Dipartimento Scienze Oncologiche
U.O. di Radioterapia
Ospedale Bellaria

G.Frezza

"Il carcinoma mammario in stadio iniziale: Il razionale dell'irradiazione parziale"

Early stage breast cancer

- *Decrease of mortality rate in recent years*
- *Early diagnosis (screening programs)*
- *More efficient local and systemic treatment*
- *Conservative local approach*

LR AND SURVIVAL RATES IN RANDOMIZED TRIALS COMPARING CS WITH AND WITHOUT RT

	BREAST LR %		OVERALL SURVIVAL %		
TRIAL	CS	CS + RT	CS	CS + RT	FU
Upp- Orebro	24	9	78	78	10-y (act)
MILAN	23	6	92	92	5-y (act)
ONTARIO	40	18	72	74	10-y (act)
NSABP B-06	36	12	58	62	12-y (act)
NSABP B-21	12	6			6-y (crude)
SCOTTISH	28	6	85	88	5-y (act)
SWEBCG	14	4	94	94	5-y (act)

IMPACT OF RT IN INFILTRATING BC AFTER CONSERVATIVE SURGERY

Seven randomized trials have compared CS and CS + RT.

The trials vary with regard to patient selection, extent of surgery and RT, use of adjuvant therapy and follow-up.

Despite these differences, all trials confirmed an average 84% crude reduction of LR in the irradiated group.

VINH-HUNG STUDY
(JNCI 2004, 96 : 115-121)

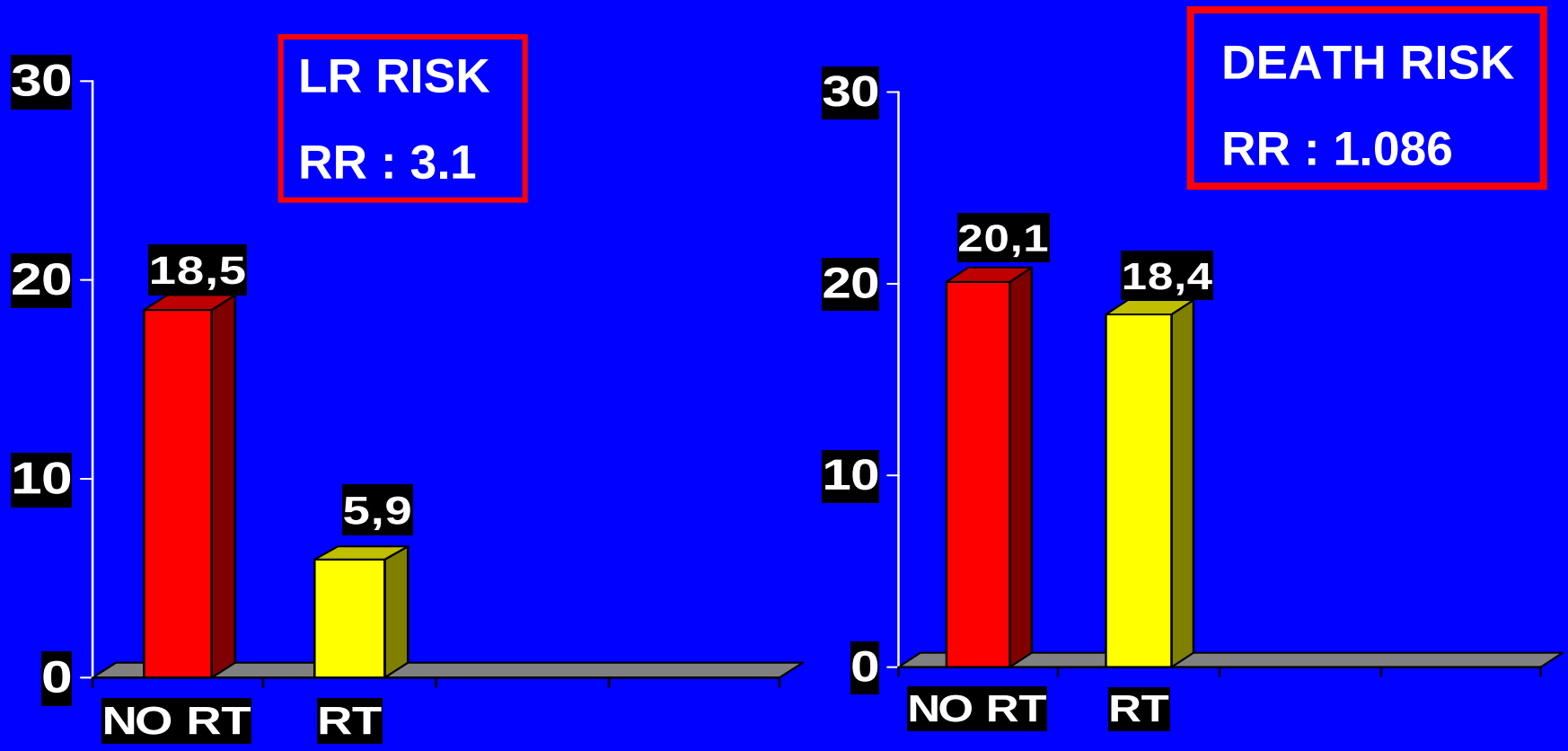
Analysis of randomized trials comparing conservative surgery without and with RT :

9422 patients included in 15 trials.

RR for patients without RT :

INFLUENCE OF RT USE ON LR AND MORTALITY. A POOLED-ANALYSIS

VINH-HUNG, JNCI 2004, 96 : 115-21



ANALYSIS OF 9422 PATIENTS IN 15 TRIALS

Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials

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

Lancet 2005; 366: 2087–2106

*Collaborators listed at end of report

Correspondence to:
EBCTCG secretariat,
Clinical Trial Service Unit (CTSU),
Richard Doll Building,
Old Road Campus,
University of Oxford,
Oxford OX3 7LF, UK
bc.overview@ctsu.ox.ac.uk

Summary

Background In early breast cancer, variations in local treatment that substantially affect the risk of locoregional recurrence could also affect long-term breast cancer mortality. To examine this relationship, collaborative meta-analyses were undertaken, based on individual patient data, of the relevant randomised trials that began by 1995.

Methods Information was available on 42 000 women in 78 randomised treatment comparisons (radiotherapy *vs* no radiotherapy, 23 500; more *vs* less surgery, 9300; more surgery *vs* radiotherapy, 9300). 24 types of local treatment comparison were identified. To help relate the effect on local (ie, locoregional) recurrence to that on breast cancer mortality, these were grouped according to whether or not the 5-year local recurrence risk exceeded 10% (<10%, 17 000 women; >10%, 25 000 women).

Findings About three-quarters of the eventual local recurrence risk occurred during the first 5 years. In the comparisons that involved little (<10%) difference in 5-year local recurrence risk there was little difference in 15-year breast cancer mortality. Among the 25 000 women in the comparisons that involved substantial (>10%) differences, however, 5-year local recurrence risks were 7% active versus 26% control (absolute reduction 19%), and 15-year breast cancer mortality risks were 44·6% versus 49·5% (absolute reduction 5·0%, SE 0·8, $2p<0·00001$).

These 25 000 women included 7300 with breast-conserving surgery (BCS) in trials of radiotherapy (generally just to the conserved breast), with 5-year local recurrence risks (mainly in the conserved breast, as most had axillary clearance and node-negative disease) 7% versus 26% (reduction 19%), and 15-year breast cancer mortality risks 30·5% versus 35·9% (reduction 5·4%, SE 1·7, $2p=0·0002$; overall mortality reduction 5·3%, SE 1·8, $2p=0·005$). They also included 8500 with mastectomy, axillary clearance, and node-positive disease in trials of radiotherapy (generally to the chest wall and regional lymph nodes), with similar absolute gains from radiotherapy; 5-year local recurrence risks (mainly at these sites) 6% versus 23% (reduction 17%), and 15-year breast cancer mortality risks 54·7% versus 60·1% (reduction 5·4%, SE 1·3, $2p=0·0002$; overall mortality reduction 4·4%, SE 1·2, $2p=0·0009$). Radiotherapy produced similar *proportional* reductions in local recurrence in all women (irrespective of age or tumour characteristics) and in all major trials of radiotherapy versus not (recent or older; with or without systemic therapy), so large *absolute* reductions in local recurrence were seen only if the control risk was large.

To help assess the life-threatening side-effects of radiotherapy, the trials of radiotherapy versus not were combined with those of radiotherapy versus more surgery. There was, at least with some of the older radiotherapy regimens, a significant excess incidence of contralateral breast cancer (rate ratio 1·18, SE 0·06, $2p=0·002$) and a significant excess of non-breast-cancer mortality in irradiated women (rate ratio 1·12, SE 0·04, $2p=0·001$). Both were slight during the first 5 years, but continued after year 15. The excess mortality was mainly from heart disease (rate ratio 1·27, SE 0·07, $2p=0·0001$) and lung cancer (rate ratio 1·78, SE 0·22, $2p=0·0004$).

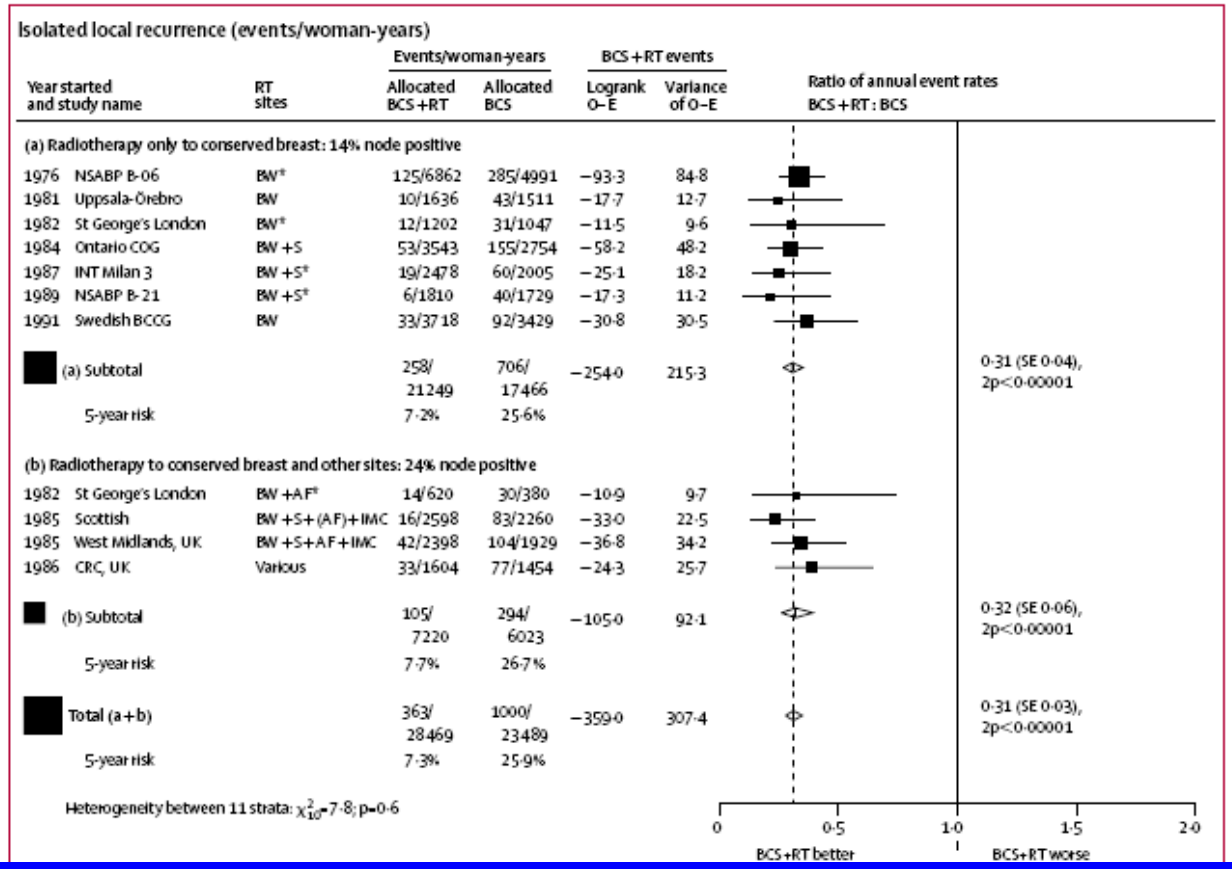
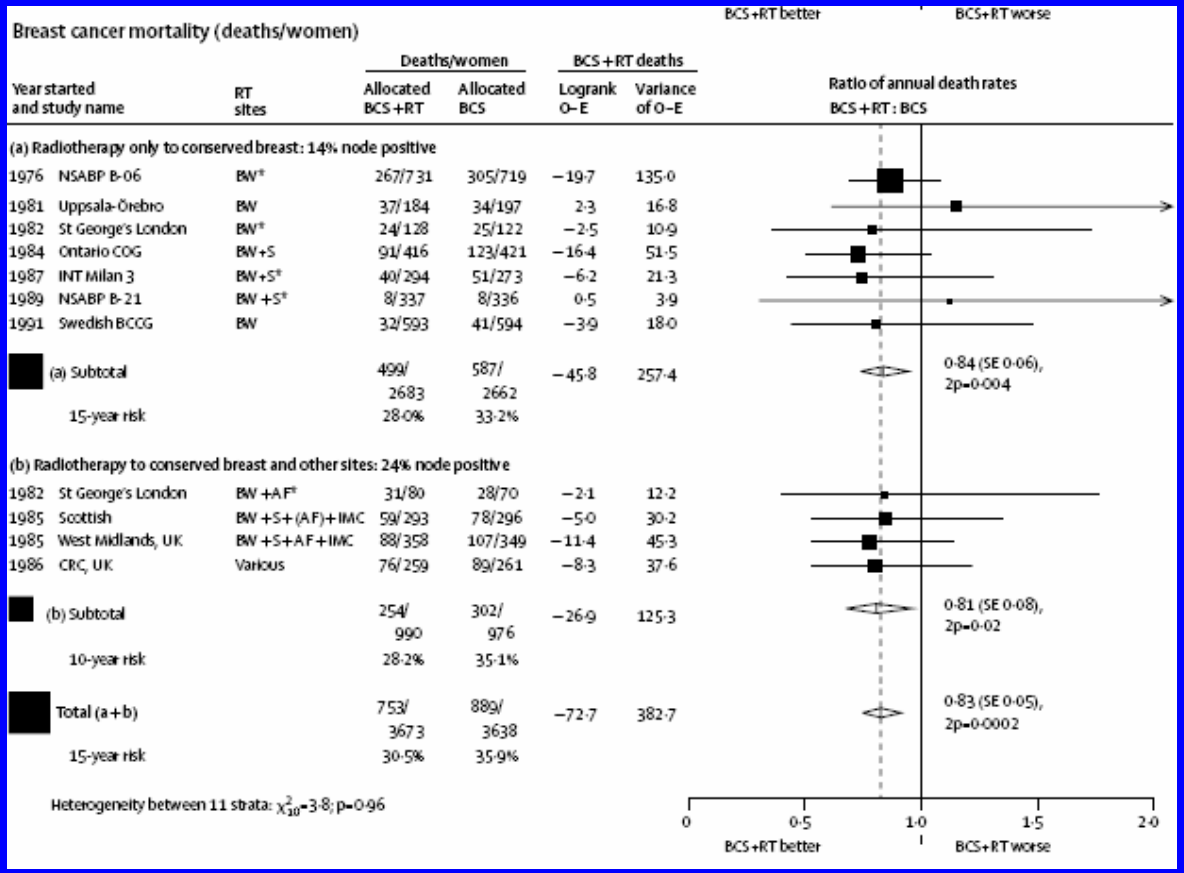


Figure 1: Effect of radiotherapy (RT) after BCS (ten trials) on local recurrence and on breast cancer mortality—event rate ratios
O–E=observed–expected.
BW=breast/chest wall.
S=scar (as site of RT boost).
AF=axilla/fossa.
IMC=internal mammary chain.
Sites in parentheses not always treated.

*Some systemic adjuvant therapy (same polychemotherapy and/or tamoxifen) in both groups.

99% CIs are given for trial-specific results (black squares) and 95% CIs are given for subtotals and totals (white diamonds).


Breast cancer mortality (deaths/women)
BCS+RT better
BCS+RT worse
Year started and study name
RT sites
Deaths/women
Allocated BCS+RT
Allocated BCS
BCS+RT deaths
Logrank O−E
Variance of O−E
Ratio of annual death rates
BCS+RT : BCS
(a) Radiotherapy only to conserved breast: 14% node positive
1976 NSABP B-06 BW* 267/731 305/719 −19·7 135·0
1981 Uppsala-Örebro BW 37/184 34/197 2·3 16·8
1982 St George's London BW* 24/128 25/122 −2·5 10·9
1984 Ontario COG BW+S 91/416 123/421 −16·4 51·5
1987 INT Milan 3 BW+S* 40/294 51/273 −6·2 21·3
1989 NSABP B-21 BW+S* 8/337 8/336 0·5 3·9
1991 Swedish BCCG BW 32/593 41/594 −3·9 18·0
(a) Subtotal 499/2683 587/2662 −45·8 257·4
0·84 (SE 0·06), 2p=0·004
15-year risk 28·0% 33·2%
(b) Radiotherapy to conserved breast and other sites: 24% node positive
1982 St George's London BW+AF* 31/80 28/70 −2·1 12·2
1985 Scottish BW+S+(AF)+IMC 59/293 78/296 −5·0 30·2
1985 West Midlands, UK BW+S+AF+IMC 88/358 107/349 −11·4 45·3
1986 CRC, UK Various 76/259 89/261 −8·3 37·6
(b) Subtotal 254/990 302/976 −26·9 125·3
0·81 (SE 0·08), 2p=0·02
10-year risk 28·2% 35·1%
Total (a+b) 753/3673 889/3638 −72·7 382·7
0·83 (SE 0·05), 2p=0·0002
15-year risk 30·5% 35·9%
Heterogeneity between 11 strata: χ^2_{10}=3·8; p=0·96
0
0·5
1·0
1·5
2·0
BCS+RT better
BCS+RT worse

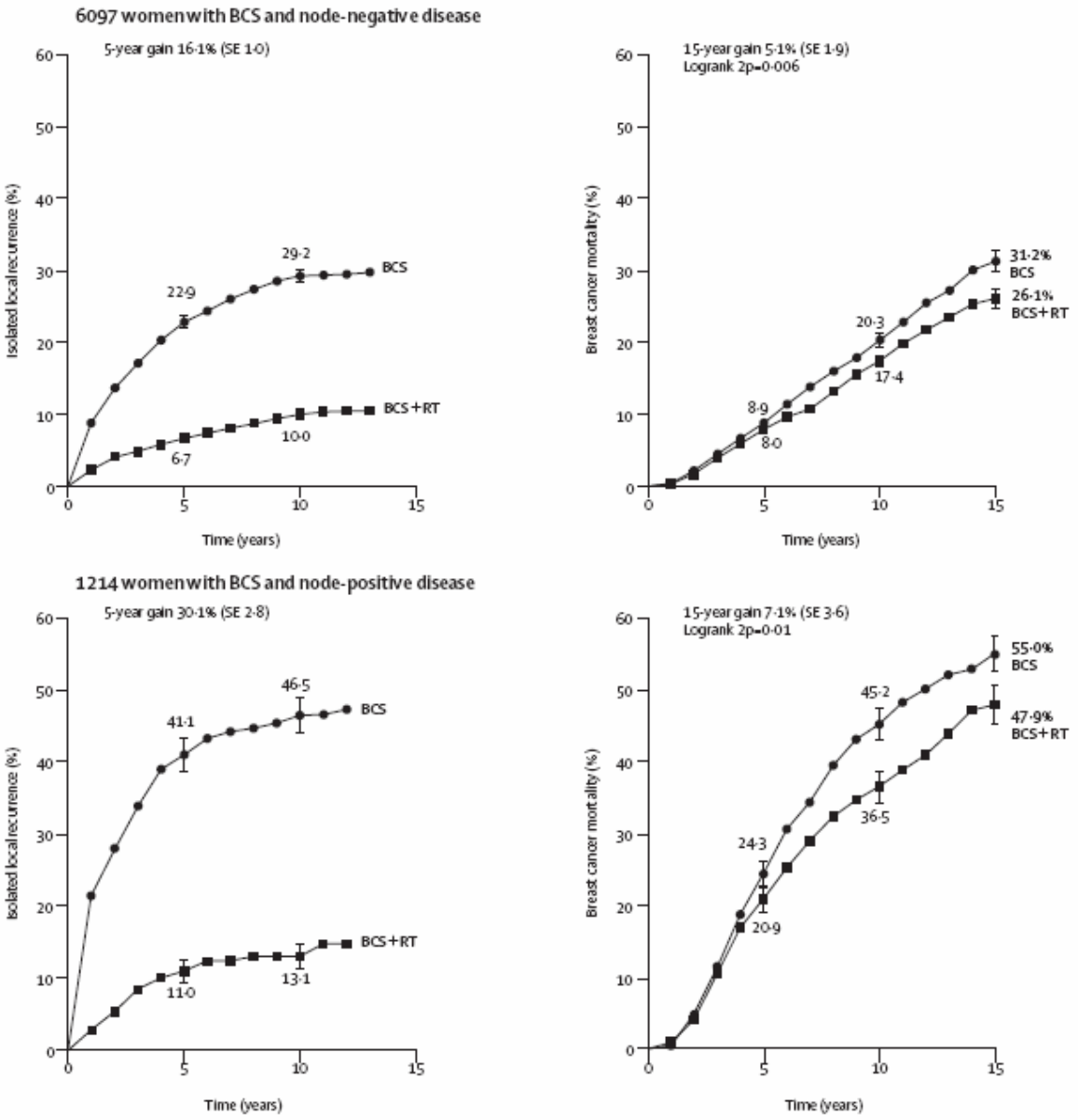
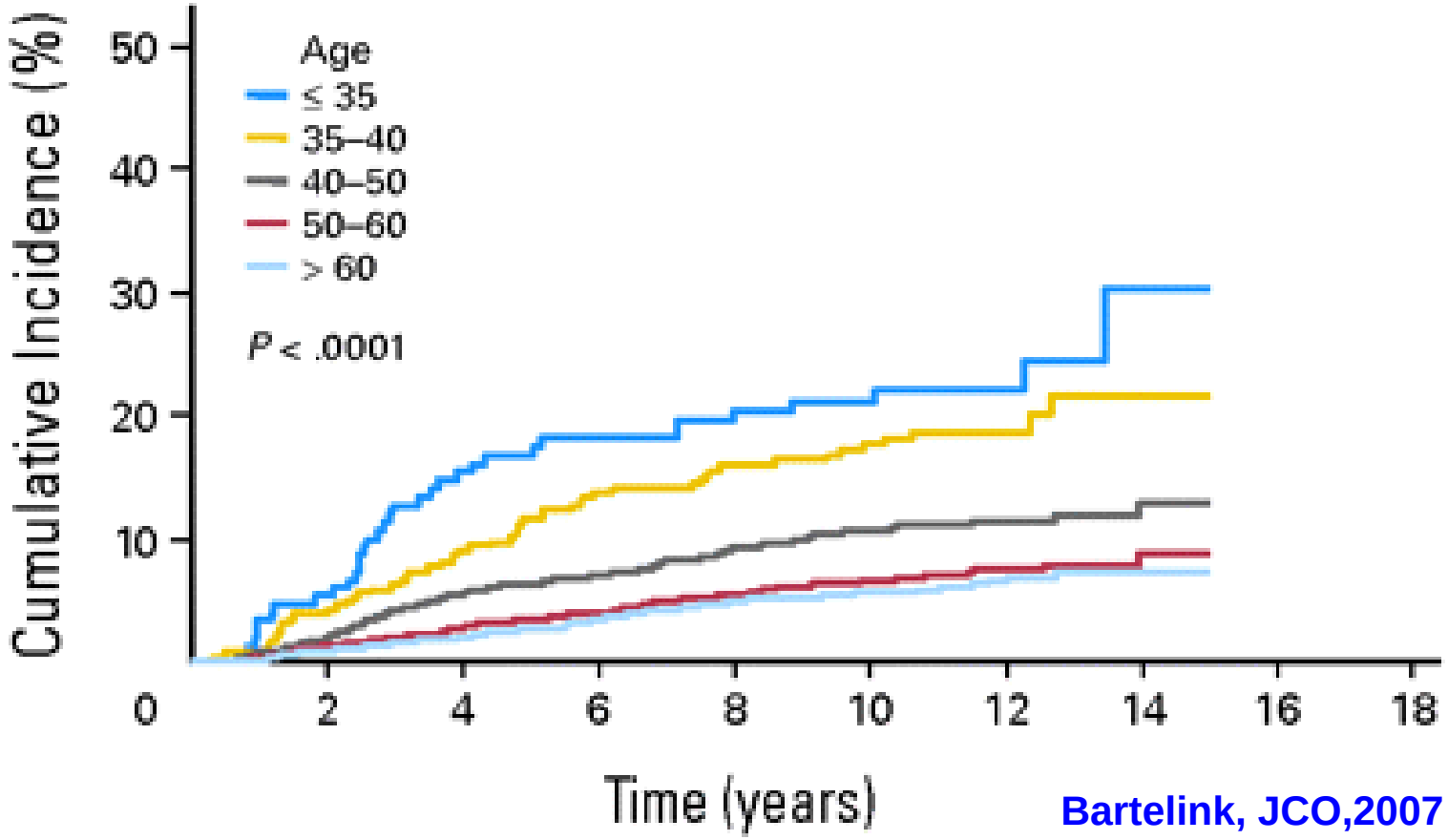


Figure 2: Effect of radiotherapy (RT) after BCS on local recurrence and on breast cancer mortality—15-year probabilities
Data from 10 trials. Vertical lines indicate 1 SE above or below the 5, 10, and 15 year percentages.

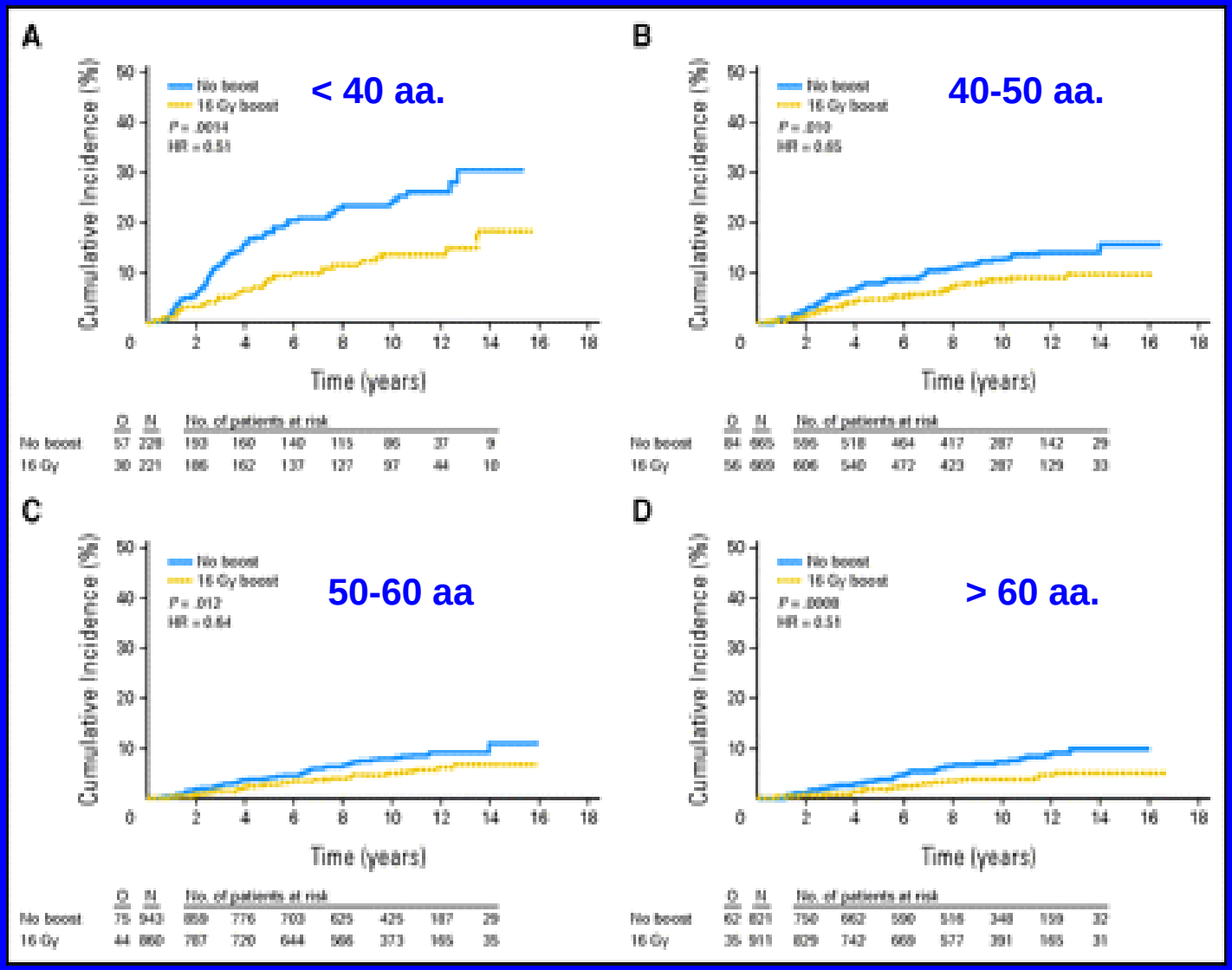
EORTC Trial design

- **Randomisation**
  - **No additional irradiation** — **2657 pts**
  - **16 Gy additional irradiation to the tumour bed** — **2661 pts**
- **Analysis by intention to treat**



Bartelink, JCO,2007

Age	O	N	No. of patients at risk						
≤ 35	34	154	127	101	88	75	56	25	6
35–40	53	295	252	221	189	167	127	56	13
40–50	140	1,334	1,201	1,058	936	840	574	271	62
50–60	119	1,803	1,646	1,496	1,347	1,191	798	351	64
> 60	97	1,732	1,579	1,404	1,259	1,093	739	324	63



Bartelink, JCO, 2007

Local Recurrence Risk Related to Microscopic Margin Status

Author	*% Local Recurrence*		*Interval (years)*
	Positive	Negative	
Vicini	4	7	6 (act)
Borger	16	2	5 (act)
Fein	5	4	5 (act)
Freedman	12	7	10 (act)
Bartelink	7	2	6 (act)
Clarke	9	4	5 (mean)
Park	14	7	8 ((crude)
Smitt	9	2	5 (act)
Pierce	10	3	5 (act)
Frazier	12	4	8 (med)
Heimann	11	2	5 (act)
Hartsell	11	2	---

8-Year Local Outcome Related to Margins of Resection

- JCRT Experience -

Margin Status	# Patients	% Local Recurrence	% D/R/0 Recurrence	% Died w/o Recurrence	%NED
Negative	204	7	25	4	63
Close	94	7	28	6	59
Focally Positive	122	14	25	7	54
> Focally Positive	66	27	35	3	35

Close = In-situ/Invasive < 1mm from inked surface (not at surface)

Focally Positive = In-situ/Invasive at inked surface (≤ 3 low power fields)

D/R/O = Distant or regional failure or opposite breast cancer

NED = No evidence of disease

IMPACT OF RT IN INFILTRATING BC AFTER CONSERVATIVE SURGERY

Age and margin status represent the most significant factors for local control after BCT: pts. with positive margins should be reexcised whenever possible; young pts. should receive a boost on the surgical bed after whole breast irradiation

Postmenopausal women with adequate excision represent a group with a low risk of recurrences in which alternative approaches to local treatment can be evaluated

Newer/Alternative Treatment Approaches

- **Efforts to reduce treatment time of RT after breast conserving surgery:**
  - ***Are more rapid fractionation schedules using increased daily whole breast fraction sizes 'acceptable'?***
  - **Is partial breast irradiation (accelerated treatment) an acceptable option?**

Major Studies Exploring the Use of Altered Fractionation Schedules to Reduce Overall Treatment Time with BCT

Series	*# Pts*	*Fractionation Schedule*	*Total Dose*	*Local Control*	*Cosmetic Result*
Ontario	294	2.5 Gy x 16 5 days/week	40 Gy	3.5% (5-yr)	77% Patients 'Satisfied'
British Columbia	186	2.75 Gy x 16 5 days/week	44 Gy	6% (5-yr)	89% Good/Excellent
Mayo Clinic	37	1.6 Gy bid x 30 1.6 Gy bid x 9 (Boost)	57.6 Gy	0%	87% Good/Excellent
Ontario Randomized Trial	622 612	2.66 Gy x 16 2.0 Gy x 25	42.5 Gy 50 Gy	2.87% 2.90%	No Significant Difference

Vicini/Harris 2003

Ontario Randomized Trial

- **1234 women randomized:**
  - *50 Gy in 25 fractions over 35 days (n=612)*
  - *42.5 Gy in 16 fractions in 22 days (n=622)*
- **Median Follow-up:**
  - *69 months*
- **5-Yr Local Recurrence:**
  - *2.8% (short-arm) vs 3.2% (long-arm)*
- **5-Yr Good/Excellent Global Cosmetic Outcome:**
  - *76.8% (short arm) vs 77.0% (long-arm)*

Vicini/Harris 2003

Conclusions from Studies Exploring the Use of Altered Fractionation Schemes to Reduce Overall Treatment Time with BCT

- Although preliminary results are good, there is concern that the larger fraction sizes in these trials may translate into increased late toxicity and a deterioration in the long-term cosmetic result.
- Long-term results from these trials are needed.
- United Kingdom is currently exploring:
  - **41.5 Gy in 13 fractions over 5 weeks (3.2 Gy/day)**
  - **39 Gy in 13 fractions over 5 weeks (3.0 Gy/day)**
  - **40 Gy in 15 fractions over 3 weeks (2.7 Gy/day)**

Vicini/Harris 2003

START A and START B trials

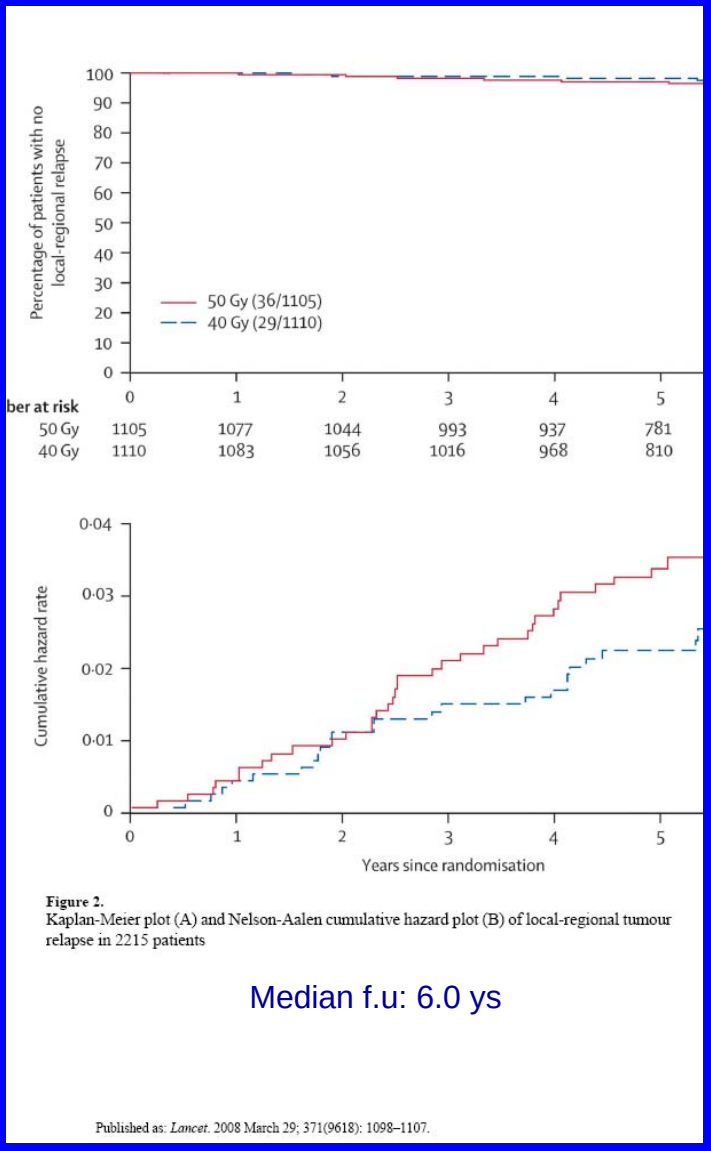


Figure 2.
Kaplan-Meier plot (A) and Nelson-Aalen cumulative hazard plot (B) of local-regional tumour relapse in 2215 patients

Median f.u: 6.0 ys

Published as: *Lancet*. 2008 March 29; 371(9618): 1098–1107.

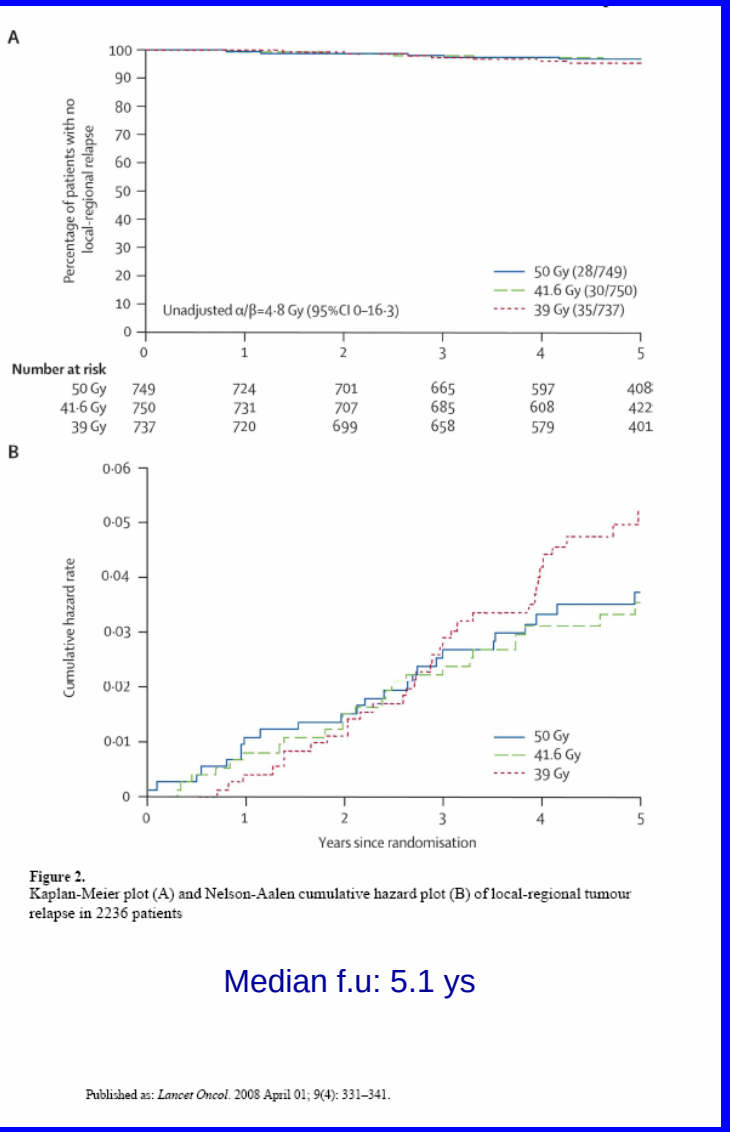
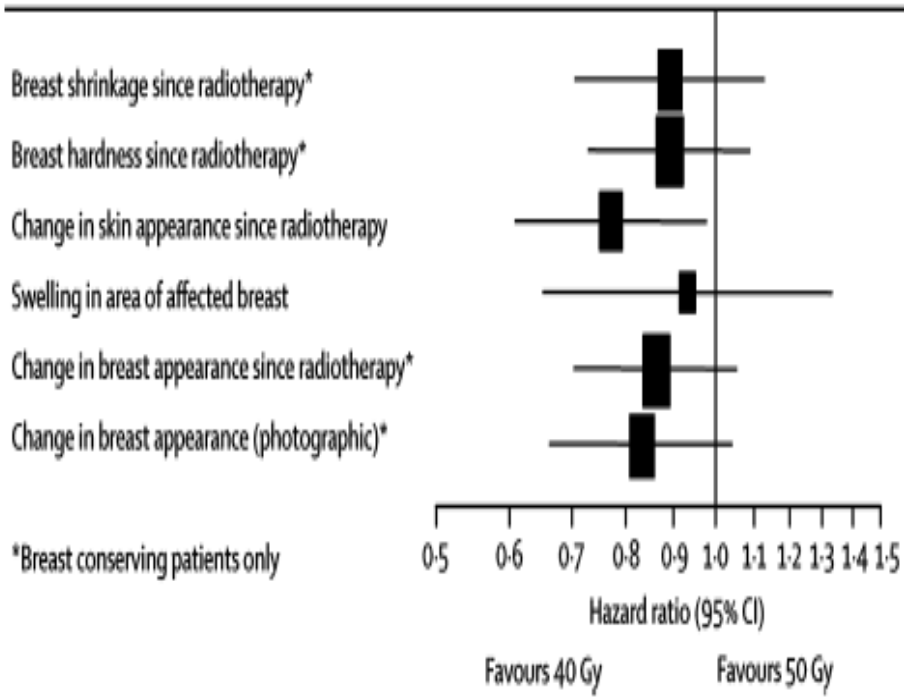


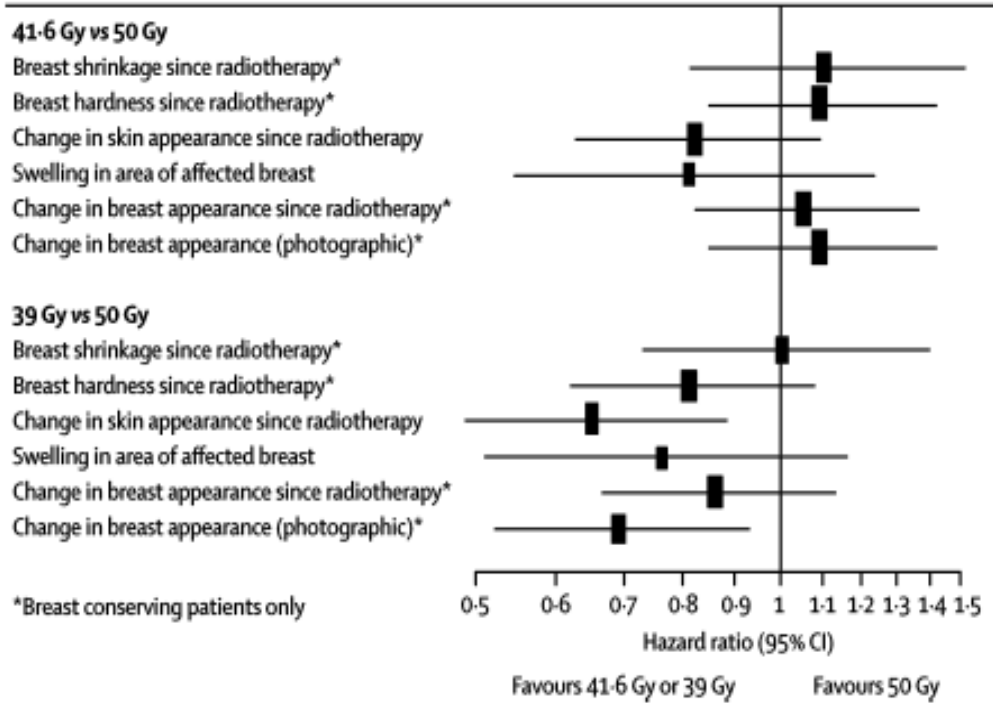
Figure 2.
Kaplan-Meier plot (A) and Nelson-Aalen cumulative hazard plot (B) of local-regional tumour relapse in 2236 patients

Median f.u: 5.1 ys

Published as: *Lancet Oncol*. 2008 April 01; 9(4): 331–341.

START A and START B trials





WBI can be performed increasing the dose per fraction according to one of the schemes described in the recent literature (Ontario trial, START trial)

Newer/Alternative Treatment Approaches

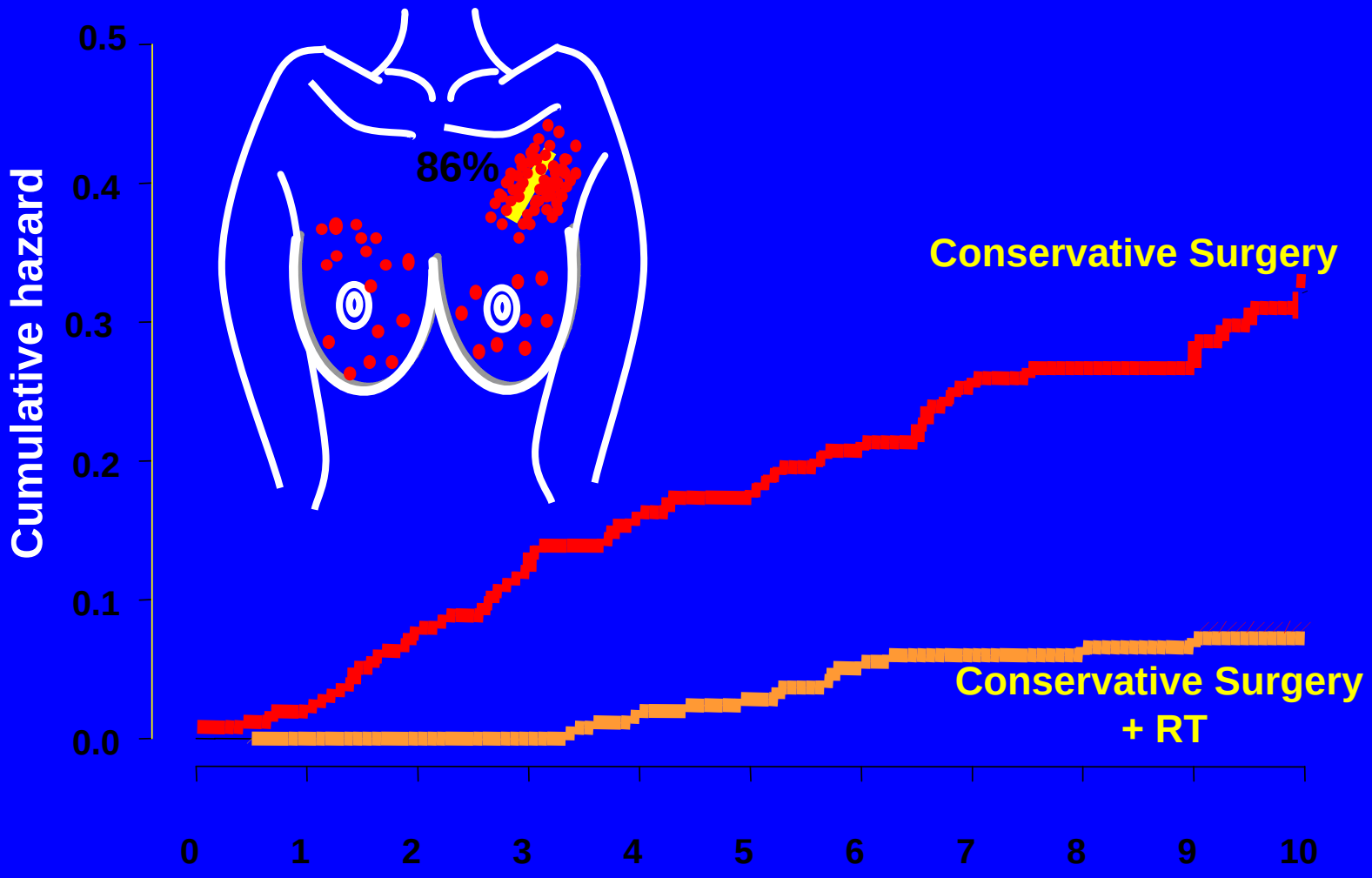
- **Efforts to *reduce treatment time* of RT after breast conserving surgery:**
  - **Are more rapid fractionation schedules using increased daily fraction sizes 'acceptable'?**
  - ***Is partial breast irradiation (accelerated treatment) an acceptable option?***

Scientific Rationale

- Partial Breast Irradiation -

- >80-90% Of Recurrences After BCT Occur In The Tumor Bed Region
- Whole Breast RT May Not Be Needed In 'Appropriately' Selected Patients
- Recurrences Away From Tumor Bed ('Elsewhere' Failures) Are Rare After Lumpectomy Alone Or Followed By Whole Breast RT

Milan III – Local Recurrences



Veronesi U et al,
Ann Oncol, 2004

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

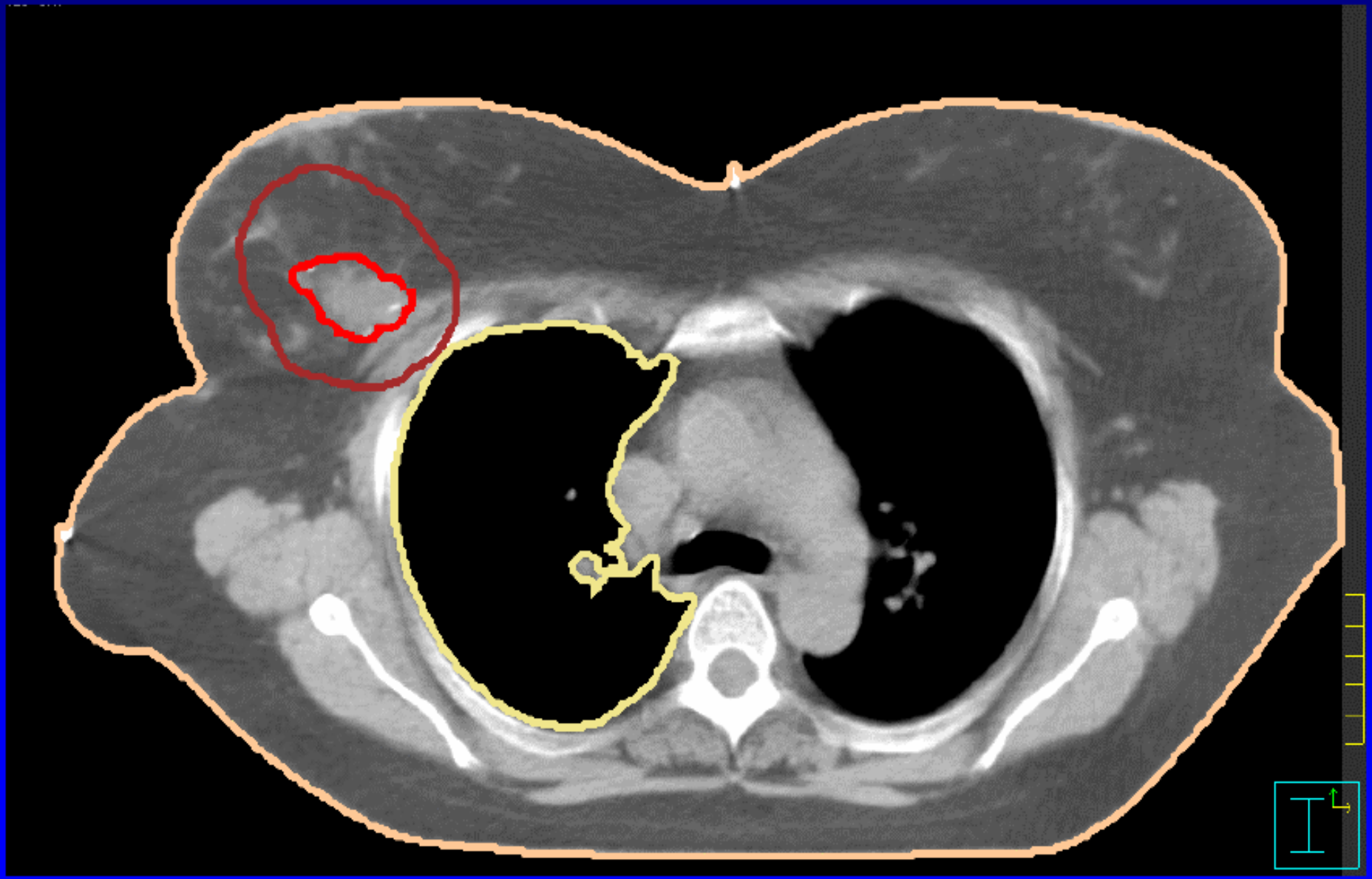
Abbreviations: LR, local recurrence; BCT, breast-conservation therapy; XRT, radiation therapy.

Partial Breast Irradiation Studies Exploring Reductions In Overall Treatment Time

- **Brachytherapy Trials**
  - **Low dose rate studies (RTOG 95-17- Completed accrual)**
  - **High dose rate studies (RTOG 95-17 Completed accrual)**
- **External Beam Radiotherapy Trials**
  - **3D conformal RT (RTOG 0319)**
  - **Conventional external beam RT (electrons)**
  - **Intraoperative RT (European Institute of Oncology)**

Partial Breast Irradiation Target

- 1.5 cm Beyond Lumpectomy Cavity -



- Partial Breast Irradiation -

SELECTION CRITERIA

- Objectives -

- Identify Patients With Minimal Risk Of Multicentric Disease (Avoid 'Elsewhere' Failures)
- Select Tumors With Low Probability Of Microscopic Extension Beyond 1-2 cm From Primary
- Avoid Controversy Associated With RT To Axilla
- Apply Optimal Mammographic Evaluation

AJR
WOMEN'S IMAGING

Breast MRI in the Evaluation of Eligibility for Accelerated Partial Breast Irradiation

Juan Godinez[1]
Eva C. Gombos[2]
Sona A. Chikarmane[2]
Gabriel K. Griffin[3]
Robyn L. Birdwell[2]

OBJECTIVE. Eligibility for accelerated partial breast irradiation is generally determined by physical examination in conjunction with conventional imaging techniques such as mammography and breast sonography. MRI is recognized as a significant imaging tool in diagnosing breast cancer and has shown the ability to identify mammographically occult carcinoma. Our purpose was to retrospectively assess preoperative breast MRI examinations in women with early-stage breast cancer who were theoretically eligible for accelerated partial breast irradiation and to explore the use of MRI in selecting patients for this treatment.

MATERIALS AND METHODS. Seventy-nine patients with core needle biopsy-proven breast cancer, who were eligible candidates for breast-conserving surgery and accelerated partial breast irradiation, underwent bilateral breast MRI examinations. At review, the presence and location of occult tumor sites (detected on MRI only) were documented and subsequently correlated with pathology findings.

RESULTS. From 79 patients, a total of 126 suspicious areas, including the index tumors, were detected by MRI. Additional sites of cancer other than the index tumor were observed in 30 patients (38%). Of these, eight (10%) had an additional cancer in a different quadrant from the index tumor.

CONCLUSION. The treatment effect of whole-breast irradiation on microscopic tumor cells and on additional occult foci in other quadrants of the breast is lost with partial breast irradiation. Our results suggest that MRI before accelerated partial breast irradiation may be of benefit to patients to ensure they do not have multifocal or multicentric disease, remote from the lumpectomy bed.

Keywords: accelerated partial breast irradiation, breast carcinoma, MRI

DOI:10.2214/AJR.07.3465

TABLE 2: Patient Characteristics and Likelihood of Additional Malignant Foci[a]

Characteristic	Patients			*p*
	Total No.	% Having Additional Foci	% Having Additional Foci in Quadrant Other Than Index Cancer	
All patients	79	38.0 (30/79)	10.1 (8/79)	
Age < 40 years	28	50.0 (14/28)	14.3 (4/28)	0.103
Age ≥ 40 years	51	31.4 (16/51)	7.8 (4/51)	0.444[b]
High risk[c]	29	41.4 (12/29)	10.3 (3/29)	0.635
Average risk and no family history	50	36.0 (18/50)	10.0 (5/50)	1.000[b]

Note—Numbers in parentheses are numbers of patients.
[a]As determined by final pathology.
[b]Calculated using Fisher's exact test because of small expected values.
[c]Based on family history of breast cancer (first-degree relative) or germline mutation.

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ORIGINAL REPORT

Relationship of Breast Magnetic Resonance Imaging to Outcome After Breast-Conservation Treatment With Radiation for Women With Early-Stage Invasive Breast Carcinoma or Ductal Carcinoma in Situ

Lawrence J. Solin, Susan G. Orel, Wei-Ting Hwang, Eleanor E. Harris, and Mitchell D. Schnall

From the Departments of Radiation Oncology, Radiology, and Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, PA.

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Lawrence J. Solin, MD, FACR, Department of Radiation Oncology, Hospital of the University of Pennsylvania, 3400 Spruce St, Philadelphia, PA 19104; e-mail: solin@xrt.upenn.edu.

0732-183X/08/2603-386/$20.00

DOI: 10.1200/JCO.2006.09.5448

A B S T R A C T

Purpose
To determine the relationship of breast magnetic resonance imaging (MRI) to outcome after breast-conservation treatment (BCT) with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ.

Patients and Methods
A total of 756 women with early stage invasive breast carcinoma or ductal carcinoma in situ underwent BCT including definitive breast irradiation during 1992 to 2001. At the time of initial diagnosis and evaluation, routine breast imaging included conventional mammography. Of the 756 women, 215 women (28%) had also undergone a breast MRI study, and 541 women (72%) had not undergone a breast MRI study. The median follow-up after treatment was 4.6 years (range, 0.1 to 13.5 years).

Results
For the women with a breast MRI study compared with the women without a breast MRI study there were no differences in the 8-year rates of any local failure (3% *v* 4%, respectively; $P = .51$) or local-only first failure (3% *v* 4%, respectively; $P = .32$). There were also no differences between the two groups for the 8-year rates of overall survival (86% *v* 87%, respectively; $P = .51$), cause-specific survival (94% *v* 95%, respectively; $P = .63$), freedom from distant metastases (89% *v* 92%, respectively; $P = .16$), or contralateral breast cancer (6% *v* 6%, respectively; $P = .39$).

Conclusion
The use of a breast MRI study at the time of initial diagnosis and evaluation was not associated with an improvement in outcome after BCT with radiation.

J Clin Oncol 26:386-391. © 2008 by American Society of Clinical Oncology

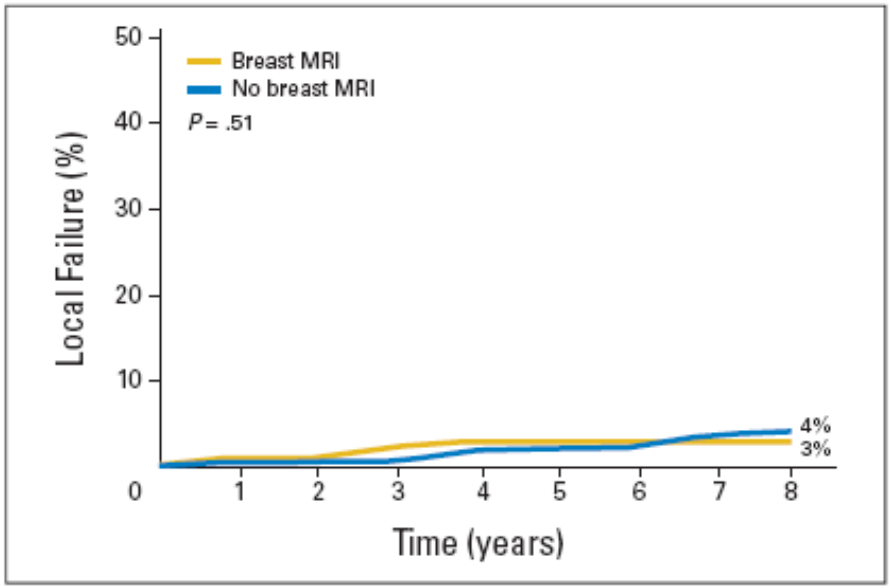
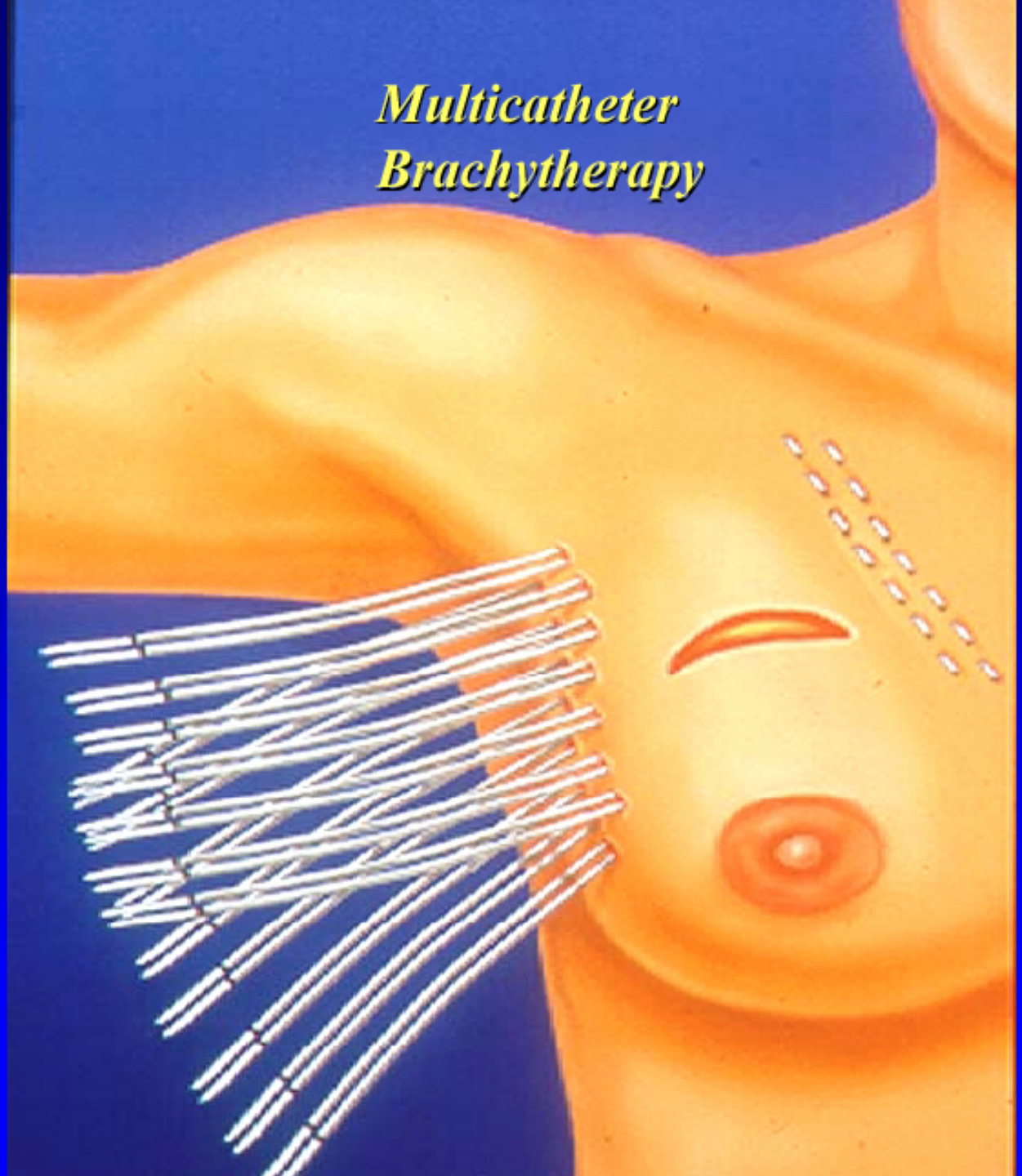


Fig 1. Curves for any local failure according to the use of breast magnetic resonance imaging (MRI) at the time of initial diagnosis and evaluation for breast conservation treatment with radiation.

Partial Breast Irradiation Techniques

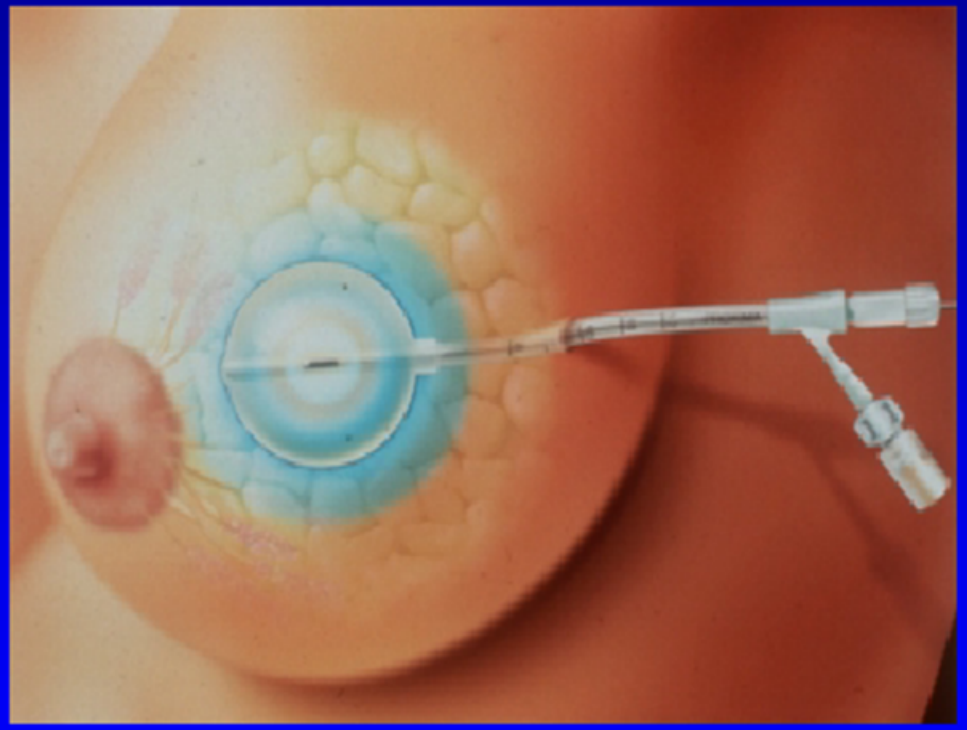
- **Interstitial Brachytherapy**
- **MammoSite Balloon Brachytherapy Catheter**
- **3D Conformal External Beam Irradiation**

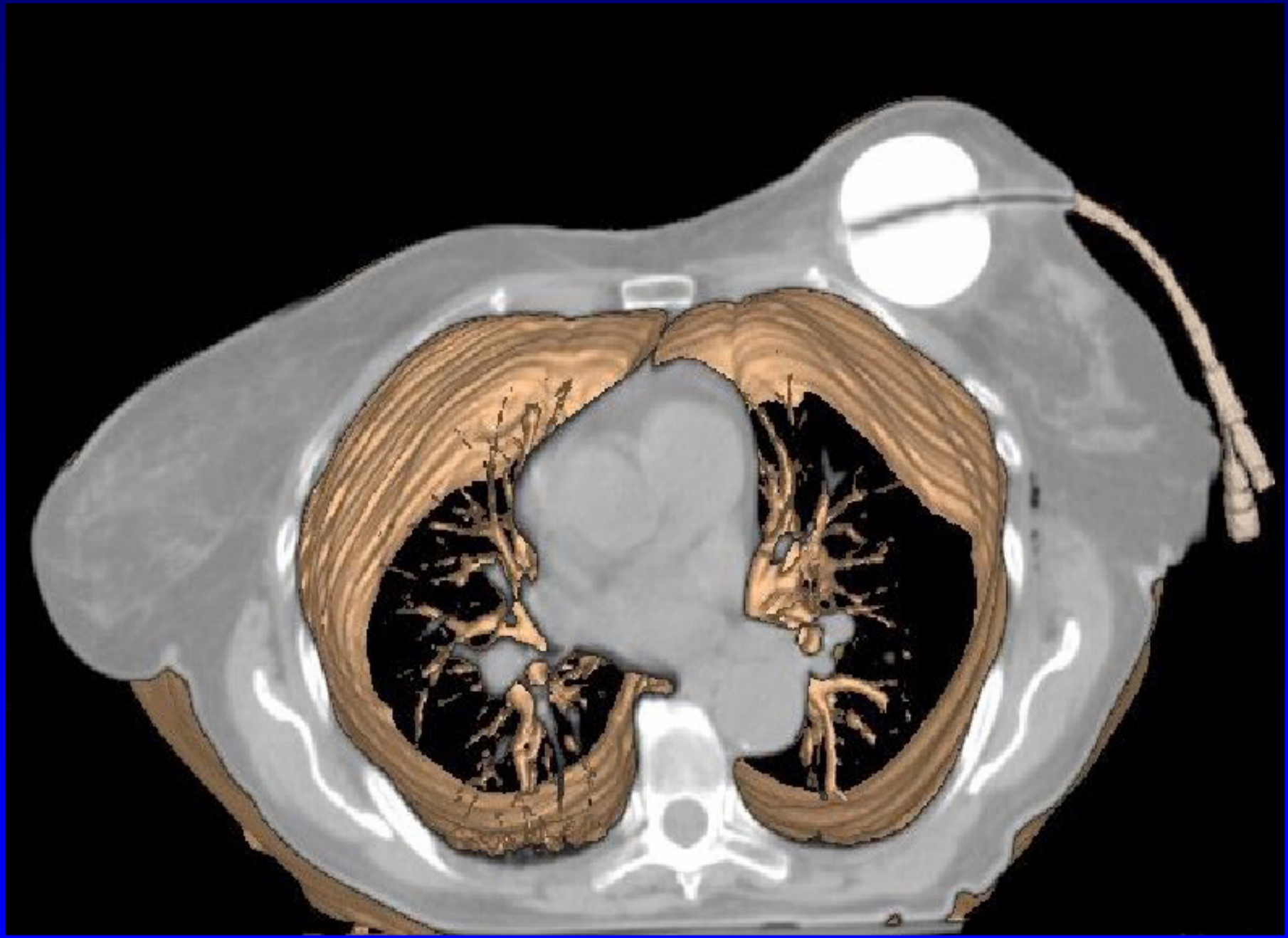

Multicatheter
Brachytherapy

Balloon Catheter

'MammoSite'

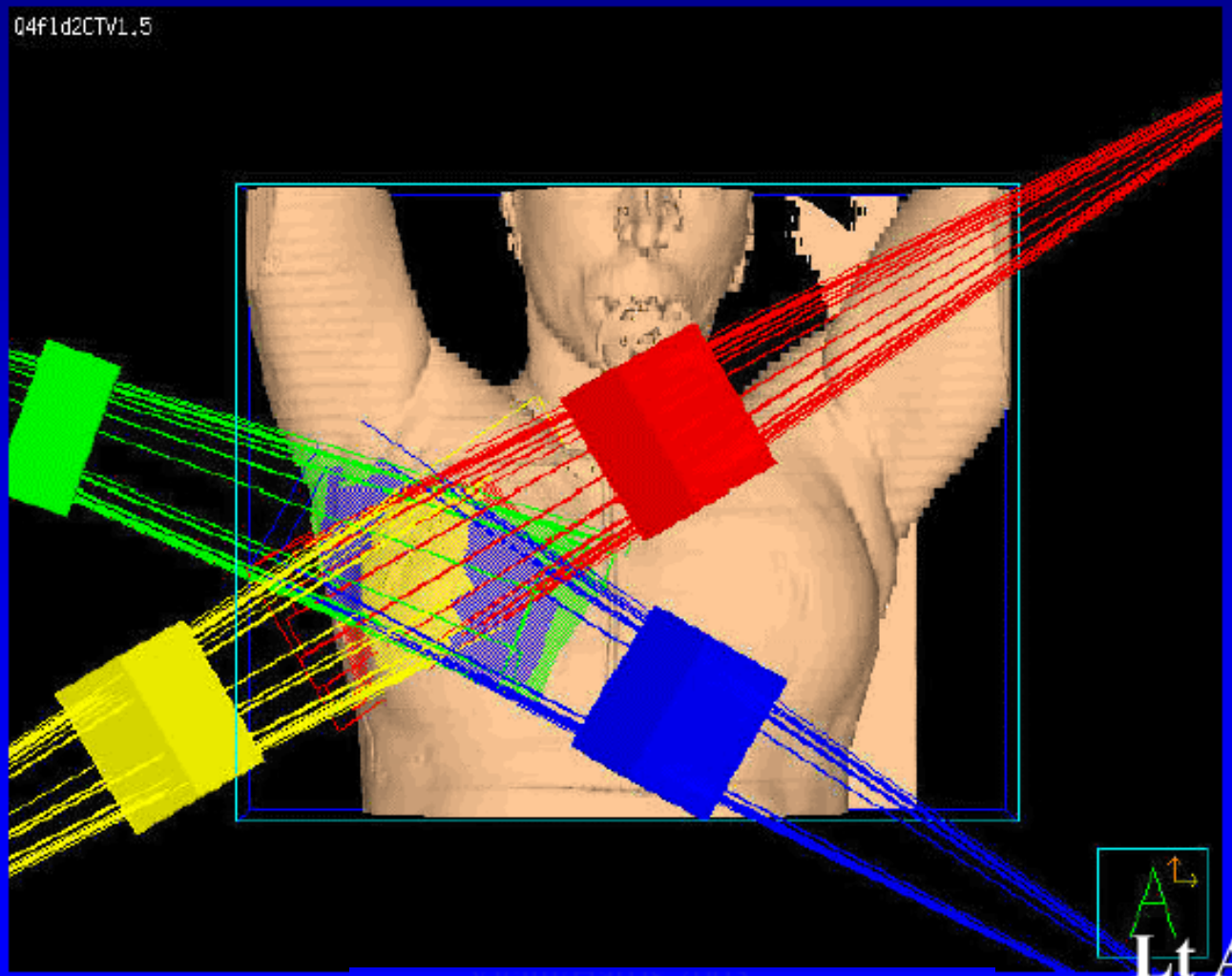
- MammoSite device
- Inflatable Balloon Placed In Lumpectomy Cavity At Surgery
- Remote Afterloading
- 3400 cGy (340 cGy X 10) in 5 days
- 43 Patients Treated
- *FDA approval May 2002*





Partial Breast Irradiation

- 3D Conformal External Beam Irradiation -



Lt ASIO

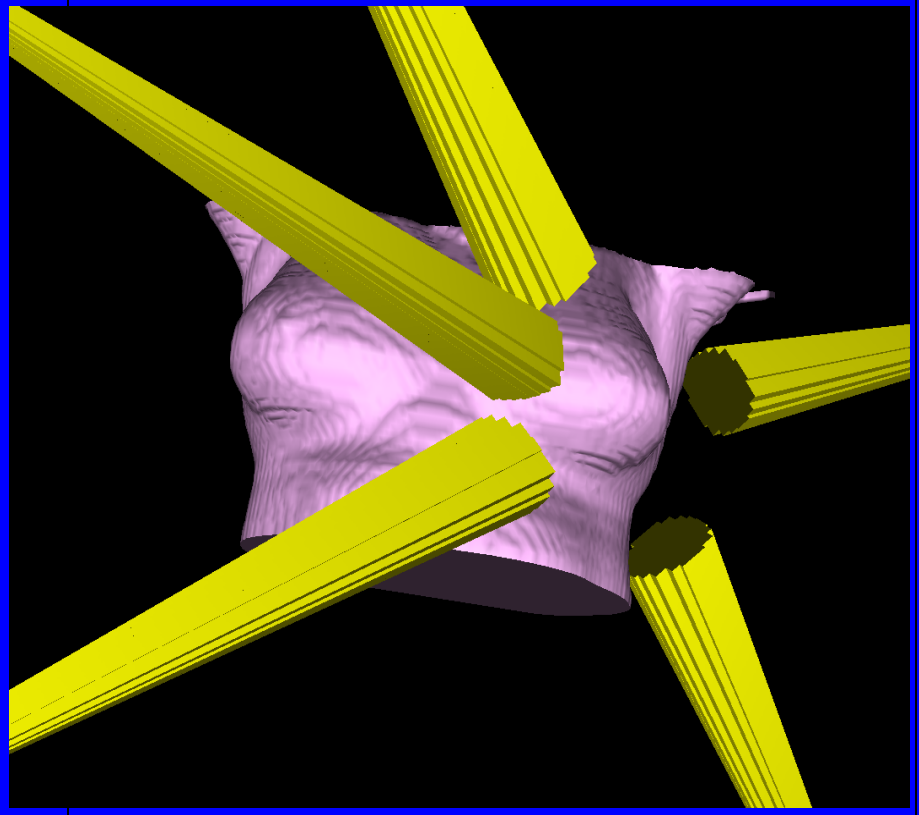
Rt PSIO

Rt AISO

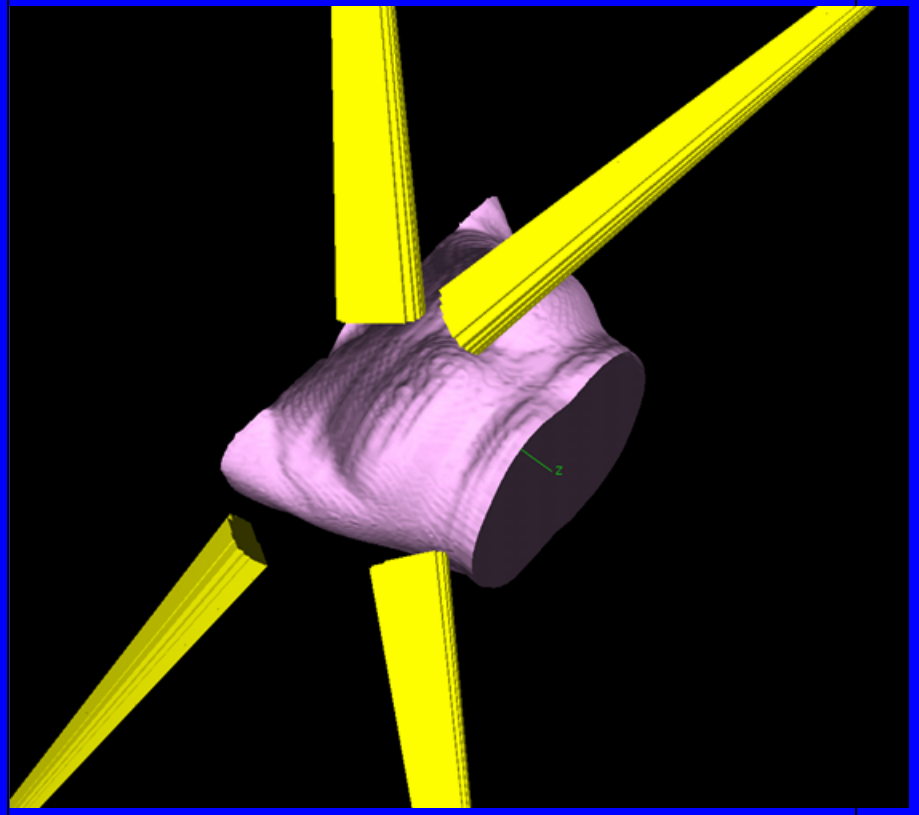
Lt AISO

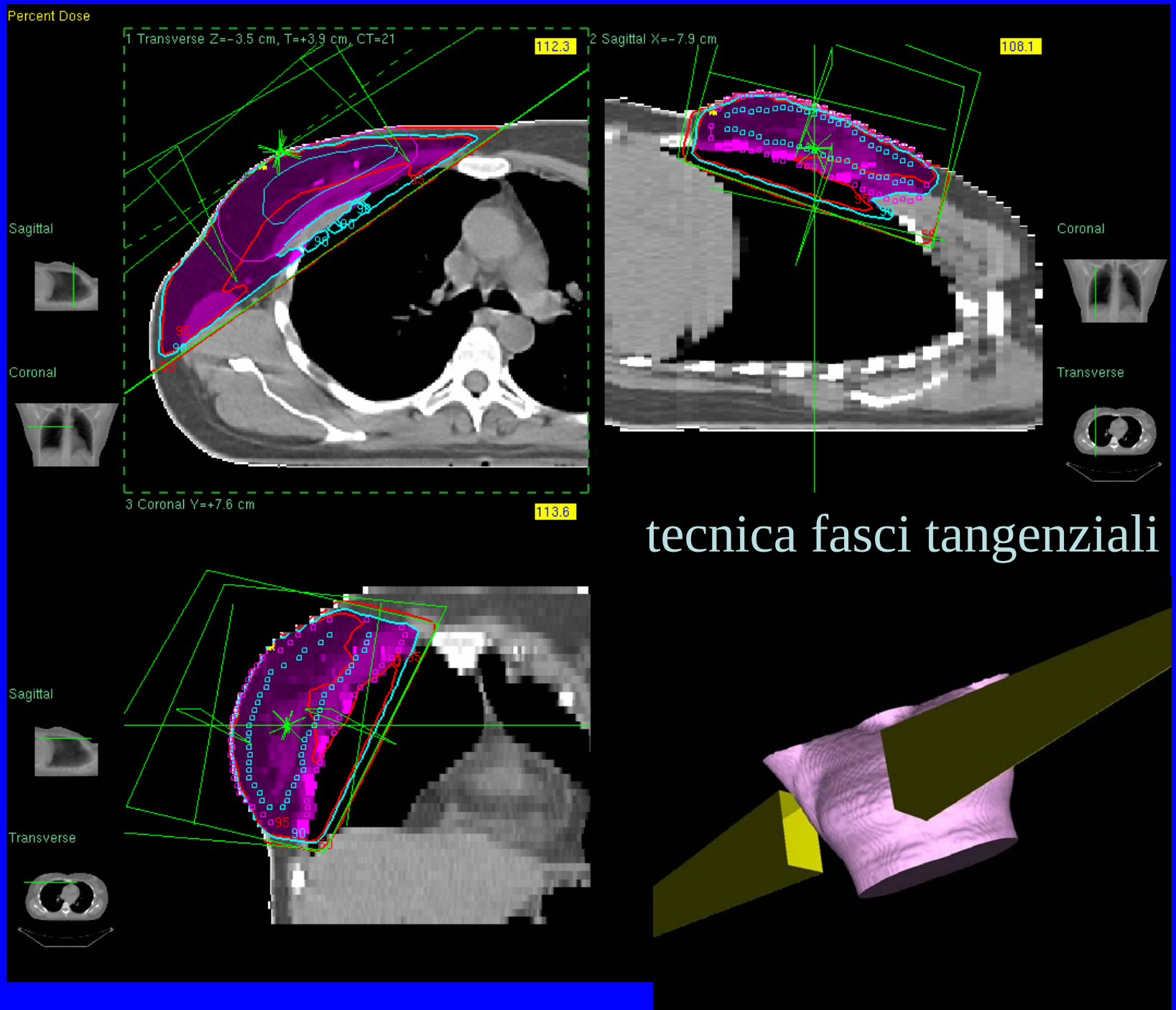
TECNICA di TRATTAMENTO

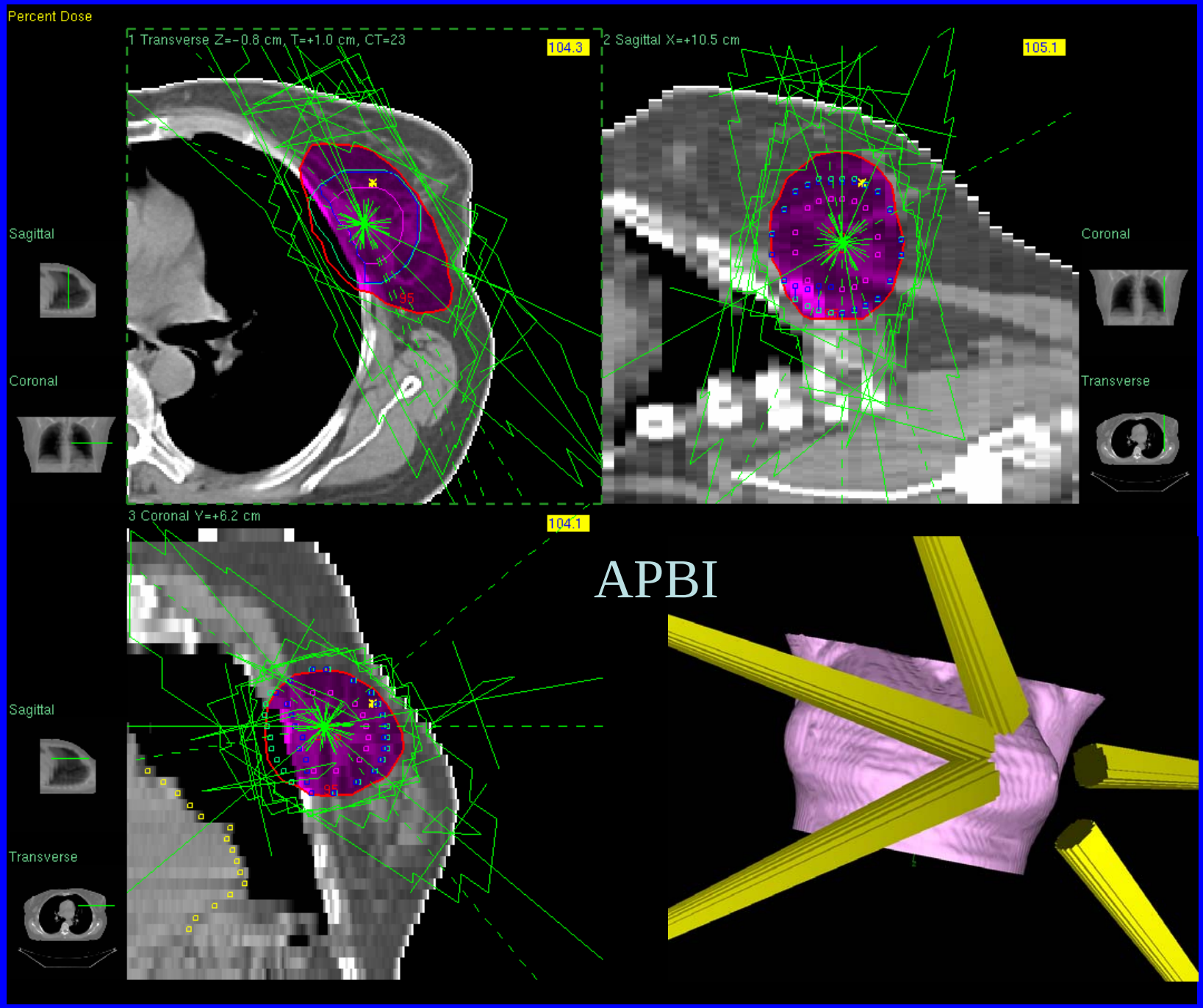
- **Mammella sin**4 fasci



- **Mammella dx**




Percent Dose
1 Transverse Z=-3.5 cm, T=+3.9 cm, CT=21
112.3
2 Sagittal X=-7.9 cm
108.1
Sagittal
Coronal
Coronal
Transverse
3 Coronal Y=+7.6 cm
113.6
tecnica fasci tangenziali
Sagittal
Transverse


Percent Dose
1 Transverse Z=-0.8 cm, T=+1.0 cm, CT=23
104.3
95
2 Sagittal X=+10.5 cm
105.1
Sagittal
Coronal
Coronal
Transverse
3 Coronal Y=+6.2 cm
104.1
APBI
Sagittal
Transverse

BREAST CONSERVING THERAPY WITH LUMPECTOMY PLUS PARTIAL BREAST IRRADIATION

Institution	# Pts.	Median F/U (mos)	Scheme (cGy)	Total dose (cGy)	% LR	% Good-Excellent cosmesis
Oncologic Inst. Budapest	41	17	520 x 7 HDR	3640	2,4	n.s.
London Cancer Centre Ontario	39	20	372 x 10 HDR	3720	2,6	n.s.
W. Beaumont Hospital	79	48	340 x 10 HDR	3400	1,0	98
University of Florence	90	27	50-60 cGy/h LDR	5000	4,4	n.s.
W. Beaumont Hospital	120	85	52 cGy/h LDR	4992	1	98
W. Beaumont Hospital	91	24	385 x 10 3D CRT	3850	0	100
New York University	47	17	600 x 5 3D CRT	3000	0	100

Intra-Operative PBI Techniques

- **European Institute of Oncology**
  - ***Veronesi et al***

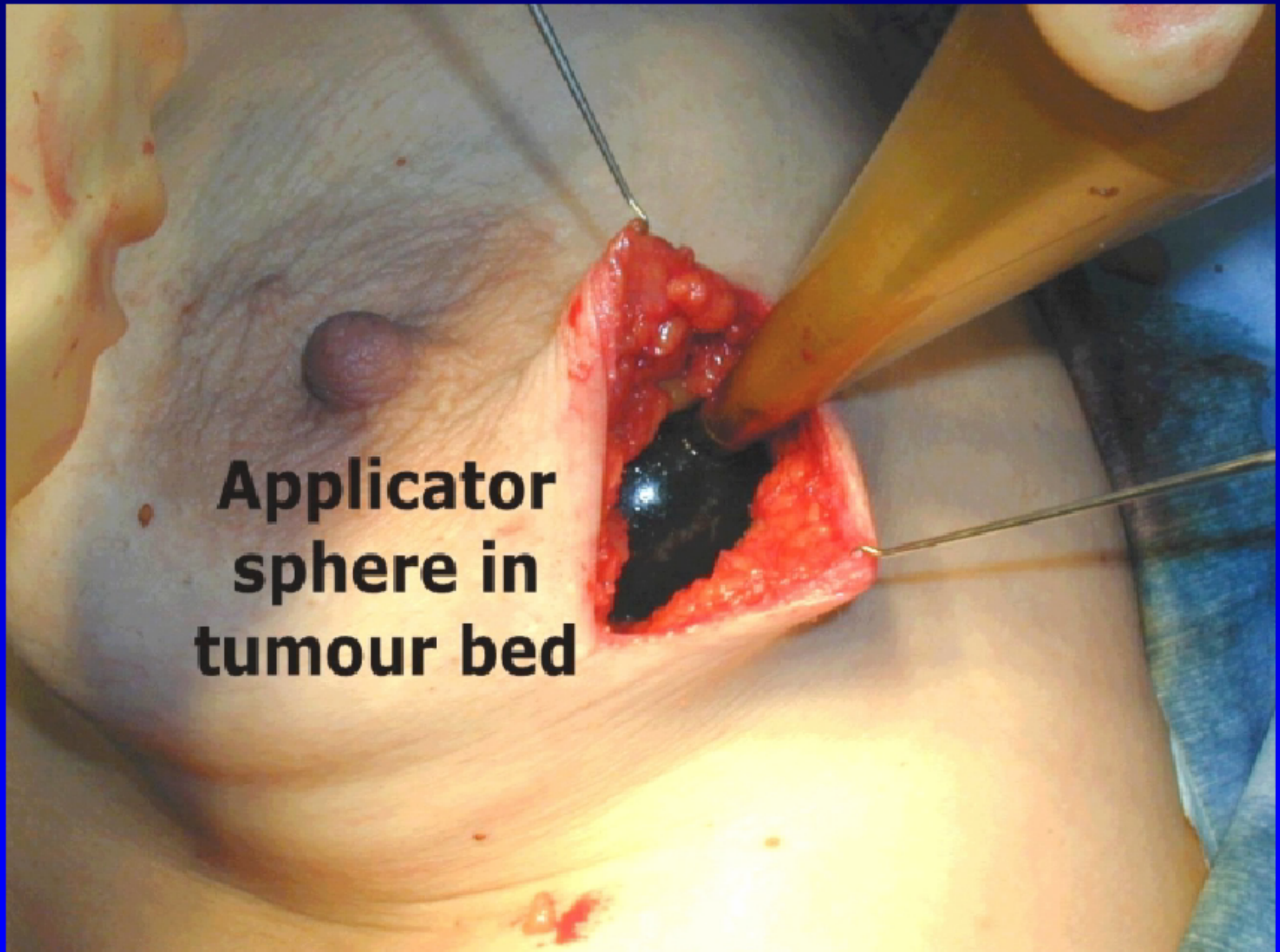
IORT MOBILE ACCELERATOR

- [redacted] IORT dedicated electron accelerator
- Conventional OR (no shielding needed)
- Mobile and easily docked
- Electron beams of 4 different energies: 3, 5, 7, 9 MeV

Intra-Operative PBI Techniques

- **University College London**
  - ***Vaidya et al***


INTRABEAM


Applicator
sphere in
tumour bed

Ongoing studies of partial breast irradiation after conservative surgery

Criteri	Targit	ELIOT	IMPORT	RAPID	NSABP/ RTOG	GEC/ ESTRO	IRMA
N° pz	2232	2000	2100	2128	3000	1170	2400
Età	>40	>48	>50	>40	>18	>40	>49
Dimensione T mm	<30	<25	<20	<30	<30	<30	<30
Numero N+	0	0	0	0	0-3N+	0-1N+	0-3N+
Grado	1-3	1-3	1-2	1-2	1-3	1-3	1-3
Distanza margini mm	negativi	>10	>2	Negativi	Negativi	>2 invasivi >5 CIS	>2
Tecnica RT	Periop. RX 50 KV	Periop. Elettroni 6-12 MeV	Postop. IMRT	Postop.RT 3D	Brachiterapia Mammosite RT 3D	Brachit. a basso o alto rateo di dose	Postop.RT 3D
Dose fraz.	20 Gy 1 fraz	21 Gy 1 fraz		38,5 Gy 10 fraz big	RTE 38,5 Gy in 10 f big	Basso DR 50 Gy	38,5 Gy 10 fraz big

PROTOCOLLO DI STUDIO

CARCINOMA DELLA MAMMELLA
A BASSO RISCHIO DI RECIDIVA LOCALE:

IRRADIAZIONE PARZIALE E ACCELERATA CON RADIOTERAPIA CONFORMAZIONALE TRIDIMENSIONALE (3D-CRT)
VS.
RADIOTERAPIA STANDARD DOPO CHIRURGIA CONSERVATIVA

(STUDIO DI FASE III)

IL PROGETTO I.R.MA. del PRI ER

Innovazioni nella Radioterapia della Mammella

IRRADIAZIONE PARZIALE

I FASE: STUDIO IRMA 1

Studio randomizzato di confronto

Irradiazione parziale accelerata della mammella vs. RT convenzionale

II FASE: STUDIO IRMA 2

Valutazione controllata della Radioterapia intraoperatoria (IORT) vs. RT convenzionale

ENDPOINTS

- ***Controllo locale***
- ***Risultato estetico***
- ***Complicanze***

I.R.MA. 1

VALUTAZIONE PREOPERATORIA DI ELEGGIBILITA':
Pazienti di età non inferiore a 49 anni; cT1 o cT2 < 3 cm di diametro massimo;
suscettibili di intervento chirurgico conservativo;
assenza di microcalcificazioni o altre neoformazioni
ad una distanza > 4 cm. dalla neoplasia primitiva.

CHIRURGIA:
Chirurgia conservativa
(inclusa ampia resezione mammaria e nodulectomia
+ biopsia del linfonodo sentinella e/o dissezione ascellare)

CRITERI DI ELEGGIBILITA’

- ✓Età > 49 anni
- ✓Carcinoma invasivo della mammella (+/- ca. in situ concomitante)
- ✓Stadio pT 1 –2 (diametro< 3 cm) pN0- N1 M0
- ✓Lesioni unifocali
- ✓Margini di resezione chirurgica indenni da neoplasia (≥ 2 mm)
- ✓Cavità tumorale delimitata da clips chirurgiche.
- ✓Assenza di metastasi a distanza
- ✓Assenza di precedenti trattamenti radianti sulla mammella

IRMA Trial

Phase III

Stage I-II breast cancer treated by lumpectomy

Randomization

WBI

- 45Gy/18 fr-50Gy/25 fr-50.4Gy/28 fr
to the whole breast
optional boost to 60 -66.6 Gy

PBI

- 38.5 Gy in 3.85 Gy fr. bid
3D-CRT

Endpoints Comparison

NSABP B39/ RTOG 0413

- Primary:
  - Ipsilateral breast tumor recurrence
- Secondary:
  - Distant disease-free survival
  - Overall survival
  - QoL: Cosmesis, fatigue, symptoms, burden of care

IRMA Trial

- Primary:
  - Ipsilateral breast tumor recurrence
- Secondary:
  - Recurrence free survival
  - Distant disease-free survival
  - Overall survival
  - QoL: Cosmesis, burden of care:

IRMA Trial

U. O. di Radioterapia - Clinical Trial Office: Dip. Int. di Oncologia ed Ematologia - Azienda Ospedaliero-Universitaria Policlinico di Modena

Contact administrator
Access problems

SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA

Reserved Area

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Password:

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You are not authenticated.

IRMA Trial

Documentation:

Trial synopsis

If you are interested to participate to the trial, please download: participation request [illegible] 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
BOLOGNA AOSP
BOLOGNA AUSL
CASTELLANZA
COMO
COTIGNOLA
FERRARA
GENOVA
HAIFA
MELDOLA
MODENA
PARMA
PIACENZA
RAVENNA
REGGIO EMILIA
RIMINI
ROMA Unicampus
SAN GIOVANNI ROTONDO
TREVIGLIO
VITERBO

21/32 Centers

IRMA trial

- May, 2007 – open for accrual
- 12th September, 2009
  - 32 centers (21 have started enrolling pts, 11 are in dummy-run phase)
  - 634 patients accrued (316 PBI and 318 WBI)

I.R.MA.: Caratteristiche dei casi reclutati

Distribuzione in frequenza in base a T, N, terapia medica

Fase di espansione !!.. “joint analysis” ?....

Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 4, pp. 981–984, 2009

0360-3016/09/$–see front matter

ELSEVIER

doi: 10.1016/j.ijrobp.2009.03.046

EDITORIAL

ACCELERATED PARTIAL BREAST IRRADIATION: CAUTION AND CONCERN FROM AN ASTRO TASK FORCE

LEONARD R. PROSNITZ, M.D., F.A.S.T.R.O., F.A.C.R.,* JANET HORTON, M.D.,*
AND PAUL E. WALLNER, D.O., F.A.S.T.R.O., F.A.C.R., F.A.O.C.R., F.A.C.R.O.†

*Department of Radiation Oncology, Duke University Medical Center, Durham, NC; and †21st Century Oncology, Moorestown, NJ

SELECTION OF PATIENTS FOR APBI

The Task Force further defines "suitable," "cautionary," and "unsuitable" groups for APBI. Consider the language carefully. All three groups are in quotation marks throughout the statement, emphasizing the lack of Phase III data. APBI is considered "acceptable" (outside of a clinical trial) for the "suitable" group.

Consider further the "suitable" group. In brief, these are the most favorable patients, over age 60, with pathologically negative nodes, T1 primary cancers, positive estrogen receptor status (ER), absence of lymphovascular space invasion (LVSI), widely negative margins (>2 mm), and no multicentricity. They might have added HER2-negative, although they did not. These are the patients who form the majority of those treated in the Phase I/II trials quoted and also represent the majority of the 3,400 patients entered into the RTOG 0413/NSABP B39 trial. Note the *exclusion* of pure ductal carcinoma in situ (DCIS) from the "suitable" group because of the paucity of even Phase I/II data regarding these patients, although they were candidates for the RTOG/NSABP trial.

For the "cautionary" group, the Task Force states that any *one* of the following criteria should "invoke caution and concern" when considering APBI: age <60, T2 primary disease, pure DCIS <3 cm, close margins (<2 mm), focal LVSI, multifocal or multicentric disease, invasive lobular carcinoma, or ER negativity.

"Unsuitable" patients were those with *any* of the following criteria: tumor size >3 cm, positive margins, any positive lymph nodes, no axillary surgery, extensive LVSI, multicentricity, DCIS >3cm, or the presence of a BRCA1 or 2 mutation. Note that if the patient received neoadjuvant systemic therapy, she fell into the "unsuitable" group, even if downstaged by that therapy. "Unsuitable" patients should *not* receive APBI outside the context of a clinical trial.

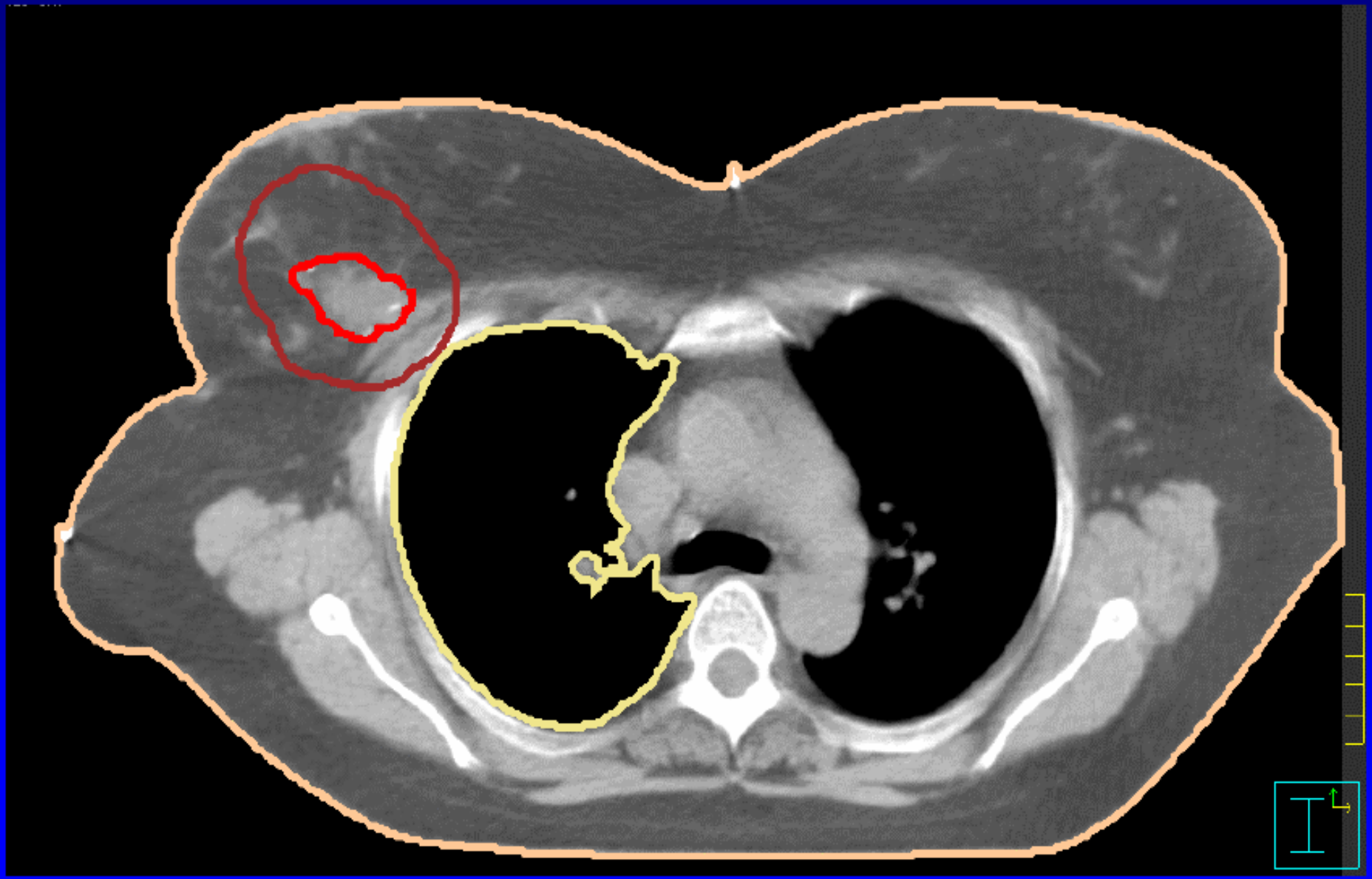
CONCLUSIONS

Data from the RTOG/NSABP trial will likely not be available for close to ten years. In the interim, the ASTRO Task Force has given us a well thought out statement with guidelines on the use of APBI outside the context of a clinical trial. To reiterate, "suitable" patients are generally older women with biologically less aggressive disease. There should be a lot of "caution and concern" if offering APBI to the "cautionary and concern" group. The "unsuitable" group is just that for the moment. As part of BCT, WBI in a conventional course of 6-1/2 to 7 weeks of radiotherapy, 180 - 200 cGy per day, remains the gold standard. Patients should be so informed. Other approaches include hypofractionated WBI, such as the Canadian and British programs we have mentioned, or even lumpectomy alone in appropriately selected patients. These alternatives at present are better supported by available data then APBI, inasmuch as Phase III trials with 5- to 10-year follow-up have been reported. It is to be hoped that these options are sufficient to insure the availability of BCT to all women who desire it and are deemed appropriate candidates by their physicians.

PBI is still an experimental approach. Pts., expecially if at high risk of local recurrence, should receive PBI only in the context of clinical trials

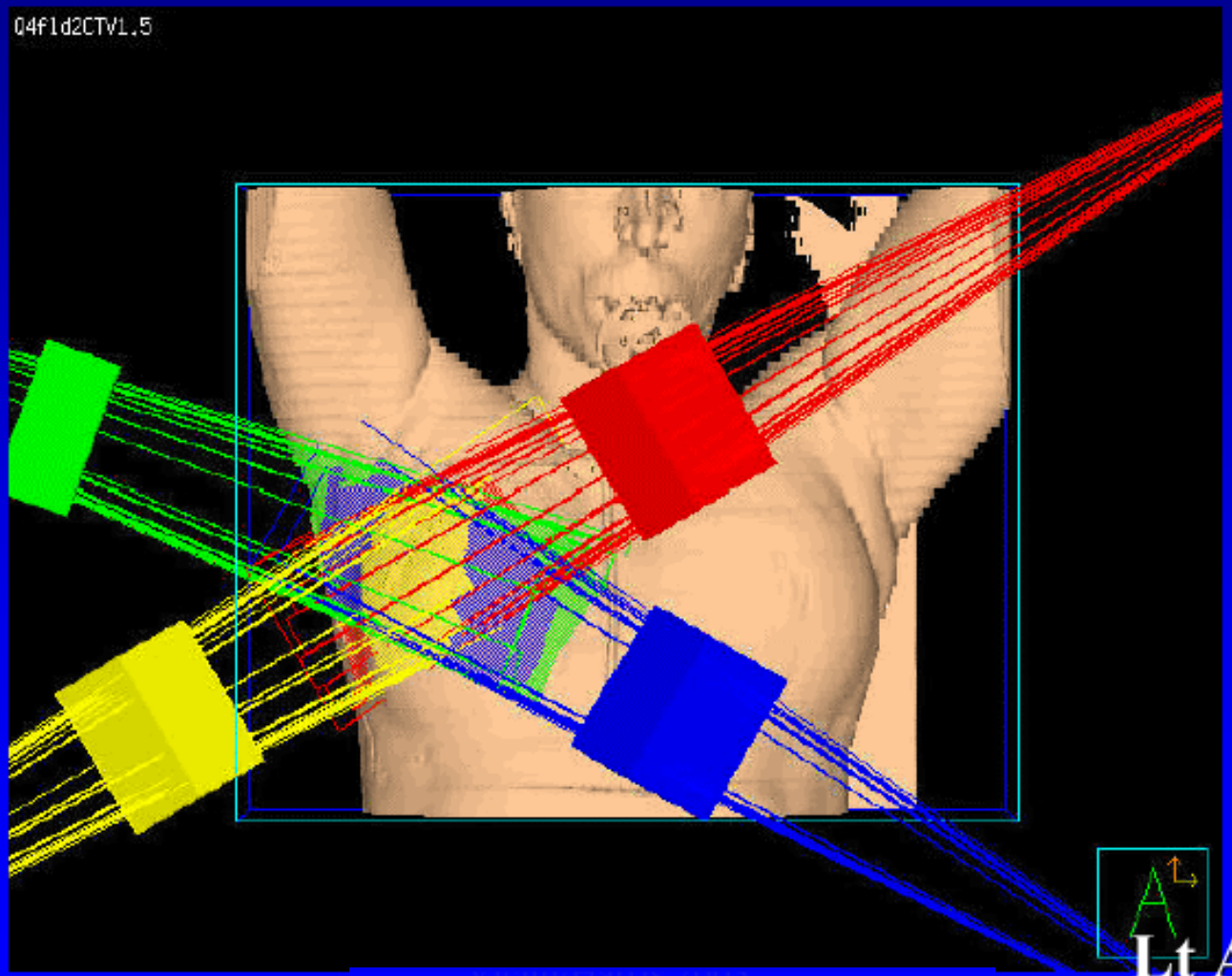
Partial Breast Irradiation Target

- 1.5 cm Beyond Lumpectomy Cavity -



Partial Breast Irradiation

- 3D Conformal External Beam Irradiation -

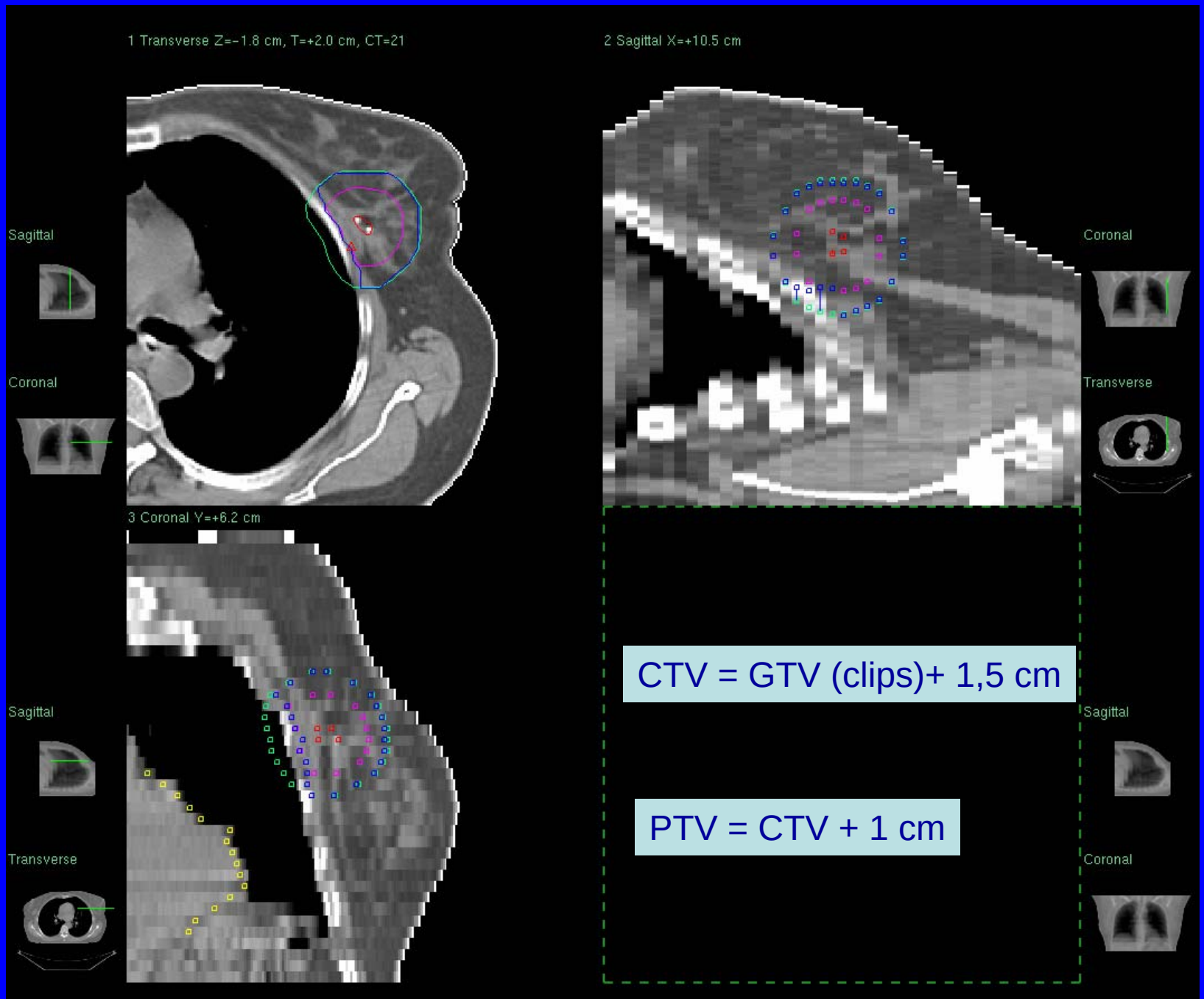


Lt ASIO

Rt PSIO

Rt AISO

Lt AISO


1 Transverse Z=-1.8 cm, T=+2.0 cm, CT=21
2 Sagittal X=+10.5 cm
3 Coronal Y=+6.2 cm
Sagittal
Coronal
Coronal
Transverse
Sagittal
Transverse
Sagittal
Coronal
CTV = GTV (clips)+ 1,5 cm
PTV = CTV + 1 cm

Protocollo	***Constraint e assicurazione qualità della distribuzione di Dose***	
PTV valutazione	Almeno 90% Volume riceve il 90% Dose	Nessun punto > 120 % Dose
Polmone	30% Dose a meno del 15% del Volume	
Cuore	M.dx: 5% Dose a meno del 5% del Volume	M.sn: 5% Dose a meno del 40% del Volume
Mammella ipsilaterale	100% della Dose a meno del 35% del volume	50% della Dose a meno del 60% del volume
Tiroide	Nessun punto > 3 % Dose	
Mammella controlaterale	Nessun punto > 3 % Dose	

DVH OAR entro ±5% dei valori specificati

IRMA Trial

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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
- BOLOGNA AOSP
- BOLOGNA AUSL
- COMO
- COTIGNOLA
- FERRARA
- MODENA
- PARMA
- PIACENZA
- RAVENNA
- REGGIO EMILIA
- RIMINI
- ROMA Unicampus
- SAN GIOVANNI ROTONDO
- VITERBO

IRMA Trial

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for information
vicini.roberto@unimore.it
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fbertoni!
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Azioni

- Home Page
- Pazienti
- Q.A.
- operatori
- Centri
- Studi Clinici

Gestione Quality assurance nello Studio: (irma)

Linea	Seleziona	Gestione Valutatori	N° centro	Città	N° Paziente	Cognome	Nome	Data nascita	Nome braccio	Data Inclusione	qa	N° valutatori	stato QA
1	Seleziona	Gestione Valutatori	1	Modena	1	Pav	Adr	01 Mar 1949	PBI	02 Mag 2007	Si	2	
2	Seleziona	Gestione Valutatori	1	Modena	2	fab	car	14 Lug 1951	WBI	07 Giu 2007	Si	0	
3	Seleziona	Gestione Valutatori	1	Modena	3	Mic	Adr	10 Ott 1934	PBI	19 Giu 2007	Si	0	
4	Seleziona	Gestione Valutatori	2	Reggio Emilia	1	zin	mir	26 Mag 1943	WBI	17 Apr 2007	Si	2	
5	Seleziona	Gestione Valutatori	2	Reggio Emilia	2	lev	fra	03 Mag 1950	WBI	18 Apr 2007	Si	2	
6	Seleziona	Gestione Valutatori	2	Reggio Emilia	3	san	gia	06 Nov 1948	PBI	03 Mag 2007	Si	2	
7	Seleziona	Gestione Valutatori	3	Rimini	1	Vas	Div	03 Lug 1946	PBI	12 Set 2007	Si	0	
8	Seleziona	Gestione Valutatori	4	Parma	1	Gua	cor	12 Lug 1933	WBI	11 Apr 2007	Si	0	
9	Seleziona	Gestione Valutatori	4	Parma	2	Ama	Lin	29 Ott 1957	PBI	01 Ago 2007	Si	0	
10	Seleziona	Gestione Valutatori	4	Parma	3	Don	Don	15 Dic 1951	WBI	02 Ago 2007	Si	0	

IRMA Trial

U. O. di Radioterapia - Clinical Trial Office: Dip. Integrato di Oncologia ed Ematologia - Azienda Ospedaliero-Universitaria Policlinico di Modena

for information
vicini.roberto@unimore.it
Risoluzione problemi di accesso

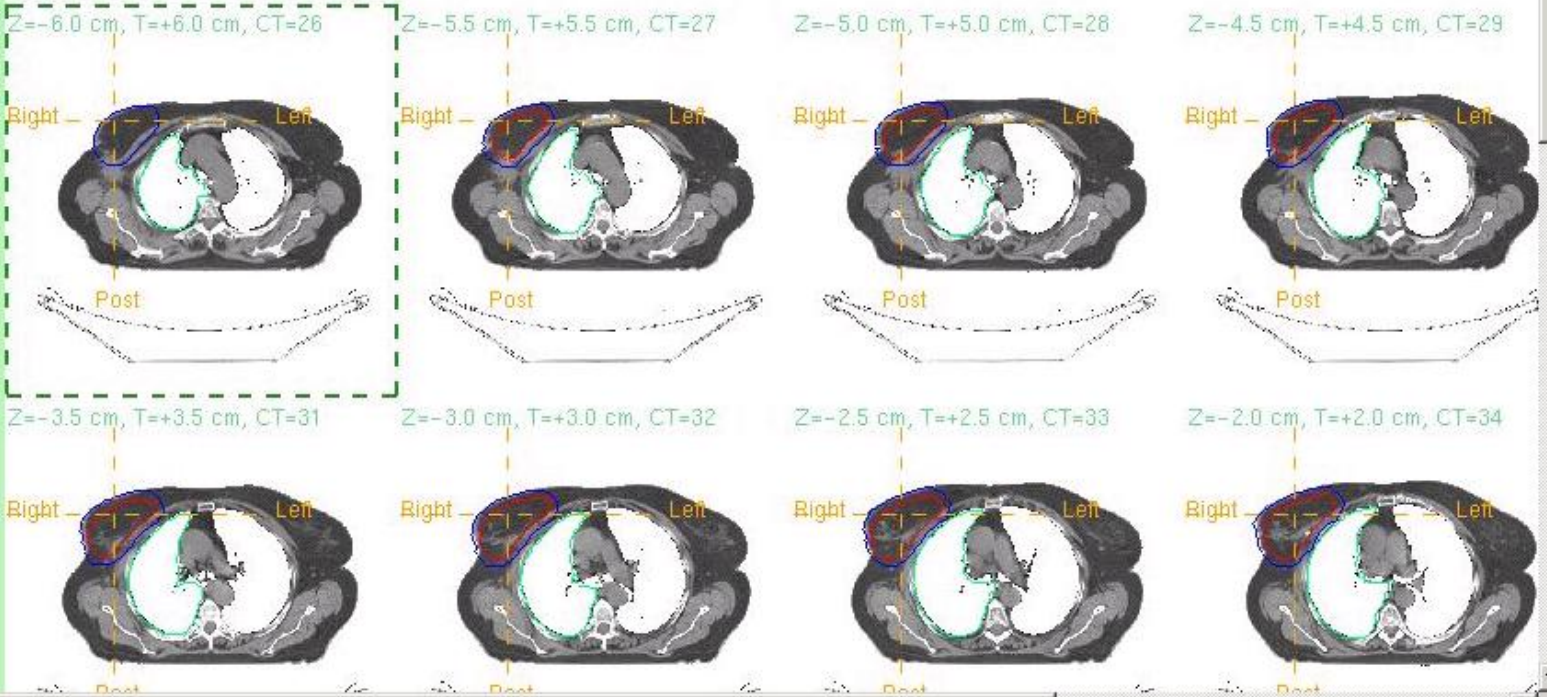
SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA

QA Passed? Yes No Not evalued **Note** Valuta

2_caretalla_tecnico_clinica_3.jpg

Section: immagini CT con reperi, volumi, dosi

QA Passed? Yes No Not evalued **Note** Valuta



Eligibility Criteria Comparison (selected)

NSABP B39/ RTOG 0413

- Stage 0, I, II breast cancer
- DCIS or invasive adenocarcinoma
- Tumor size ≤ 3 cm (unifocal) N-0, N-1 (≤ 3 positive nodes)
- Negative margins (NSABP)
- Life expectancy of at least 10 years
- MUST be randomized within *42 days* of last breast/axillary surgery
- Lumpectomy/whole breast ratio on CT ≤ 30%

IRMA trial

- Stage I, II breast cancer
- Invasive adenocarcinoma
- Tumor size ≤ 3 cm (unifocal) N-0, N-1 (≤ 3 positive nodes)
- Negative margins (=/> 2mm)
- Life expectancy of at least 10 years
- Randomization takes place before RT , within 12 weeks of last breast/axillary surgery or > 2 weeks after adjuvant chemotherapy
- Lumpectomy/whole breast ratio on CT ≤ 30%

Method Comparison

NSABP B39/ RTOG 0413

- Sample size - 3000 patients
- Projected accrual 2.5 (4,6) years
- Randomization stratified by
  - Stage (DCIS, node neg, node pos)
  - Age (less than 50, 50+)
  - ER-negative, ER-positive
  - Chemotherapy intention

Rigorous Q/A for PBI methods: rapid review for first case, timely review for next 4.

IRMA Trial

- Sample size - 2400 patients
- Projected accrual 5 years
- Randomization stratified by
  - Stage (T1-T2, N0 - N1)
  - Chemotherapy intention

Rigorous Q/A for PBI method: rapid review for first case, timely review for next 3 and random every 30 randomized patients.

Outcome: ricaduta locale a 5 anni

Radioterapia standard	Radioterapia parziale è considerata non inferiore alla standard se l'incidenza delle ricadute locali è:	N° pazienti per braccio
2%	<3%	2424
3%	<4.5%	1600
4%	**<6%**	**1187**
5%	**<7.5%**	**940**
6%	**<9%**	**775**
7%	<10.5%	657
8%	<12%	569
9%	<13.5%	500

Alfa=0.05 Potenza=0.80

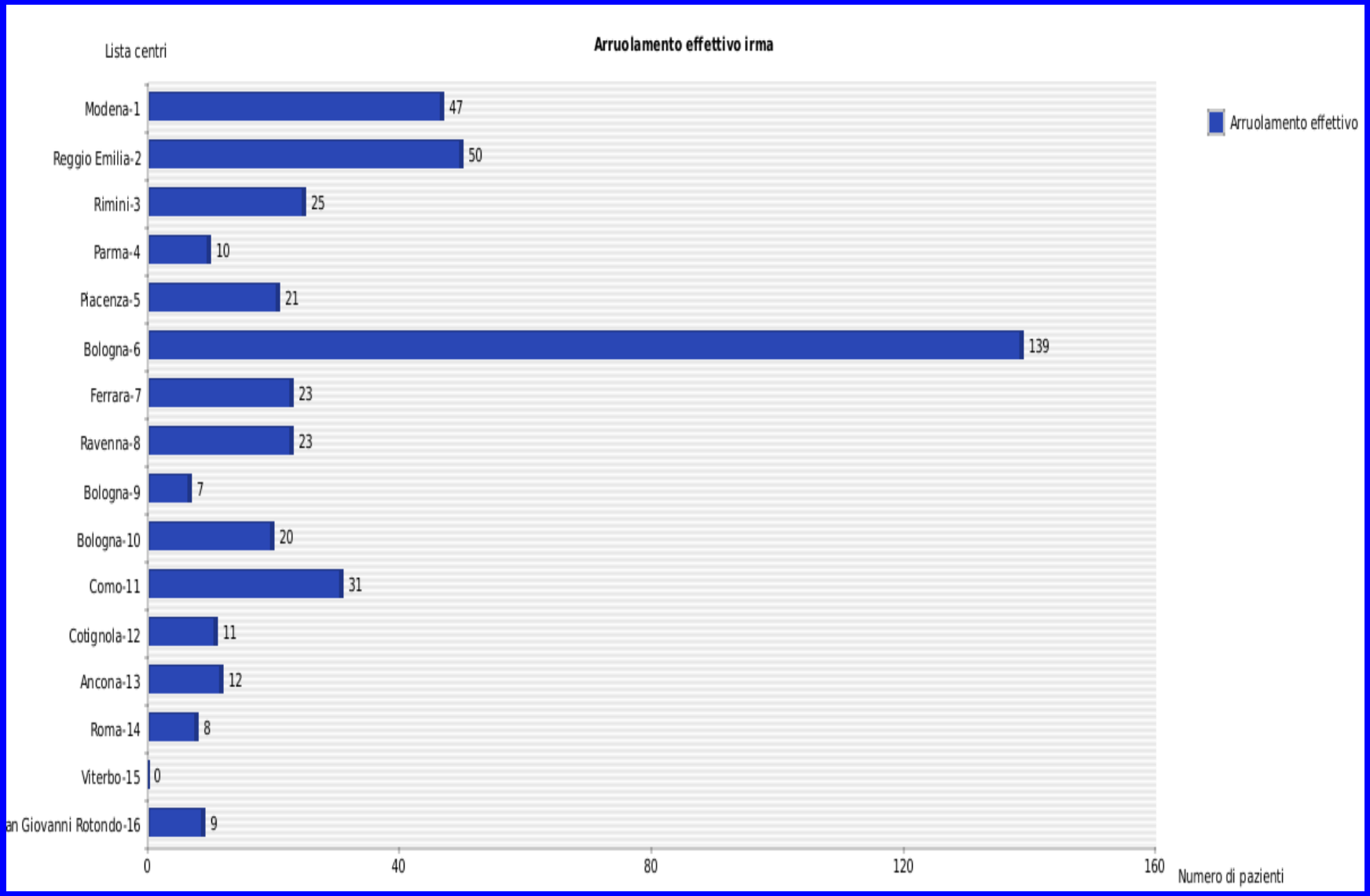
IRMA trial

- March, 2007 – open for accrual
- 26th August, 2009
  - 28 centers (16 have started enrolling pts, 12 are in dummy-run phase)
  - 736 patients accrued (366 PBI and 370 WBI)

STUDI IRMA DEL PRI ER
CONCLUSIONI

- **Implementare un modello di introduzione controllata delle nuove tecnologie nella pratica clinica, nel contesto della rete nazionale dei Centri di Radioterapia**
- **Migliorare la collaborazione tra i Centri di Radioterapia elevando lo standard complessivo del trattamento locale del tumore della mammella**
- **Ridurre il rischio che il trattamento conservativo sia sottoutilizzato**
- **Ridurre la durata della RT nel trattamento conservativo del tumore della mammella**
- **Migliorare la qualità di vita delle pazienti**

Nome Centro	Città	Stato Centro	N° centro	Data attivazione	N° Pazienti	n_paz_pbi	n_paz_wbi
Policlinico	Modena	attivato	1	02/03/07	47	25	22
Arcispedale S. Maria Nuova	Reggio Emilia	attivato	2	02/03/07	50	23	27
Ospedale Infermi	Rimini	attivato	3	02/03/07	25	15	10
Az. Osp. Parma	Parma	attivato	4	02/03/07	10	3	7
AUSL "G. da Saliceto"	Piacenza	attivato	5	02/03/07	21	14	7
Ospedale Bellaria	Bologna	attivato	6	02/03/07	139	72	67
Az. Osp. Universitaria S. Anna	Ferrara	attivato	7	02/03/07	23	7	16
Osp. S.M. Croci	Ravenna	attivato	8	02/03/07	23	12	11
A.O. Policlinico S. Orsola	Bologna	attivato	9	05/03/07	7	3	4
A.O. Policlinico S. Orsola	Bologna	attivato	10	05/03/07	20	9	11
Azienda Ospedaliera S. Anna	Como	attivato	11	11/04/07	31	14	17
Villa Maria Cecilia	Cotignola	attivato	12	12/06/07	11	6	5
Azienda Ospedali Riuniti	Ancona	attivato	13	17/09/07	12	6	6
Università Campus biomedico	Roma	attivato	14	04/03/08	8	3	5
Ospedale Belcolle	Viterbo	attivato	15	27/06/08	---	---	---
Casa sollievo sofferenza	San Giovanni Rotondo	attivato	16	27/06/08	9	4	5
A.O. SS Antonio e Biagio	Alessandria	contattato	---	---	---	---	---
ASL8 Osp. S. Donato	Arezzo	contattato	---	---	---	---	---
ospedale Cardinal Massaia	Asti	contattato	---	---	---	---	---
Ospedali Galliera	Genova	contattato	---	---	---	---	---
RAMBAM medical center	Haifa	contattato	---	---	---	---	---
SOC Radioterapia Asl 9	Ivrea	contattato	---	---	---	---	---
Univ. L'Aquila - scuola spec. radioterapia	L'Aquila	contattato	---	---	---	---	---
CHUV	Lausanne	contattato	---	---	---	---	---
IRST Meldola	Meldola	contattato	---	---	---	---	---
Divisione universitaria di radioterapia	Novara	contattato	---	---	---	---	---
A.O. S. Giovanni Battista	Torino	contattato	---	---	---	---	---
Azienda Ospedaliera Treviglio	Treviglio	contattato	---	---	---	---	---
A.O. Macchi	Varese	contattato	---	---	---	---	---
				totale	436	216	220


Arruolamento effettivo irma
Lista centri
Modena-1
Reggio Emilia-2
Rimini-3
Parma-4
Piacenza-5
Bologna-6
Ferrara-7
Ravenna-8
Bologna-9
Bologna-10
Como-11
Cotignola-12
Ancona-13
Roma-14
Viterbo-15
an Giovanni Rotondo-16
47
50
25
10
21
139
23
23
7
20
31
11
12
8
0
9
0
40
80
120
160
Numero di pazienti
Arruolamento effettivo

Anno	Mese	Pazienti arruolati/mese	Arruolamento effettivo
2007	Mar	1	1
2007	Apr	10	11
2007	Mag	17	28
2007	Giu	19	47
2007	Lug	19	66
2007	Ago	22	88
2007	Set	20	108
2007	Ott	23	131
2007	Nov	31	162
2007	Dic	19	181
2008	Gen	21	202
2008	Feb	43	245
2008	Mar	18	263
2008	Apr	25	288
2008	Mag	27	315
2008	Giu	19	334
2008	Lug	27	361
2008	Ago	16	377
2008	Set	19	396
2008	Ott	17	413
2008	Nov	23	436

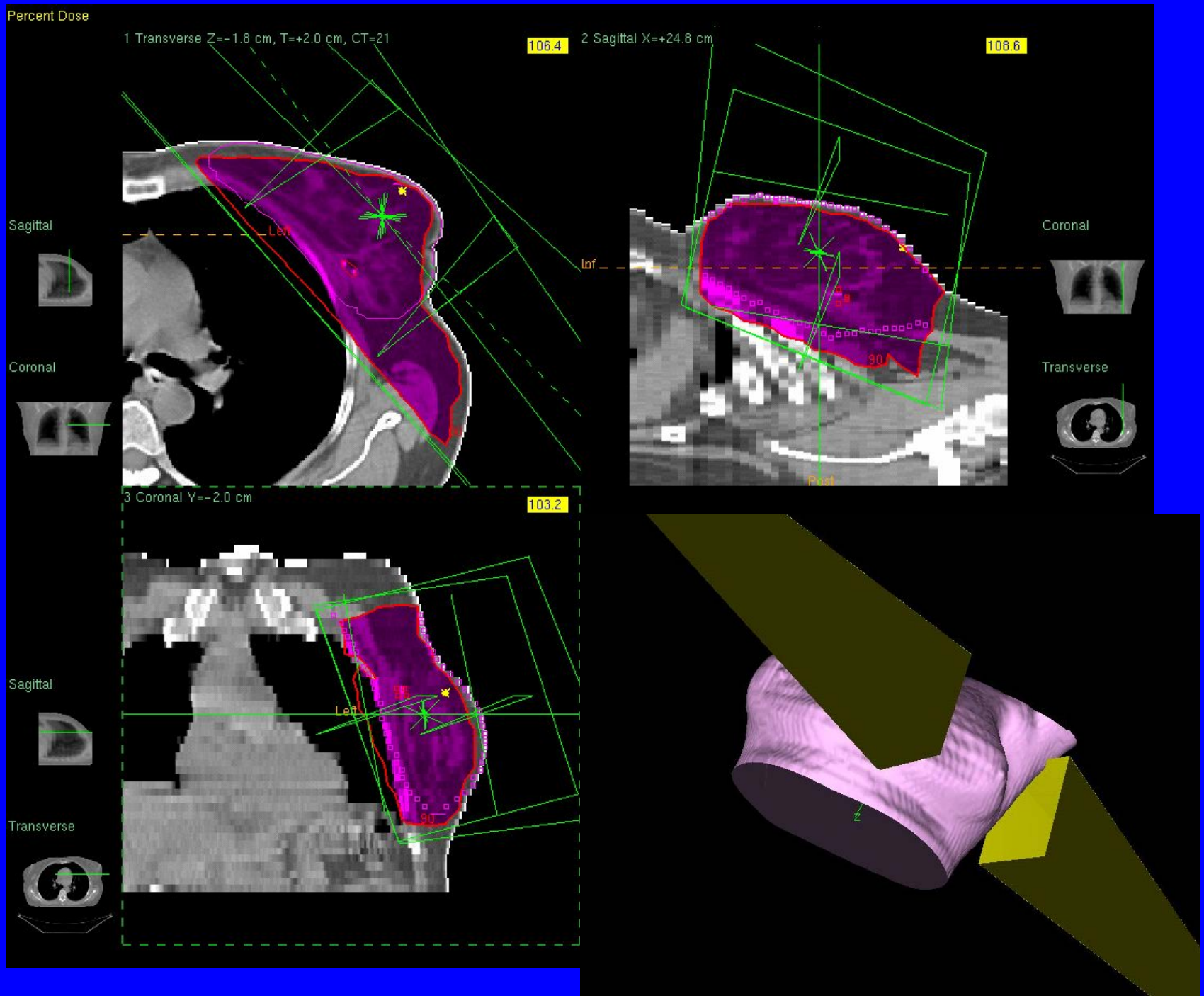
21 Gy in-out trial

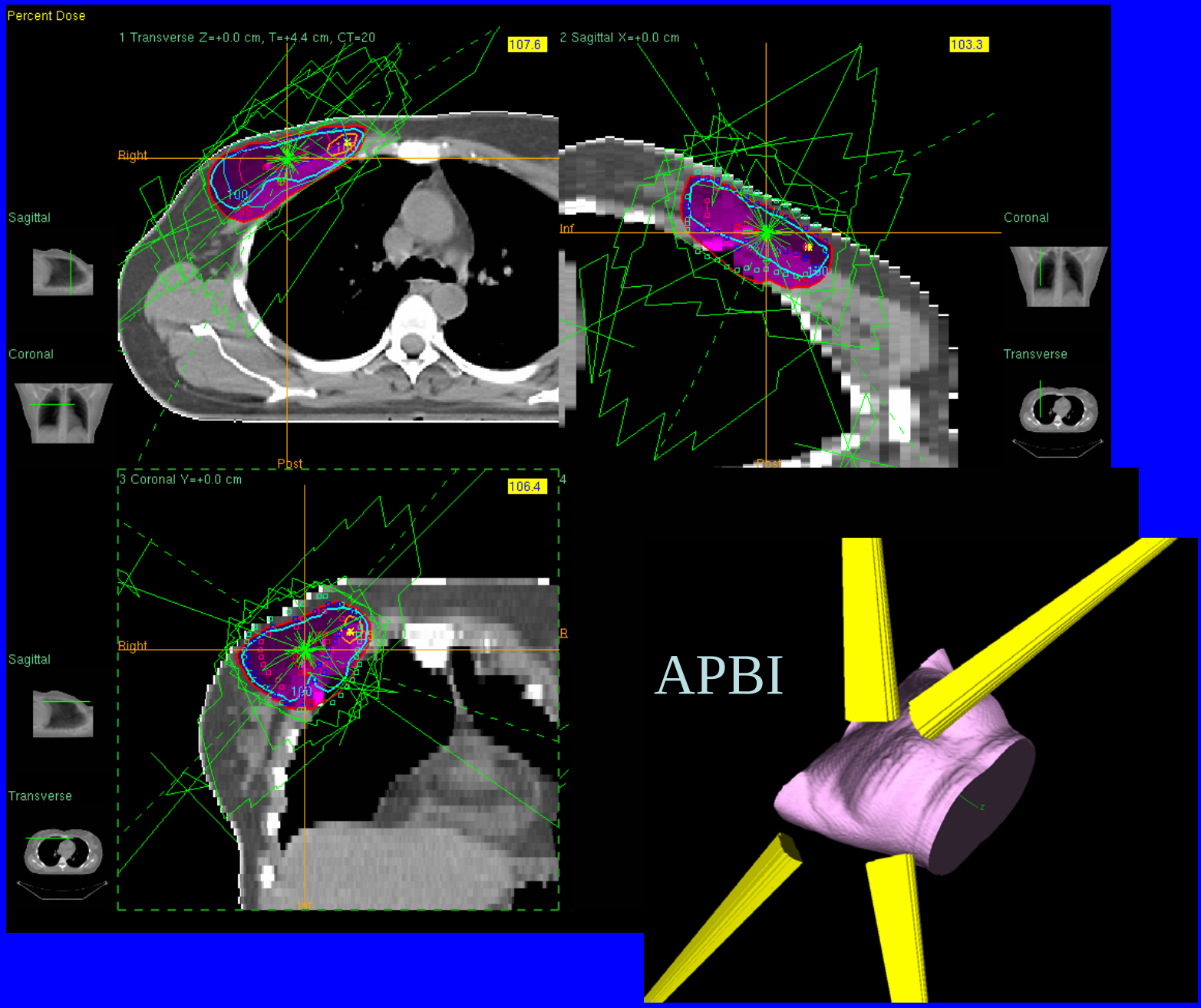
31-12-2003

Number of patients: 590

(Orecchia, comunicazione personale)

Events	pts / %
Local relapse	3 (0.5)
II ipsilateral tumour	3 (0.5)
Contra and ipsilateral tumour	1 (0.2)
Contralateral tumour	4 (0.6)
N+ axillary lymph node	1
Distant metastases	12
Other tumour	3
Death	1


Percent Dose
1 Transverse Z=-1.8 cm, T=+2.0 cm, CT=21
106.4
2 Sagittal X=+24.8 cm
106.6
Sagittal
Coronal
Coronal
Transverse
Inf
Left
Post
90
3 Coronal Y=-2.0 cm
103.2
Sagittal
Transverse
Left
90


Percent Dose
1 Transverse Z=+0.0 cm, T=+4.4 cm, CT=20
107.6
Right
100
Sagittal
Coronal
2 Sagittal X=+0.0 cm
103.3
Inf
Post
Coronal
Transverse
3 Coronal Y=+0.0 cm
106.4
Right
100
Sagittal
Transverse
APBI