OVERVIEW OF RADIOTHERAPY IN BREAST CONSERVATION

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RT in Breast Cancer

- Combined Modality is the mainstay of treatment
- The adjuvant treatment after surgery should address
  - -Local recurrence (RT)
  - -Systemic disease (chemo, hormone)

Breast Conservation Therapy

Removal of only the tumor with a safe margin with axillary lymphadenectomy instead of mastectomy followed by radiotherapy to the breast

BCT History

THE PLACE OF RADIUM IN
THE TREATMENT OF
CANCER OF THE BREAST

- 325 patients with local removal of the breast tumor and radium implantation at the site of local incision as well as in the axilla.
- In 250 patients, the 5-year survival rate

  71.4% for group 1 (disease confined to the breast),
  29.3% for group 2 (confined to breast and axilla),
  23.6% for group 3 (advanced or inoperable).
- Results comparable with radical mastectomy.

Keynes G. Ann Surg. 1937 Oct;106(4):619-30

Prospective Randomized Trials Comparing Conservative Surgery and Radiation with Mastectomy for Early-Stage Breast Cancer

	Institut Gustave-Roussy	**Milan**	**NSABP B-06**	**NCI**	**EORTC**	**Danish**
No. of patients	179	701	1,219	237	874	904
Stage	1	1	1 and 2	1 and 2	1 and 2	1, 2, 3
Surgery	2-cm gross margin	Quadrantectomy	Lumpectomy	Gross excision	1-cm gross margin	Wide excision
Follow-up (y)	15	20	20	18	10	6
Overall survival						
CS+RT (%)	73	42	46	59	65	79
Mastectomy (%)	65	41	47	58	66	82
Local recurrence						
CS+RT (%)	9	9	14	22	20	3
Mastectomy (%)	14	2	10	6	12	4

BCS followed by RT equivalent to mastectomy for appropriately selected patients with EBC

Early Stage Breast Cancer

NIH Consensus Development Conference Statement (1990)

"Breast conservation treatment is an appropriate method of primary therapy for the majority of women with Stage I and II breast cancer and is preferable because it provides survival equivalent to total mastectomy and axillary dissection while preserving the breast"

"The recommended technique for breast conservation includes:

- local excision of primary tumor with clear margins
- Level I-II axillary node dissection
- breast irradiation to 4,500-5,000 cGy with or without a boost"

Rationale of BCT

- Breast cancer is a systemic disease with hematogenous spread early in the disease process
- Surgery and Radiation as a combined modality
  - Surgery alone- More failure at margins
  - Radiotherapy alone- More failure at the epicenter

- Using surgery to remove grossly visible tumor with a small margin and moderate-dose radiotherapy to treat the larger volume of tissue that may harbor residual disease

Criteria for BCT

Indications

- Motivated Pts
- R T facilities
- Mammography
- Tumor < 5 cms
- Node N0/N1
- Good tumor breast ratio

Contraindications:

ABSOLUTE

- *High probability of recurrence*
  - Multicentric disease
  - Positive surgical margins
- *High probability of complications from irradiation*
  - CVD
  - Prior irradiation
  - Early pregnancy

Contraindications to BCT

RELATIVE:

- High probability of subsequent breast cancers
- Poor cosmetic results
  - Unfavorable tumor-breast ratio
  - Oncologically necessary removal of nipple-areola complex
  - Large medial lesions
- Personal preference of the patient

BCT: Technical aspects

- Pre-op evaluation of tumor by Radiation Oncologist
- Minimum margin 1 cm all around
- Separate incisions preferred for primary and axilla
- Pectoralis minor may be divided or preserved
- Surgical clips are left if brachytherapy not planned

Standard approach in BCT

- BCS
  - WLE + ALND
- Whole breast RT
  - 45-50 Gy/25#/5 weeks
  - Tangential fields – medial and lateral (Co-60 or 6 MV photons)
  - Newer techniques- IMRT, proton beam etc
- Regional RT- only when indicated by post-op HPR
- Boost to tumor bed
  - 10-16 Gy
  - Photon/ Electron/ Brachytherapy

Factors affecting cosmesis after BCS

- Removal of large volume of breast tissue
- Removal of Nipple-areola complex
- Location of tumor (Medial vs lateral)
- Post radiation fibrosis

Risk Factors for Local Relapse

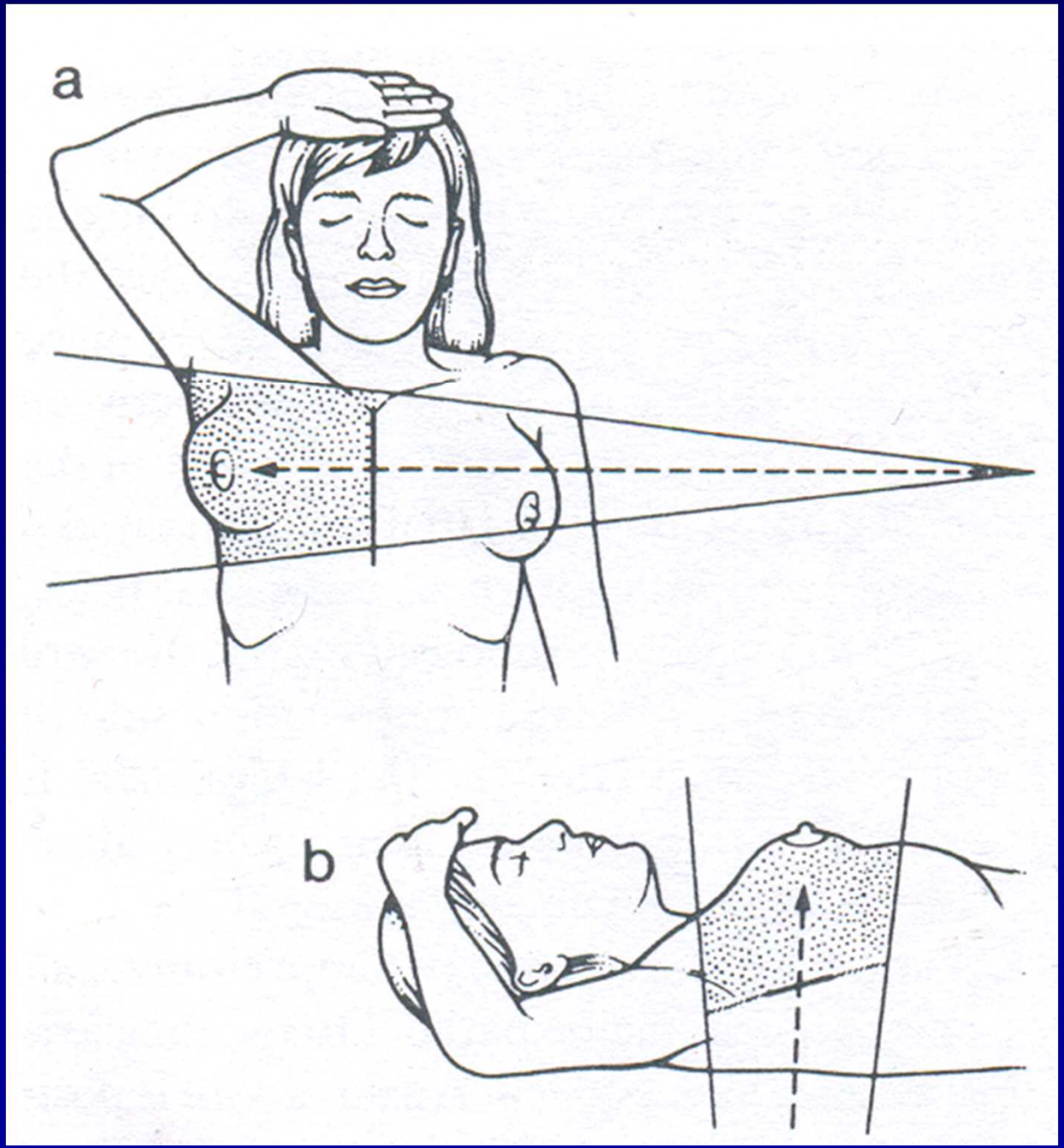
- Young age increase risk
- Positive margins increase risk
- Systemic therapy lowers risk
- Higher RT doses lowers risk
- Extensive intra-ductal component increase risk
- LCIS increase risk
- Lobular histology - higher risk
- BRCA1-2 - higher relapse
- Larger tumors - higher local relapses
- Node-positive - higher local relapse
- ER/PR negative- higher local relapse
- Her 2+ tumors

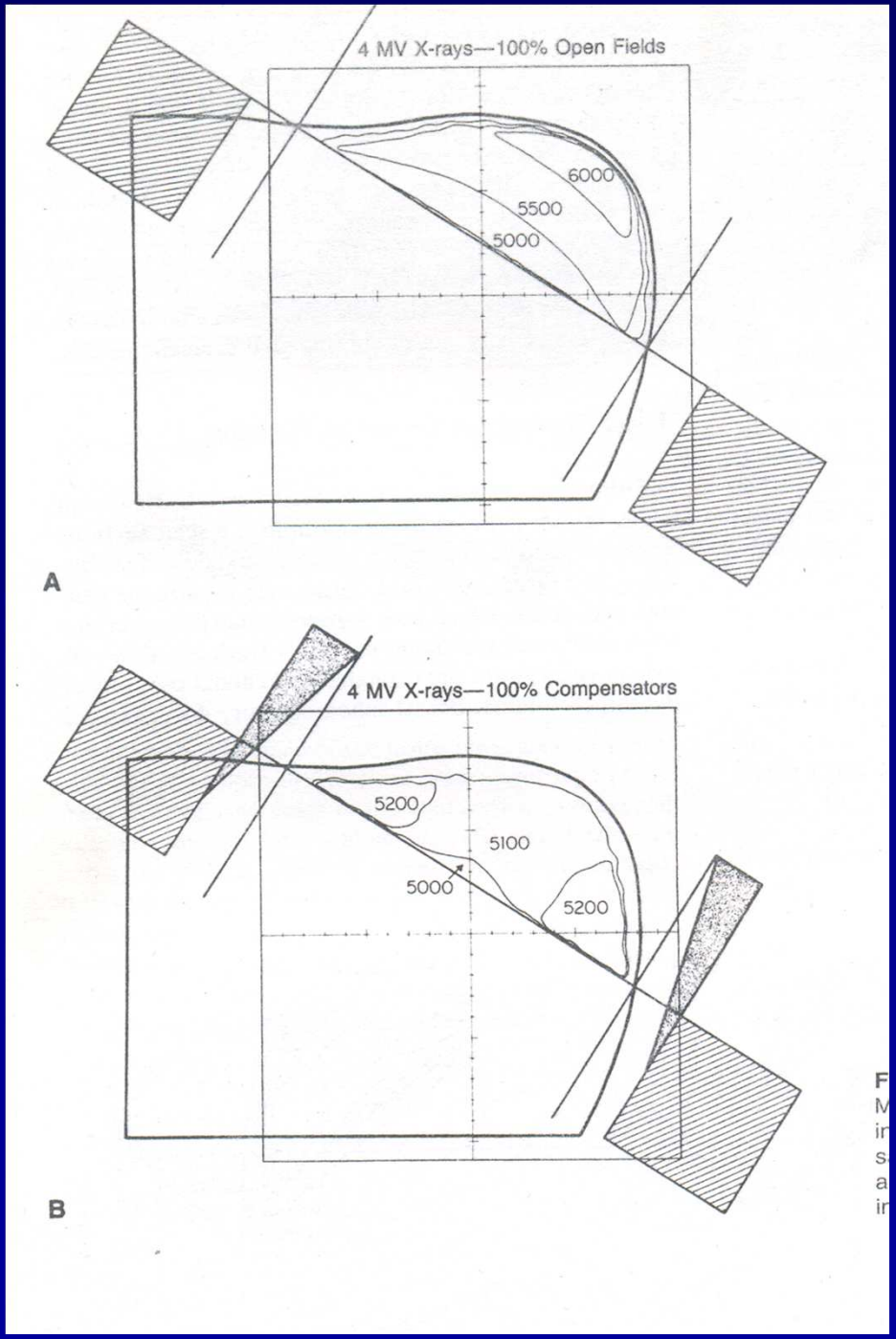
RT in BCT

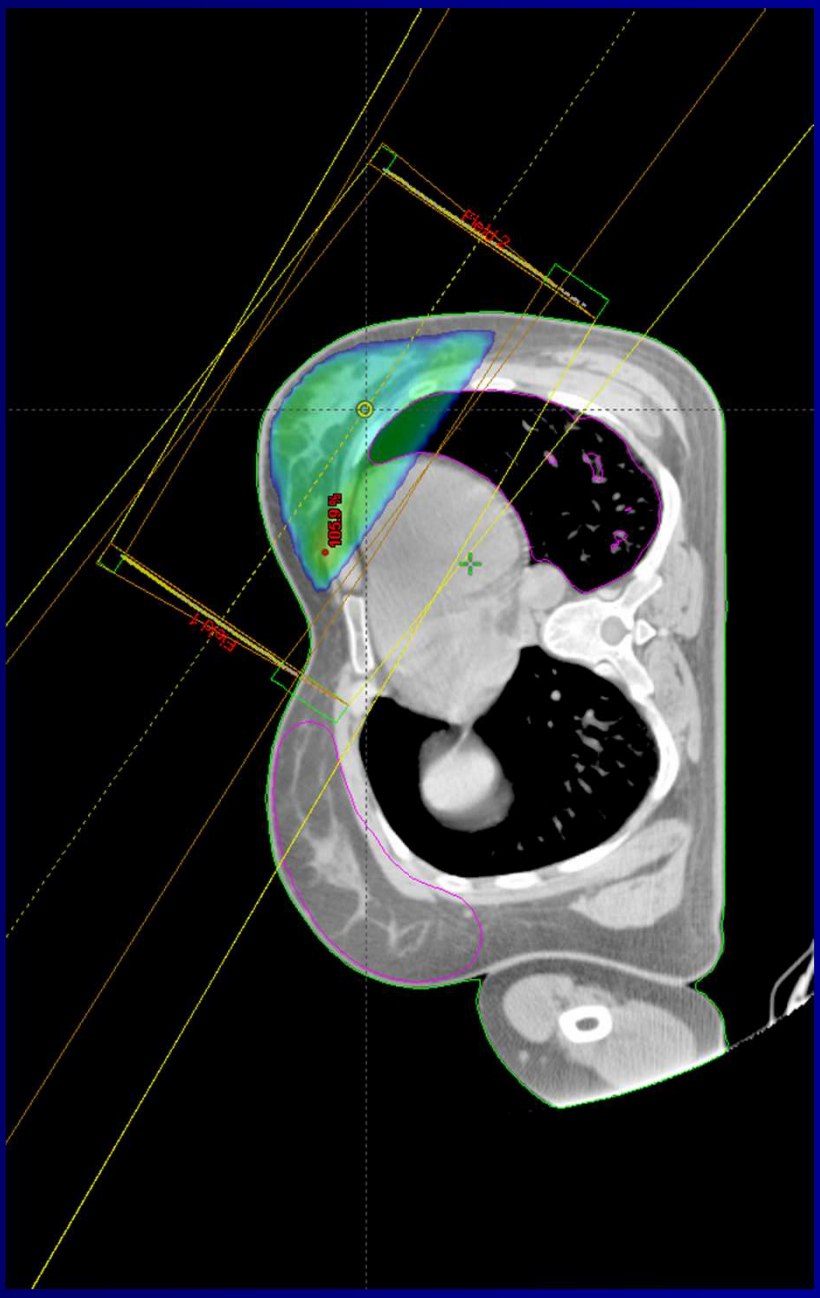
- Volume of irradiation

  Whole breast ----→ boost to the tumor site

  Axilla and SCF if necessary
- 45-50 Gy to whole breast by Ext RT
- 10-16 Gy boost by electron/photon/brachy


a
b


4 MV X-rays—100% Open Fields
6000
5500
5000
A
4 MV X-rays—100% Compensators
5200
5100
5000
5200
B


Field 2
105.9 %
Field 3

Limitations with conventional radiotherapy

- Dose inhomogenity
  - Due to continuous change of contour of breast .
  - 15-20 % dose inhomogenity may result in superior and inferior plane of breast.
  - Medial and lateral aspect of breast may get higher dose of radiation.

- Radiation accompaniments (lung, heart)
  aim of newer techniques is to further minimize the accompaniments.

RATIONALE FOR NEWER TECHNIQUES

- Improving dose homogenity within the tumor
- Avoidance of radiation to normal structures
- Reduction of treatment related toxicites.
- Reduction of treatment time.
- Improvement in local control and survival.

NEWER EB-RADIOTHERAPY TECHNIQUES IN EBC

- 3D CRT
- IMRT
- CT scan based planning
- Use of Tissue Compensators
- Gated Radiotherapy
- Partial Breast Irradiation

IMRT

- IMRT is an approach to conformal therapy that not **o**nly conforms high dose to tumor tissue but also conforms low dose to surrounding normal tissue.

- Dose intensity is varied in the tumor volume
  A higher dose can be delivered to tumor tissue
  Minimal dose is delivered to surrounding normal tissues.

Higher tumor control probability
Minimal side effects of radiotherapy

GATED RADIOTHERAPY

- Tumor motion taken into account while radiation treatment is being delivered.

- Techniques of Gating

A. Breath hold technique
- Active- airway of patient is temporarily blocked by a valve
- Passive- the patient temporarily holds the breath

B. Synchronized Gating
external devices are used to predict the phase of respiratory cycle while patient breathes freely

USE OF TISSUE COMPENSATORS

- Compensator- is a device which compensates for missing tissues.
- Use of tissue compensators improve dosimetry and reduce complications.
- Various types of tissue compensators are used

  - Tissue equivalent materials

  - MLC

Boost in BCT

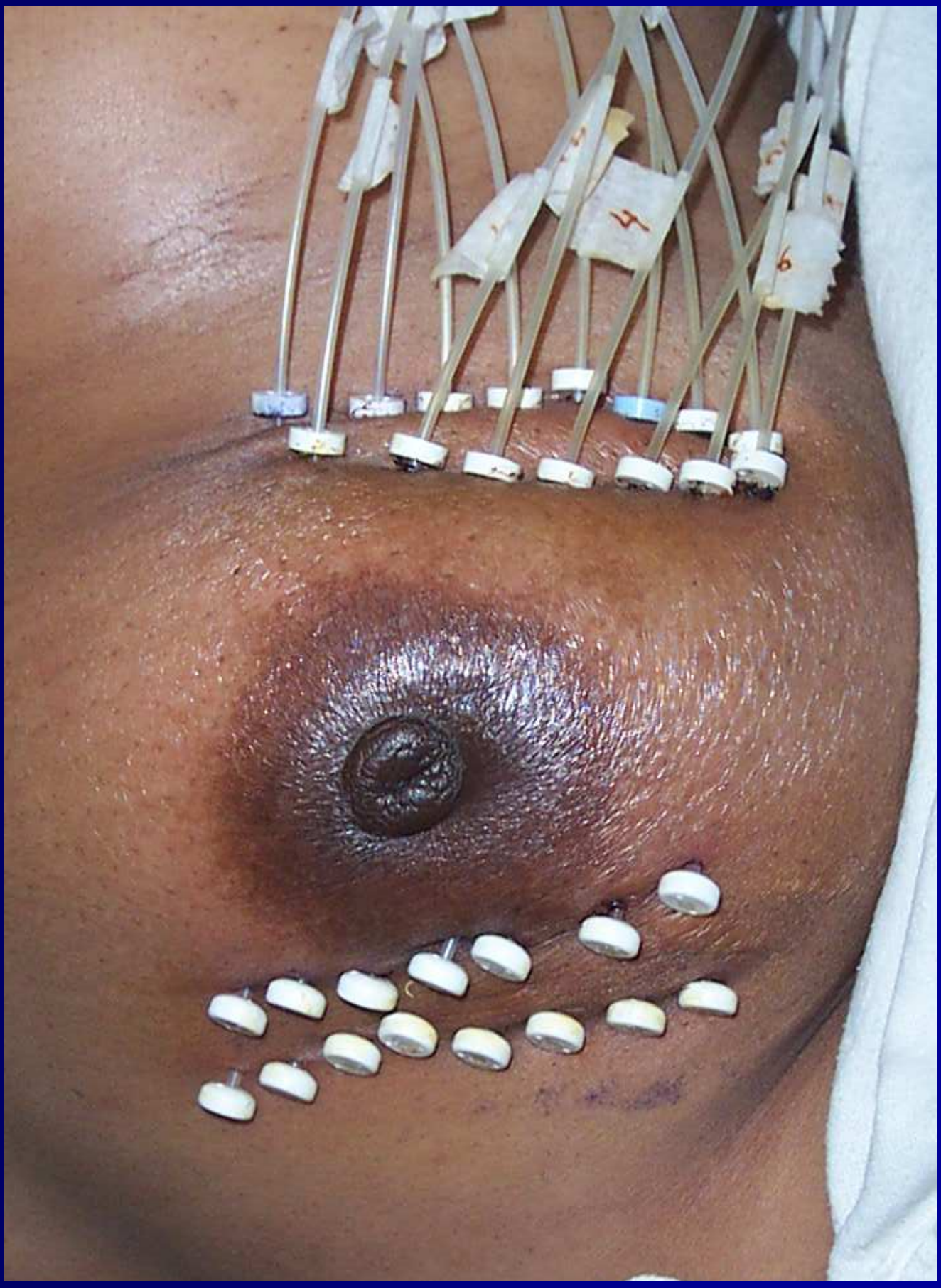
METHODS

- Electron beam
- Photon beam- 3DCRT/IMRT
- Interstitial Brachytherapy
- IORT
- Mammosite

INTERSTITIAL BRACHYTHERAPY

- Main advantage lies in ability to tightly conform dose to a specified volume.
- Used as a boost following BCT along with EBRT

- Clinical situations where brachytherapy may be more useful than EBRT include – Large breasts
  -Deep seated tumors
  -Extensive intra-ductal comp.
  -Uncertain margins.
- Shorter treatment times



INTRAOPERATIVE RADIOTHERAPY (IORT)

- IORT is a radiotherapeutic technique which delivers a single dose of radiation to tumor bed or to exposed tumor during surgery.
- It is used mainly as a boost to be followed by EBRT.
- Rationale : 85 % of relapses in BCT after RT occur in the operated area.

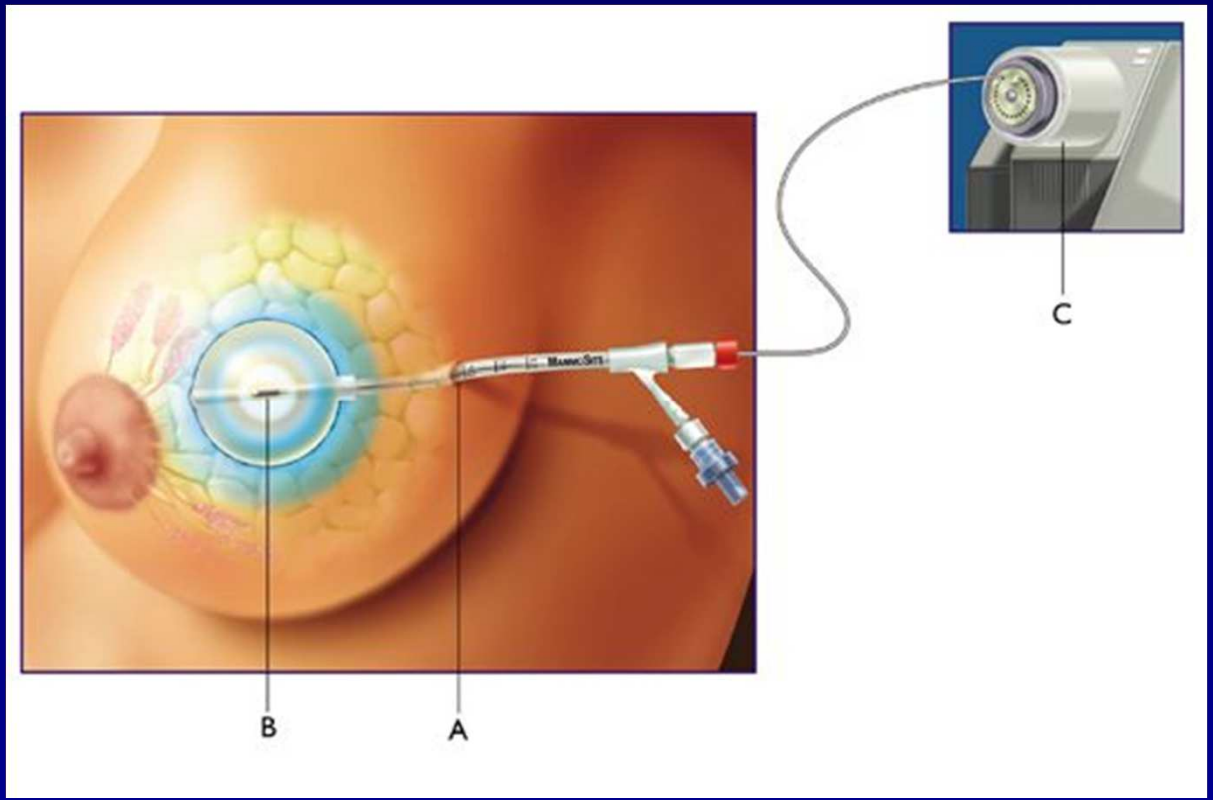
Techniques:

IOHDR

IOERT

MAMMOSITE

- Can be used for primary radiation or as a boost
- HDR with Iridium –192 source is used.
- Places the radiation source inside the lumpectomy cavity.
- Cosmetic results are good to excellent in 88% of cases.



- Dose prescribed at 1cm from applicator surface
- Treatment usually completed in 5 days
- A minimum skin to balloon surface distance of 5mm required
- The principal dose limiting factor is the dose to overlying skin

- Accompaniments :
  - Due to device placement-
    Mild erythema, pain, drain leakage,ecchymosis.
  - Due to radiation therapy-
    erythema, dry desquamation

- Factors limiting use of mammosite
  Balloon- cavity conformance
  Skin – balloon cavity surface distance

Better Local Control with RT Boost

Dose fractionations used in various prospective randomized studies of boost versus no boost.

Trial	Number of patients	EBRT (dose/fraction)	Boost (dose/fraction)	LR (%)	Median Follow-up (year)
Bartelink et al. 11	2657	-50Gy/25 fr	-	10.2	10
	2661	50 Gy/25 fr	16 Gy/8 fr	6.2	
Romestaing et al. 24	503	47-50 Gy/20 fr	-10 Gy/4 fr	4.5	3.3
	521	50 Gy/20 fr		3.6	
Teissier et al. 25	327	48-50 Gy/25 fr	-	6.8	6.1
	337	50 Gy/25 fr	10 Gy/5 fr	4.3	
Polgar et al. 26, 27	103	49-50 Gy/25 fr	-	15.5	5.3
	104	50 Gy/25 fr	12-16Gy/3-8 fr	6.7	
Graham et al. 28*	674	50 Gy/25 fr	-	NR	NR
	674	45 Gy/25 fr	-	NR	
Nagykalnai et al. 29	55	50 Gy/25 fr	-	10.7	3.8
	56	50 Gy/25 fr	10 Gy HDR/20 Gy LDR	5.4	

Acta Oncologica 2007; 46:879 - 892

Delineation of Tumor Bed for Boost

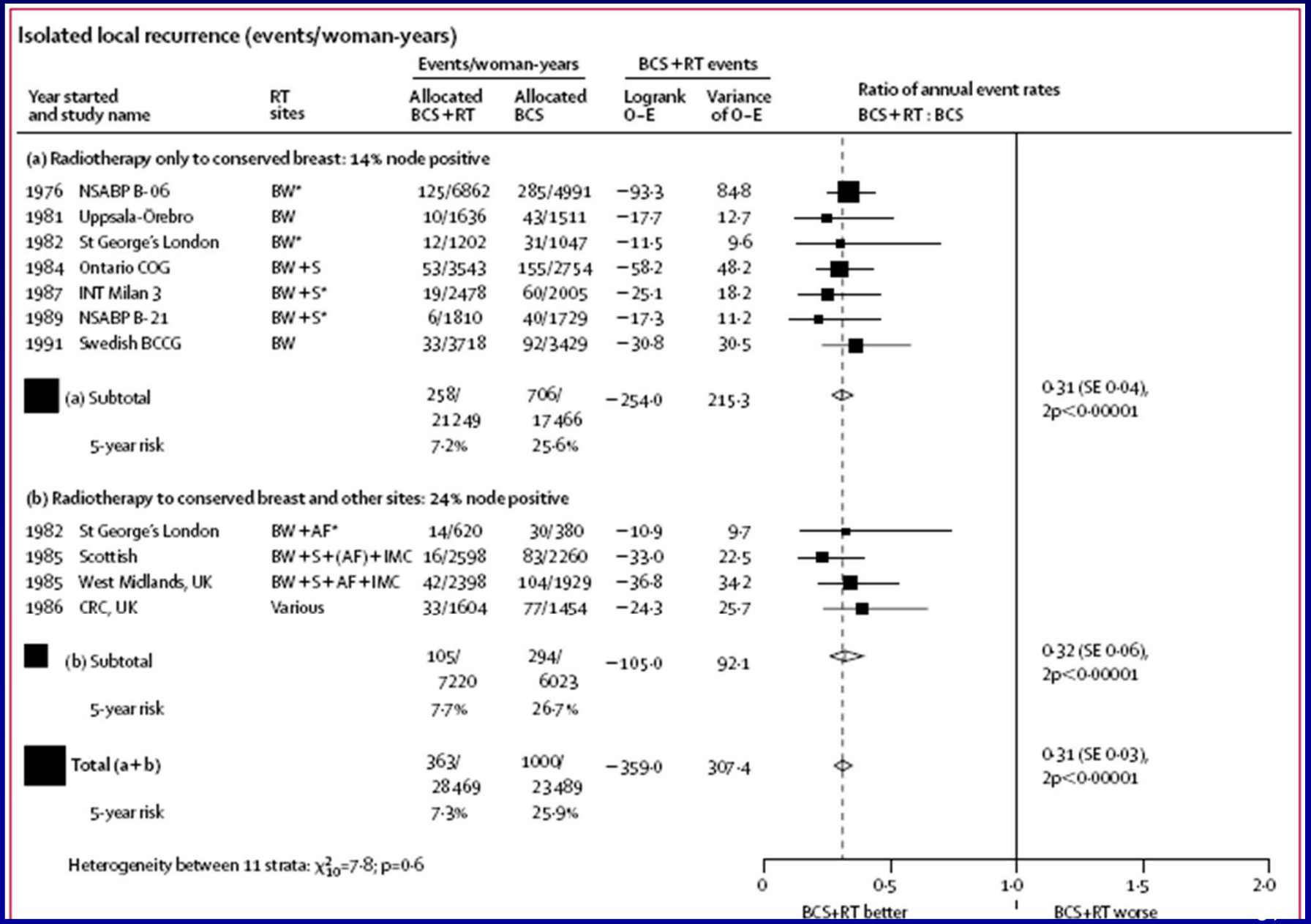
- Clinical-

  history and patients' recollection of tumor position, clinical photographs, tattoos, surgical scar
- Mammography
- Surgical clips
- Ultrasonography
- Computerized tomography (CT) scan
- Magnetic resonance imaging (MRI)
- *Peroperative placement of catheters*

Selected Randomized Trials of Breast-conserving Surgery with or without Radiation

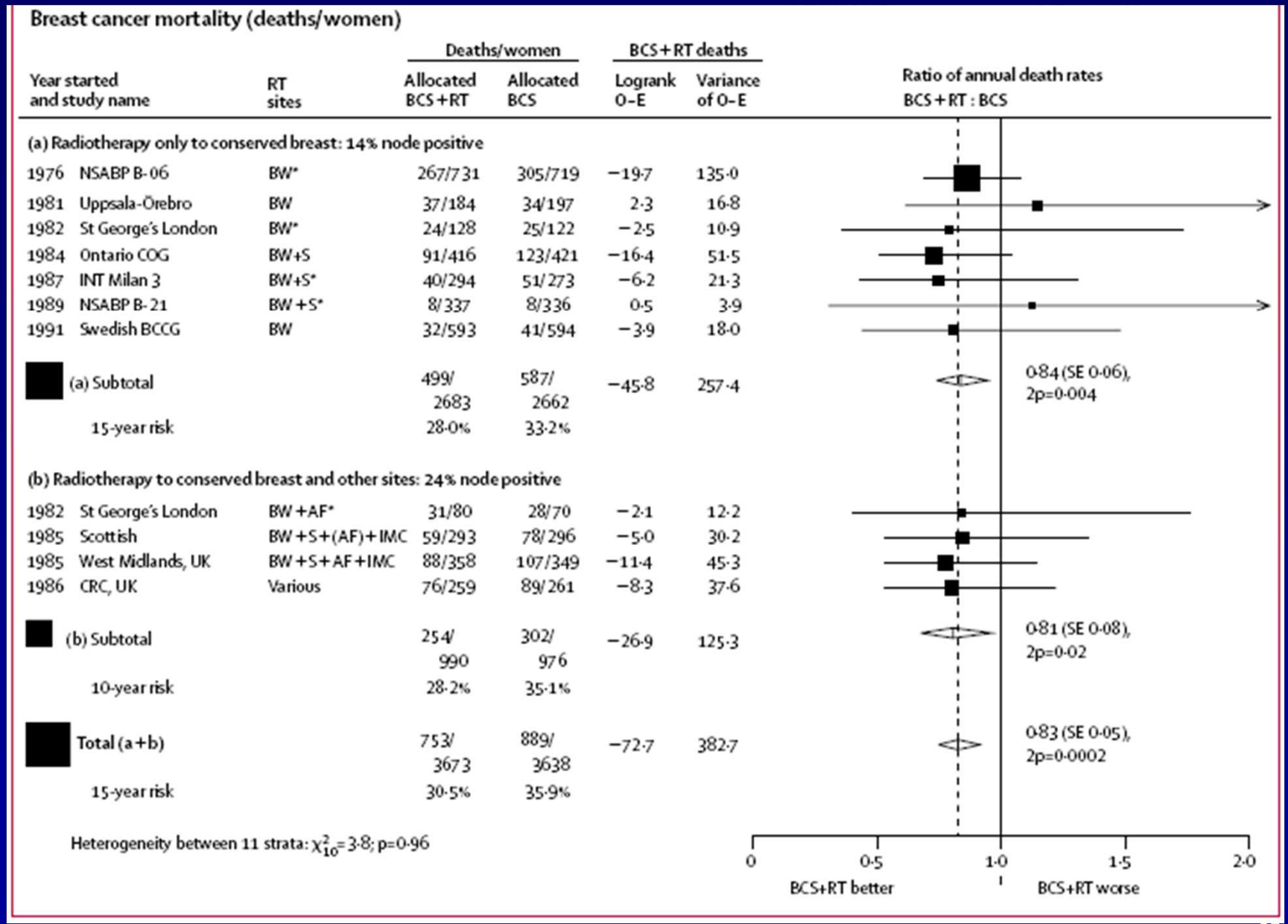
Study	T, N	No. of Patients	Follow-Up (yrs)	LR		
				With RT(%)	Without RT (%)	*p* Value
Fisher et al.	<4 cm node positive/negative	930	10	12.4	40.9	<.001
Liljegren et al.	<2 cm node negative	381	10	8.5	24.0	.0001
Veronesi et al.	<2.5 cm	579	10	5.8	23.5	<.001
Clark et al.	<2 cm node negative	837	3	5.5	25.7	<.001
Fisher et al.	<2 cm node negative	1,009	8	2.8	16.5	<.001
Winzer et al.	<2 cm node negative	347	5.9	3.2	27.8	<.001

Meta-analysis of local control EBCTCG



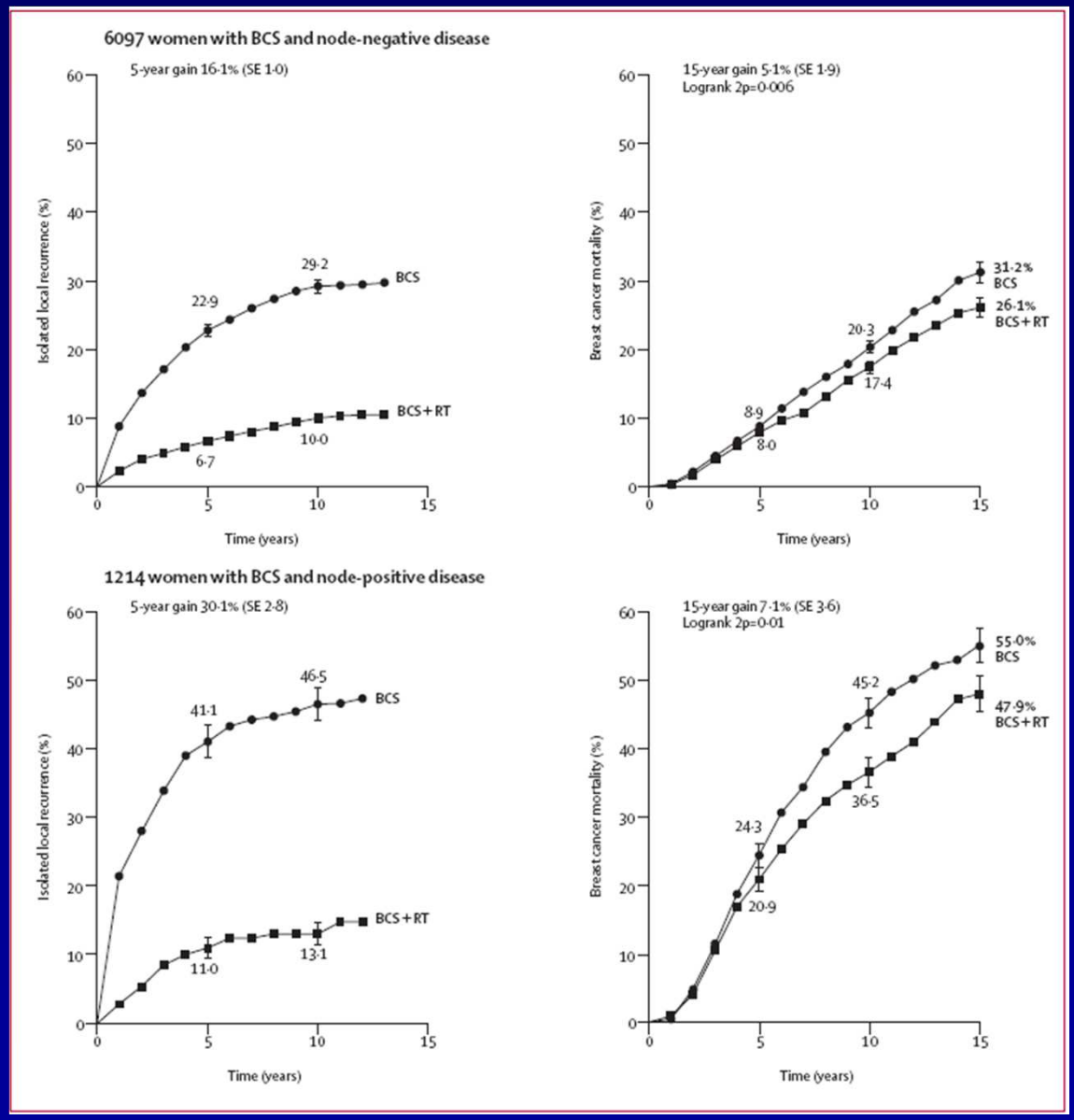
Lancet 2005;366:2087–2106,

Meta-analysis of survival EBCTCG



Lancet 2005;366:2087–2106,

Effect of RT after BCS on local recurrence and on breast cancer mortality—15-year probabilities. EBCTCG Meta-analysis



Lancet 2005;366:2087–2106,

AIIMS DATA

Attitudes and treatment outcome of breast conservation therapy for stage I & II breast cancer using peroperative iridium-192 implant boost to the tumour bed.

- Surgery with peroperative implantation of iridium-192 to deliver a boost.
- Whole breast irradiation was delivered 3-4 weeks after the boost.
- Cosmesis was assessed at the end of 6 months from completion of therapy.
- There were no locoregional failures at a median follow up of 42 months.
- One patient experienced a systemic relapse.
- Cosmesis was good to excellent in 80% of patients.
- Breast conservation therapy using peroperative iridium-192 implant provides excellent locoregional disease control and cosmesis.

Deo SS, Mohanti BK, Shukla NK, Chawla S, Raina V, Julka PK, Rath GK.
Australas Radiol. 2001 Feb;45(1):35-8

AIIMS DATA

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Breast conservation therapy for breast cancer: Patient profile and treatment outcome at a tertiary care cancer centre

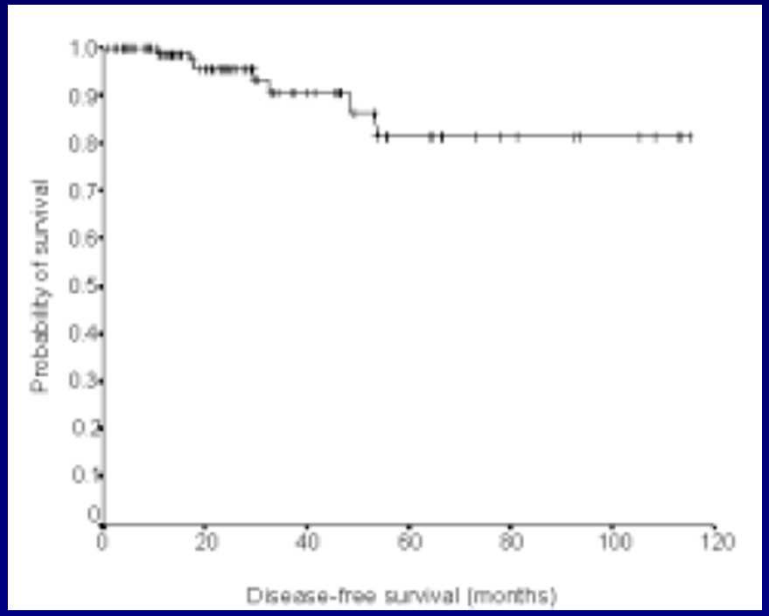
S. V. S. DEO, A. SAMAIYA, N. K. SHUKLA, B. K. MOHANTI, V. RAINA, J. PURKAYASTHA, M. BHUTANI, M. KAR, S. HAZARIKA, G. K. RATH

TABLE I. Profile of patients who had breast conservation therapy (n=102)

Characteristic	n	(%)
Age (years)		
<35	20	(19.6)
35–50	57	(55.9)
>50	25	(24.5)
Menopausal status		
Premenopausal	53	(52)
Postmenopausal	49	(48)
Parity		
Nulliparous	4	(4)
Multiparous	98	(96)
Tumour location (quadrant)		
Upper outer	61	(59.8)
Upper inner	19	(18.6)
Lower outer	14	(13.7)
Lower inner	3	(2.9)
Central	5	(4.9)
pTNM stage		
I	24	(23.5)
II A	40	(39.2)
II B	26	(25.4)
III A	9	(8.8)
III B	3	(2.9)
IV	0	

Treatment	Number of patients
Surgery	
Quadrantectomy	08
Wide Excision	64
Re-excision of tumor bed	**30**
ALND	102
Radiotherapy	
Whole breast	102
Tumor bed boost	102
Brachytherapy	**22**
Electron	80
Axilla	28

Results



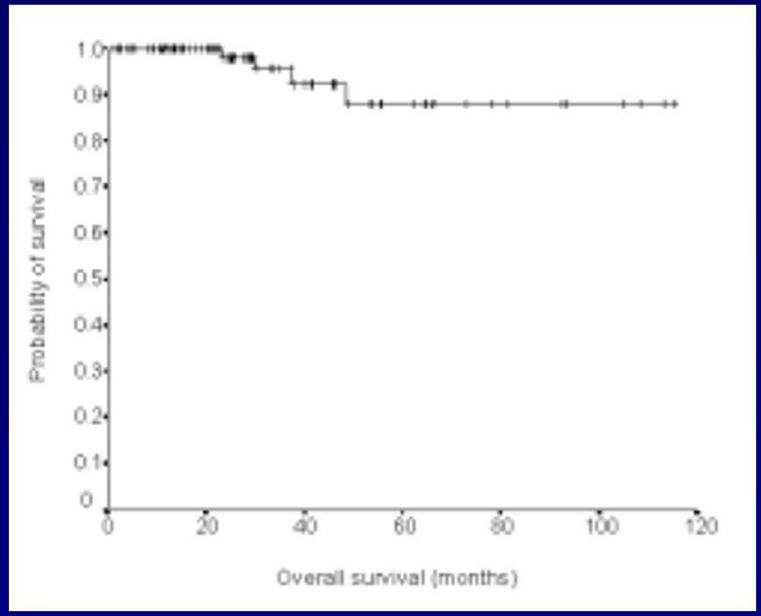


TABLE II. Sites of relapse (n=7)

Site	*n*	(%)
Local	1	(1)
Contralateral primary	2	(1.9)
Systemic	7	(6.8)
Liver	1	
Brain	1	
Skeletal	2	
Liver and lung	1	
Lung and brain	1	
Skeletal and brain	1	

Only 19.6 % of EBC underwent BCT

5YR Projected DFS 82% and OS- 88%

Partial Breast Irradiation

Definition

Delivery of larger doses/fraction of radiation to the lumpectomy cavity (plus 1-2 cm margin) after breast conserving surgery in patients with early stage breast cancer

PBI: Concept

Selected cases (low risk)

- Partial breast
  - Only the breast tissue adjacent to the tumor bed is irradiated
- Accelerated schedules
  - Dramatic reduction in duration of RT to 1-5 days

➔ Accelerated Partial Breast Irradiation (APBI)

PBI: Scientific rationale

- 80% of breast recurrences after BCS occur at or near the tumor bed, implicating residual tumor foci from the original index tumor
- Major effect of post-lumpectomy radiotherapy: reduce risk of recurrence in tumor bed region
- Incidence of ‘elsewhere’ failures 3-5%
- Some ‘elsewhere’ failures- new primaries, unaffected by whole breast irradiation
- Whole breast radiation may not be needed in “appropriately” selected cases

Failures Outside of the Tumor Bed in Randomized Trials Comparing Lumpectomy with/without Postop RT

		Surgery alone		Surgery plus RT	
Trial	Median f/u (mo)	N	%	N	%
NSABP-B06	125	17 / 636	2.7	24/629	3.8
Milan	39	4 / 273	1.5	0/294	0
Uppsala-Orebro	64	7 / 197	3.5	-	-
Ontario	43	15 / 421	3.5	4/416	1.0

Baglan KL et al. *Int J Radiat Oncol Biol Phys*. 2001;50:1003-11.

PBI: Potential advantages

- Reduces overall treatment time
  - Improves acceptability of BCT
  - Reduces waiting time for radiotherapy
  - Improves access to radiotherapy treatment machines
- Smaller treatment volumes
  - Large dose per fraction may be delivered without an increase in toxicity
  - Normal structures like heart, lungs, contralateral breast may be spared
- Better cosmetic results (lower skin & breast parenchyma integral dose)
- Eliminate scheduling problems with systemic chemotherapy
- Cost savings
  - Reduces hospital visits
  - Reduces absence from work and associated income losses
- Improves quality of life

Patient selection

- Age: Postmenopausal
- T2 or less
- N0
- Low grade
- Negative surgical margins
- ER +

- Exclude
  - Young patients
  - Large tumors
  - N+
  - High grade
  - Multicentric
  - Invasive lobular histology
  - EIC
  - Positive surgical margins

Patient Selection Criteria

	ABS [1]	ASBS[2]	William Beaumont Hospital [3]
Age (years)	≥45	≥50	≥45
Histology	Unifocal, IDC	IDC or DCIS	IDC
Tumor size	≤ 3cm	≤ 2cm	≤ 2cm
Surgical margins	Negative	Negative ≥ 2mm	Negative
Nodal status (Axillary/ sentinel)	N0	N0	N0
Cavity to skin distance	Not stated	Not stated	>5 mm

1 Arthur D, et al. Brachytherapy. 2003
2 ASBS Consensus statement for APBI. April 30, 2003.
3 Edmundson GK, el al. Int J Radiat Oncol Biol Phys. 2002

PBI: Techniques

- Brachytherapy
  - Interstitial Brachytherapy
  - Mammosite balloon brachytherapy
- Intraoperative radiotherapy
  - Intraoperative electrons (IOERT)
  - Targeted intraoperative radiotherapy (TARGIT)
  - Brachytherapy
- EBRT
  - Electrons
  - 3D-CRT
  - IMRT
  - Protons

ASBS consensus statement for APBI

- Outside of multi-institutional studies and institutional protocols, patients should be carefully selected for APBI and properly informed of the benefits and risks of this type of radiation treatment.
- The following selection criteria when considering patients for treatment with APBI:

- • Age 45 years old or greater
- • Invasive ductal carcinoma or ductal carcinoma in situ
- • Total tumor size (invasive and DCIS) less than or equal to 3 cm in size
- • Negative microscopic surgical margins of excision
- • Axillary lymph nodes/sentinel lymph node negative

ASBS consensus statement for APBI contd..

- Surgeons, radiation oncologists and physicists who will be utilizing the various APBI techniques should be adequately trained to allow for optimum radiation therapy planning and treatment.
- All patients should be monitored regularly to identify adverse events as well as local recurrences.
- Continuous, long-term, outcomes-based monitoring of APBI is desirable.

Comparison of selected APBI techniques

Technique	Advantages	Disadvantages
Interstitial brachytherapy	•Oldest method, so extensive FU data available •Most adaptable to oddly shaped surgical cavities •New image-guided methods for catheter placement available	•Learning curve required •Relies heavily on operator experience •Most invasive of the APBI techniques—often requires GA for catheter placement
3-D Conformal EBRT	•Noninvasive •↑ dose homogeneity •Potential for best cosmesis	•Newest technique, so experience relatively limited •Time-consuming planning process •Larger volume of breast treated
Mammosite	•Easiest for patient and oncology team •Widely available	•Requires close communication between surgeon and radiation oncologist •Limited ability to adapt to less-than-ideal surgical cavity

Conclusions

- Radiotherapy is an integral part of BCT
- RT improves local control and survival
- Evidence of better Local Control with RT Boost
- APBI may be an alternative to whole breast radiotherapy
  - Smaller treatment volume
  - Shorter treatment time
  - Dose intensity
  - Reduced toxicity
  - Increased acceptability (patient / physician)
- APBI Requires:
  - Optimal patient selection
  - Appropriate target delineation
  - Meticulous QA

THANK YOU