GTV identification and contouring can be problematic (RT delayed after surgery)

- High variability in GTV contouring, even among experienced radiation oncologist (mean CI 0.6 range 0.27-0.84)



Landis DM, Int J Radiat Oncol Biol Phys 2007;67:1299–308

Petersen RP, Int J Radiat Oncol Biol Phys 2007;69:41–8

Target delineation

- The use of surgical clips may reduce inter-observer variability, superiority to locate the tumor bed compared with clinical methods
- Training and contouring guidelines can improve consistency in seroma delineation
- Multi-modality imaging: feasibility of using 3D ultrasound for delineation of tumor bed, improve interobserver consistency, especially in case with dense breast parenchyma.

Dzhugashvili M, Radiat Oncol 2009;4:70

Berrang TS, Int J Radiat Oncol Biol Phys 2009;73:375–83

3D APBI: critical issues

- Patient setup:
  - Patient position
  - Setup errors and organ motion
- Target delineation
- **Dose fractionation**
- Patient selection

Dose fractionation

•There is still the question of the appropriate dose and fractional schedule for 3D-CRT–APBI

•Different doses and fractionation schedules

Author	No of cases	Fractionation scheme	IBF	Follow up (months)
Vicini et al. [73]	52	3.85 Gy × 10 (bid)	6%	54
Vicini et al. [74]	91	3.85 Gy × 10 (bid)	0%	24
Chen et al. [75]	94	3.85 Gy × 10 (bid)	1.1%	51
Taghian et al. [76]	99	3.2 Gy × 4 (bid)[$]	2%	36
Formenti et al. [77]	10	5.0, 5.5, 6.0 Gy × 5 (10 days)	0%	36 (minimum)
Formenti et al. [78]	47	6.0 Gy × 5 (10 days)	0%	18
Magee et al. [79]	353	5.0–5.31 Gy × 8 (10 days)[&]	25%	96 (mean)
Leonard et al. [80]	55	3.85 Gy × 10 (bid)	0%	34 median
Hepel et al. [81]	60	3.85 Gy × 10 (bid)	n/a	15
Jagsi et al. [82]	34	3.85 Gy × 10	n/a	>24

Cuttino et al. determined that the fraction size needed to deliver a ipofractionation treatment biologically equivalent to a standard post-operative RT schedule is 3.82 Gy/fr (TD 38.2 Gy in 10 fractions)

Cuttino LW, Am J Clin Oncol 2006;29: 474–8

3D APBI: critical issues

- Patient setup:
  - Patient position
  - Setup errors and organ motion
- Target delineation
- Dose fractionation
- **Patient selection**

3D –CRT Trial

Data from recent phase II clinical studies evaluating the efficacy and safety are available

Author	No of cases	Follow up (months)	Fractionation scheme	IBF	Good/Excellent cosmesis
Vicini et al. [73]	52	54	3.85 Gy × 10 (bid)	6%	n/a
Vicini et al. [74]	91	24	3.85 Gy × 10 (bid)	0%	90%
Chen et al. [75]	94	51	3.85 Gy × 10 (bid)	1.1%	89%
Taghian et al. [76]	99	36	3.2 Gy × 4 (bid)[$]	2%	97%
Formenti et al. [77]	10	36 (minimum)	5.0, 5.5, 6.0 Gy × 5 (10 days)	0%	100%
Formenti et al. [78]	47	18	6.0 Gy × 5 (10 days)	0%	n/a
Magee et al. [79]	353	96 (mean)	5.0–5.31 Gy × 8 (10 days)[&]	25%	n/a
Leonard et al. [80]	55	34 median	3.85 Gy × 10 (bid)	0%	n/a
Hepel et al. [81]	60	15	3.85 Gy × 10 (bid)	n/a	81.7%
Jagsi et al. [82]	34	>24	3.85 Gy × 10	n/a	79.5%

Patient selection
ASTRO

Factors	"Suitable" group	"Cautionary" group	"Unsuitable" group
Patient factors			
Age, y	≥60	50 to 59	<50
BRCA1/2 mutation	Not present	NA	Present
Pathologic factors			
Tumor size, cm	≤2†	2.1–3.0†	>3†
T stage	T1	T0 or T2	T3 or T4
Margins	Negative by at least 2 mm	Close (<2 mm)	Positive
Grade	Any	NA	NA
LVSI	No‡	Limited/focal	Extensive
ER status	Positive	Negative§	NA
Multicentricity	Unicentric only	NA	If present
Multifocality	Clinically unifocal with total size ≤2 cm‖	Clinically unifocal with total size 2.1 to 3.0 cm‖	If microscopically multifocal >3 cm in total size or if clinically multifocal
Histology	Invasive ductal or other favorable subtypes**	Invasive lobular	NA
Pure DCIS	Not allowed	≤ 3 cm in size	If >3 cm in size
EIC	Not allowed	≤ 3 cm in size	If >3 cm in size
Associated LCIS	Allowed	NA	NA
Nodal factors			
N stage	pN0 (i^-, i^+)	NA	pN1, pN2, pN3
Nodal surgery	SN Bx or ALND††	NA	None performed
Treatment factors			
Neoadjuvant therapy	Not allowed	NA	If used

Smith BD, Int J Radiat Oncol Biol Phys 2009;74:987–1001

Patient selection

Table 6 ASTRO and GEC-ESTRO suitable patient recommendation selections for APBI outside of clinical trials

	Suitable group by ASTRO [138]	Low Risk group by GEC-ESTRO [137]
Factors	**Criterion**	**Criterion**
Age	> 60 y	> 50
BRCA 1, 2 Mutation	Not present	na
Tumor Size	< 2 cm	< 3 cm
T stage	T1	T1-2
ER status	positive	any

Njeh et al. Radiation Oncology 2010, 5:90

Patient selection

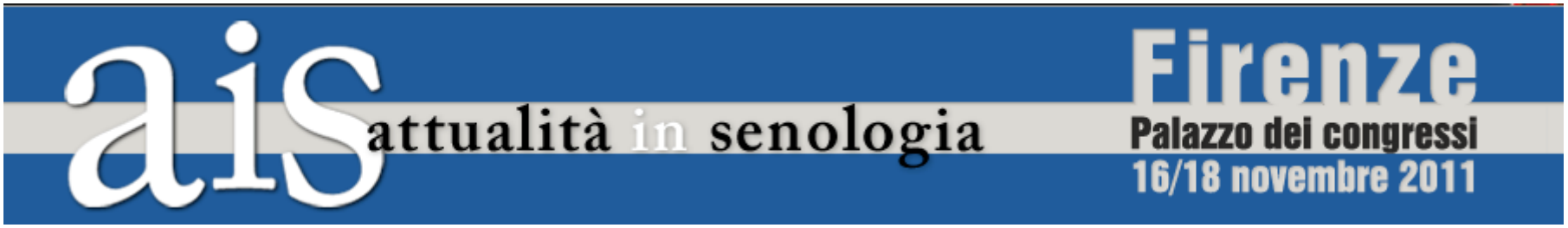
Organization	Patient age	Tumor size	Histology	Lymph node status	Margin status
ABS	≥50	≤3	Infiltrating ductal carcinoma	Negative (by sentinel lymph node or axillary dissection)	Negative (at inked margin)
ASBS	≥45	≤2	Invasive ductal carcinoma or ductal carcinoma in situ	Negative (by sentinel lymph node or axillary)	Negative (>2 mm)
ASTRO [181]	≥60	≤2	Invasive ductal carcinoma or or other favorable subtypes (mucinous, tubular and colloid)	Negative (by sentinel lymph node or axillary dissection)	Negative (>2 mm)
GEC-ESTRO [180]	≥50	≤3	Invasive ductal carcinoma or or other favorable subtypes (mucinous, tubular and colloid)	Negative (by sentinel lymph node or axillary dissection)	Negative (>2 mm)
NSABP B39/RTOG-0413	≥18	≤3	Invasive ductal carcinoma or ductal carcinoma in situ	Allows for 0–3 nodes involved (with negative sentinel lymph node or >6 nodes sampled	Negative (at inked)

Njeh et al. Crit Rev Oncol Hematol (2011)

The selection criteria for patient off-protocol could be:

- Age > 60
- Tumor size <2.5 cm
- Lymph node status: negative
- Histology: non-lobular and negative margin (>2 mm)

Patient selection



Consensus “Partial Breast Irradiation”

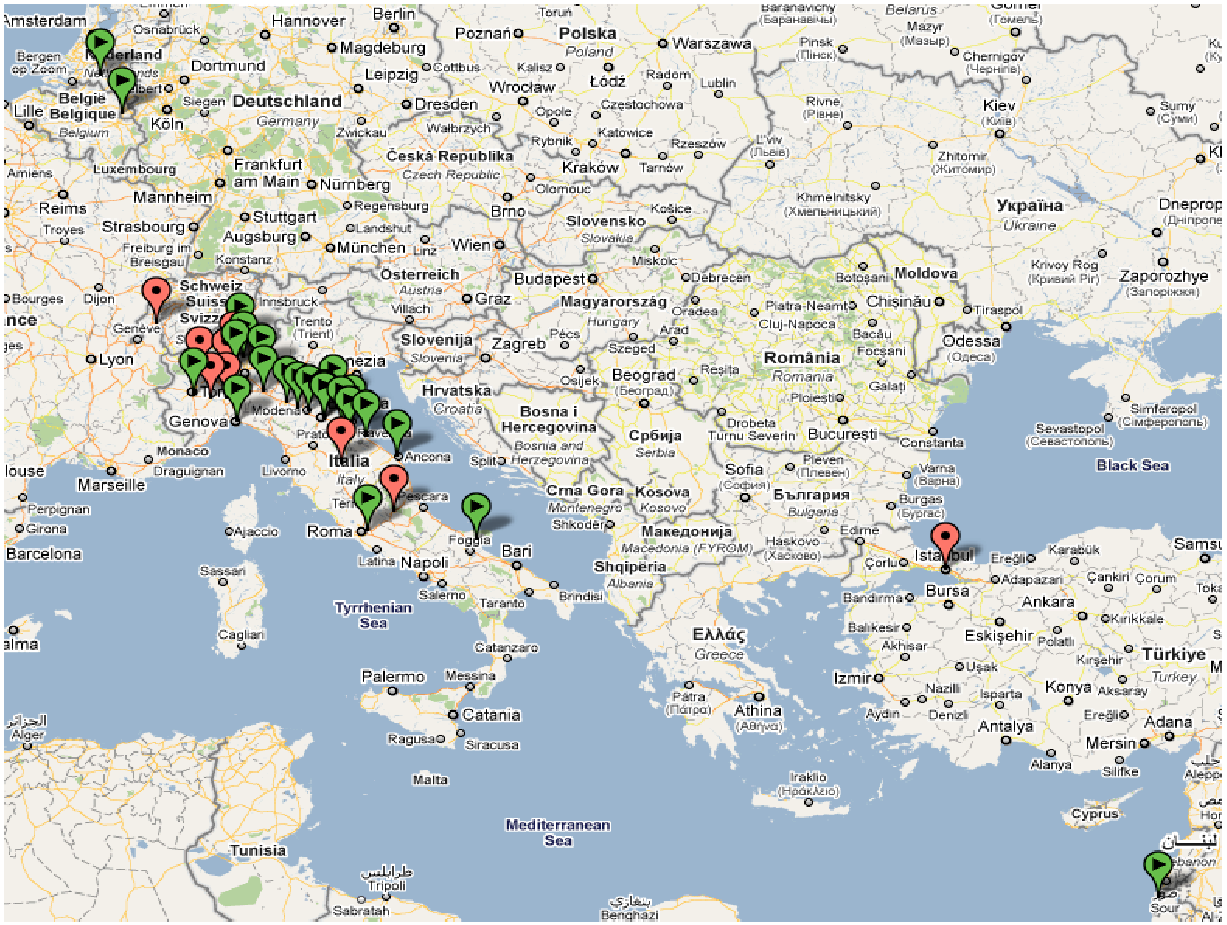
Comitato di coordinamento: L. Cataliotti, R. Orecchia, L. Marotti

Chair: Roberto Orecchia (Milano)

Trial	Trial Design	N	Inclusion	Control Arm	APBI technique (Experimental Arm)	Status
TARGIT [123]	Equivalence	2232	≥ 45 years T1 small T2, N0, 1, Ductal	WBI as per institutional guidelines	IORT, Low energy X-rays 50 KV, 20 Gy/1 fraction	Started March 2000, completed enrollment march 2010
ELIOT [115]	Equivalence	824	≥ 66 years Invasive carcinoma T ≤ 2.5 cm, pN0, Quadrantectomy	WBI 50 Gy/25 fractions + optional 10 Gy Boost	IOERT 21 Gy/1 fraction electrons up to 9 MeV	Started in Dec 2000
GEC-ESTRO	Non-inferiority, non irrelevant, 3% difference	1170	≥ 40 years stages 0-II ductal/lobular carcinoma T ≤ 3 cm, pN0-pNmi, margin ≥ 2 mm	WBI 50 Gy/25 fractions/5 weeks + optional 10 Gy boost	MIB 34 Gy/10 fractions HDR, 30.3 Gy/7 fractions HDR, 50 Gy PDR	Started 2004
NSABP/ RTOG 0413	Equivalence	4300	≥ 18 years stage 0, I, II (T < 3 cm) DCIS or invasive adenocarcinoma, ≤ 3 nodes positive, Margin negative	WBI 50-50.4 Gy/25-28 fractions, optional 10- 16 Gy boost	MIB Mammosite 34 Gy/10 fractions (5-10 days) 3D EBCRT 38.5 Gy/10 fractions (5-10 days)	Started in 2005 (accrual now closed to low risk patients)
RAPID	Equivalence	2128	≥ 40 years DCIS or invasive carcinoma T< 3 cm, margin negative, node negative, not BRCA 1/ BRCA 2	WBI 42.5 Gy/16 fractions/22 days (small breast) 50 Gy/25 fractions/35 days (large breast plus optional boost 10 Gy/4-5 fractions	3D CRT 38.5 Gy/10 fractions (5-8 days) Minimum daily fraction separation 6 -8 hours	Started in January 2006
IMPORT-LOW	Non-inferiority	1935	≥ 50 years invasive adenocarcinoma (not lobular) T ≤ 3 cm, margin ≥ 2 mm, node negative	WBI 40 Gy/15 fractions/21 days	EBRT (IMRT) Arm 1 40 Gy/15 fractions to primary tumour region + 36 Gy/ 15 fractions to low risk region Arm 2 40 Gy/15 fractions to primary tumour region	Started in 2006
IRMA	Non-inferiority	n/a	≥ 49 years pT1-2 (< 3 cm) invasive carcinoma pN0- N1 Margins ≥ 2 mm	WBI 45 Gy/18 fractions, or 50 Gy/25 fractions, or 50,4 Gy/ 28 fractions	3D CRT 38.5 Gy total in 10 fractions (3.85 Gy per fraction), twice a day with an interval of at least 6 hours	Started in 2007

Ongoing 3D CRT Phase III trial

IRMA Trial



www.irmatrial.it

Reserved Area

Username:

Password:

Login

IRMA Trial

Documentation:

Trial synopsis

If you are interested to participate to the trial, please download: participation request notes and the: protocol participation form
fill in all fields of the form and send to the fax number reported on it

Operative Units of Radiotherapy involved into IRMA trial

ANCONA
BELLINZONA
BOLOGNA AOSP
BOLOGNA AUSL
CASTELLANZA
COMO
COTIGNOLA
FERRARA
GENOVA
HAIFA
MELDOLA
MODENA
PARMA
PIACENZA
RAVENNA
REGGIO EMILIA
RIMINI
ROMA Unicampus
SAN GIOVANNI ROTONDO
TREVIGLIO
TORINO
VITERBO

IRMA Trial

Selection Criteria

- Stage I, II breast cancer >49 ys
- Invasive adenocarcinoma
- Tumor size $\leq$ 3 cm (unifocal)
- N-0, N-1 ($\leq$ 3 positive nodes)
- Negative margins ($\geq$ 2mm)
- Lumpectomy/whole breast ratio on CT $\leq$ 30%
- Lumpectomy cavity marked with at least 3 clips

Technique

- GTV: seroma cavity and surgical clips
- CTV: GTV with a 1.5 cm margin limited by 0.5 cm from the skin and chest wall
- PTV: CTV with 1 cm uniform 3D expansion
- 3-5 non-coplanar beams
- 3.85 Gy twice daily to a total dose of 38.5 Gy delivered within 1 week

IRMA Trial

Primary Endpoint:

- Ipsilateral breast tumor recurrence

Secondary endpoints:

- Recurrence free survival
- Distant disease-free survival
- Overall survival
- QoL: Cosmesis

IRMA Trial

Start: May 2007

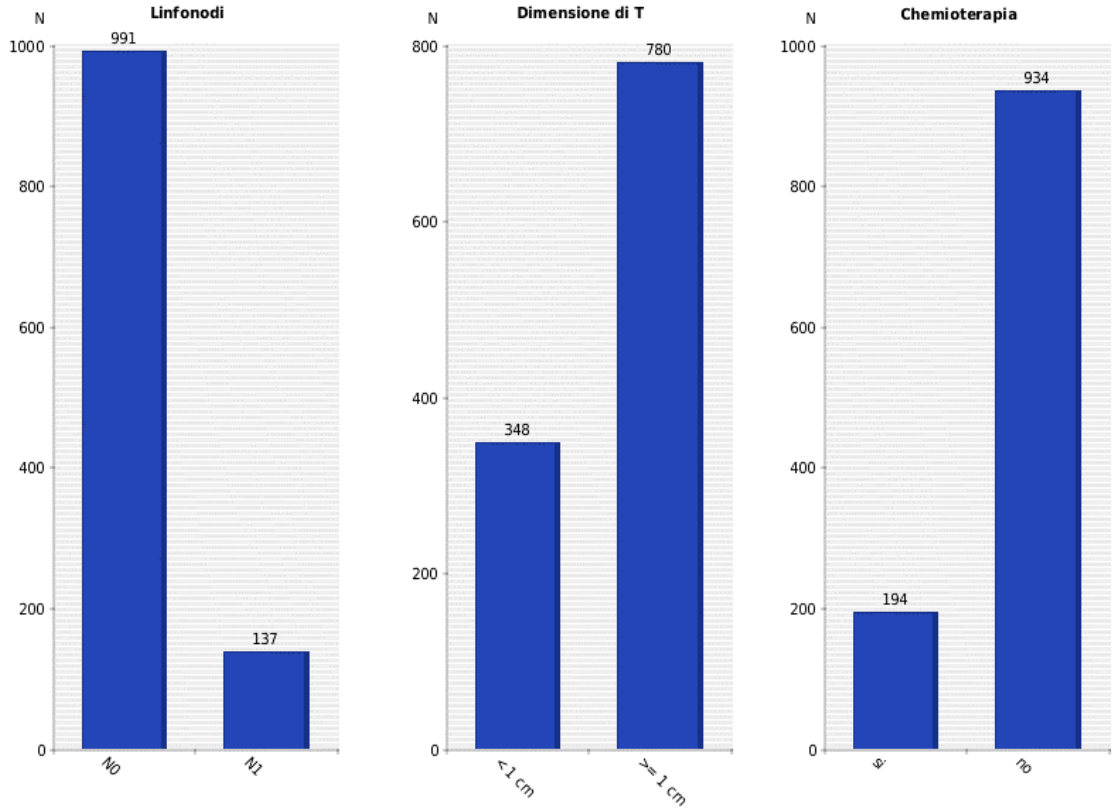
Current accrual: 1128

WBI Arm => 563

- Average age: 63.6 ys

PBI Arm => 565

- Average age: 63 ys



Conclusions

•Partial breast irradiation has to be considered an experimental technique, although there are beginning evidence for a role in the management of a selected group of early breast cancer

•3D CRT has significant potential for APBI, but further research is required to identify the optimal technique

Conclusions

- Patient selection is critical to the appropriate application of 3D CRT APBI
- The medical community has to wait for the phase III clinical trials demonstrating the efficay and safety of APBI

We have to enroll in ongoing phase III clinical trials