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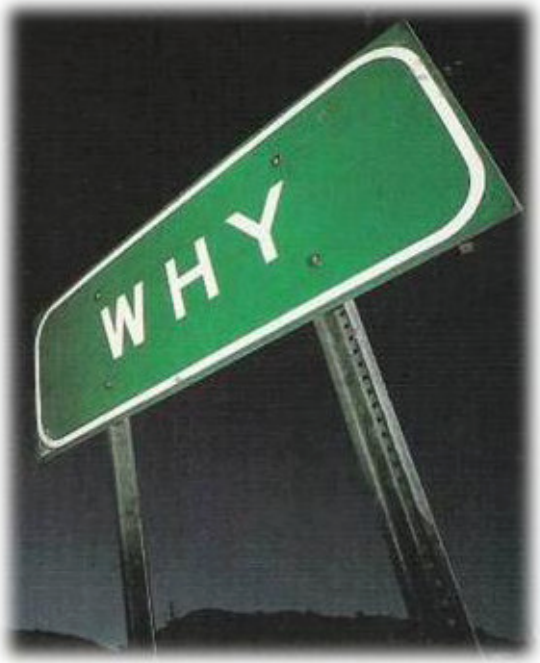
Brescia Meetings in Radiation Oncology – 2011 Edition

RADIOTHERAPY: SMALLER VOLUMES FOR SHORTER TIMES. WHY? HOW? WHEN?

APBI: IMRT

Icro Meattini, MD
AOU Careggi, Florence

PARTIAL BREAST IRRADIATION
AFTER BREAST-CONSERVATIVE SURGERY



RADIOTHERAPY: SMALLER VOLUMES FOR SHORTER TIMES

WHY? HOW? WHEN?

INTENSITY-MODULATED RADIOTHERAPY (IMRT): WHY

- Advanced form of 3D-CRT **uses non-uniform radiation beam intensities**

- **Can sculpt the high-dose volume around the site of disease; inhomogeneous dose painting is possible**

- **"Inverse treatment planning" procedure**

(Starting from the desired dose distribution the modulated beams fluence is determined)

IMRT – Advantages

OPTIMIZING DOSE DISTRIBUTION

- Improving "target/s" *coverage*
- Avoiding *"unnecessary"* normal tissue irradiation

Dose distribution improvement

- May potentially increase *tumor control*

- Can avoid "unnecessary" *acute and chronic toxicities*
- May cause more optimal *cosmetic results*

APBI IMRT IMPROVED DOSE DISTRIBUTION WHEN COMPARED WITH 3D TREATMENT-PLANNING TECHNIQUES

63 patients with Tis-1N0M0 breast cancer were treated on a Phase II prospective accelerated partial-breast IMRT protocol.

Cases were *replanned* with 3D-CRT techniques using the same contours, to compare the dose distribution patterns of 3D-CRT vs. IMRT.

IMRT improves normal tissue sparing in the homolateral breast without compromising dose delivery to the lumpectomy cavity and clinical target volume ($p<0.01$).

The irradiated heart and lung volumes were small with both techniques but also favoured IMRT.

Rusthoven KE et al, IJRBOP, 2008

APBI IMRT – Advantages

- Reduced overall treatment time

Morganti AG et al, Radiother Oncol, 2009

- Further reduction of dose to homolateral **lung**

Remouchamps et al, Int J Radiat Oncol Biol Phys, 2003

- Further reduction of dose to the **heart**

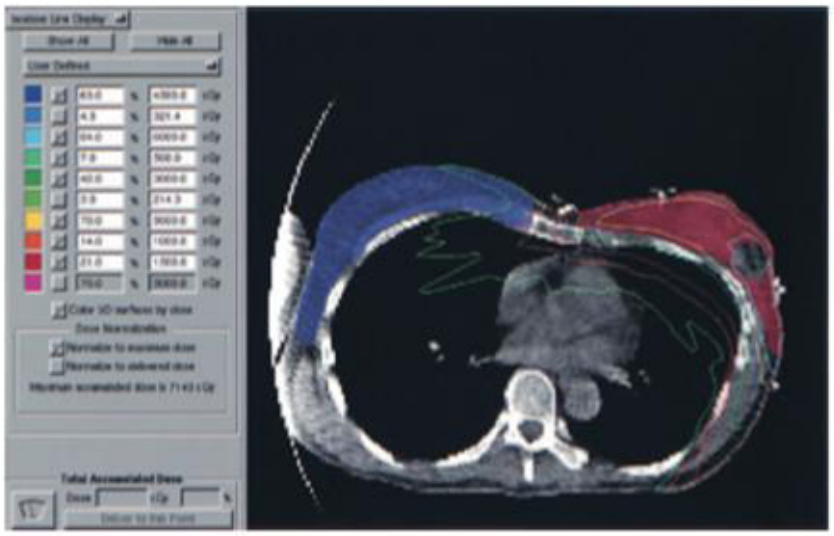
Gagliardi et al, Radiother Oncol, 1998

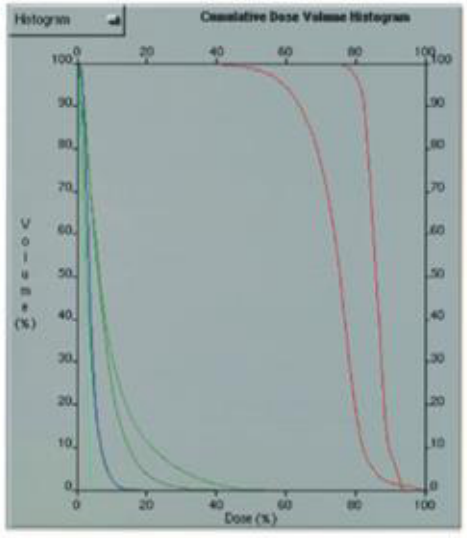
IMRT in Women with Pectus Excavatum Desiring Breast-Conserving Therapy

The conventional opposed tangential technique usually delivers too much radiation to the surrounding normal tissues, especially the **homolateral lung**.

IMRT offers a **more favourable toxicity profile** over conventional radiation therapy.

Teh BS et al, The Breast Journal, 2001





Not always→ IMRT= one more **option** for Clinical Oncologist

IMRT and Acute Radiation Dermatitis

Breast **IMRT** significantly **reduced** **the occurrence of moist desquamation** compared with a standard wedged technique. Moist desquamation was correlated with increased pain and reduction in the quality of life.

Pignol JP et al, JCO, 2008

Breast IMRT is associated with a **significant decrease** both in the time spent during treatment with Grade 2/3 dermatitis and in the **maximum severity of dermatitis**, regardless of breast size.

Maximum toxicity by technique was as follows:
48%, Grade 0/1, and 52%, Grade 2/3, for **IMRT**
25%, Grade 0/1, and 75%, Grade 2/3, for **conventional RT** ($p<0.0001$)

Freedman GM, IJROBP, 2009

IMRT and Late Toxicity

The use of **IMRT** in the treatment of the *whole breast* results in a **significant decrease in acute dermatitis, edema, and hyperpigmentation and a reduction in the development of chronic breast edema** compared with conventional fractionation RT.

Harsolia A, IJROBP, 2007

Patients in the **conventional** group were more likely to develop **telangiectasia** than those in the **IMRT** group ($p = 0.009$).

In patients who had **good surgical cosmesis**, those randomized to **IMRT** were **less likely to deteriorate** to a moderate or poor overall cosmesis than those in the control group ($p = 0.061$).

Barnett GC, IJROBP, 2011

APBI AND IMRT
DEBATED ISSUE AND POSSIBLE DISADVANTAGES

Irradiation with low dose of the surrounding normal tissue with possible increased **risk of secondary tumours**.

- 10-year incidence of contralateral breast cancer: 7%
- 10-year incidence of all-second non breast cancer malignancies: 8%

Fowble B, IJROBP, 2001

- RR for lung cancer: 1.6 – 3 (10 years)
- RR for oesophageal cancer: 1.3 – 2.2 (10 years)

Roychoudhuri R, Br J Cancer, 2004
Matesich SM, Semin Oncol, 2003
Zablotska LB, Am J Epidemiol, 2005

Adequate BED to reach an excellent local control of disease.

Rosenstein BS et al, IJROBP, 2004

RADIOTHERAPY: SMALLER VOLUMES FOR SHORTER TIMES

WHY? **HOW?** WHEN?

APBI and IMRT
Evidence Based Medicine

- 38 Gy in 3.8 Gy per fraction/twice daily for a total of 5 consecutive days.

Lewin AA, IJROBP, 2011

- 38.5 Gy in 3.85 Gy per fraction/twice daily for a total of 5 consecutive days.

Reeder R, IJROBP, 2009

- 40 Gy in 5 Gy per fraction/daily in 2 weeks.

Magee B, Radiother Oncol, 1996

- 30 Gy in 6 Gy per fraction/daily in 2 weeks.

Livi L, IJROBP, 2009

APBI and IMRT
Phase III ongoing randomized Florence Trial

ACCELERATED IMRT TO TREAT THE INDEX QUADRANT
30 Gy in 5 fractions (6 Gy/fr in 2 weeks)

versus

STANDARD WHOLE BREAST RADIOTHERAPY
50 Gy + boost 10 Gy in 30 fractions (2 Gy/fr in 6 weeks)

*AFTER CONSERVING SURGERY IN HIGHLY **SELECTED** EARLY BREAST CANCER **PATIENTS***
(pT < 20 mm; surgical margins > 5 mm; aged > 40 year)

Livi L, IJROBP, 2009

TARGET IDENTIFICATION

Surgical Clips

(mandatory)

to CTV identification

⇩

CTV

Surgical Clips + 1 cm 3D expansion

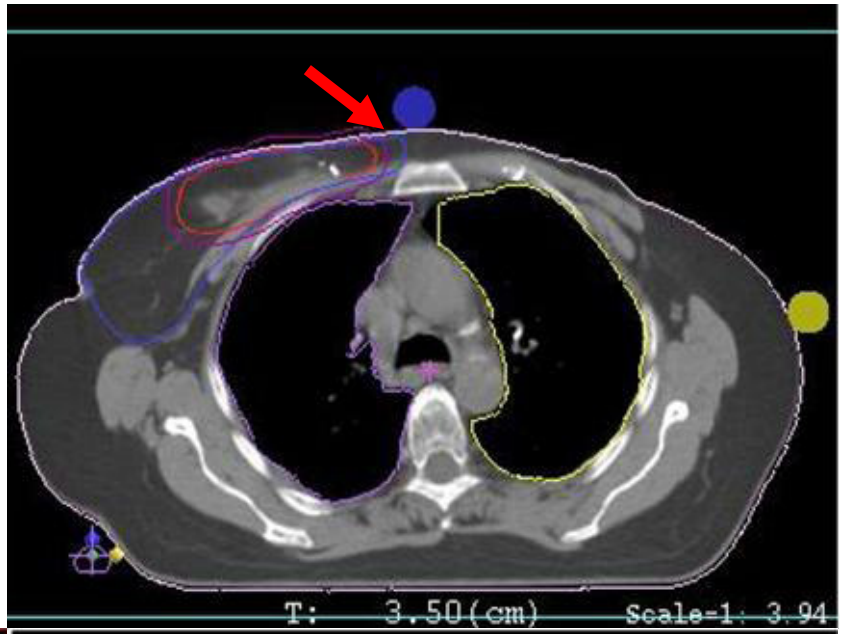
⇩

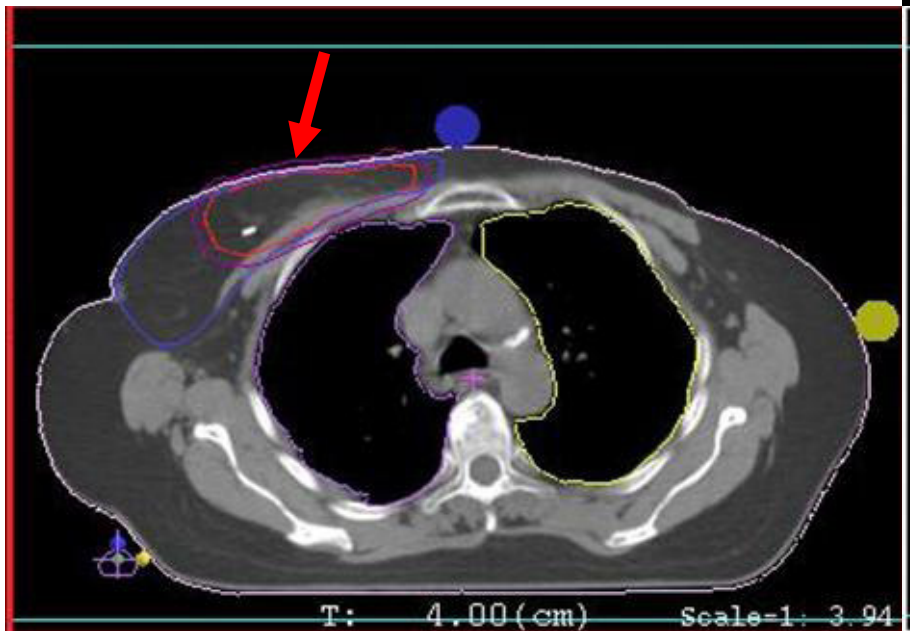
PTV

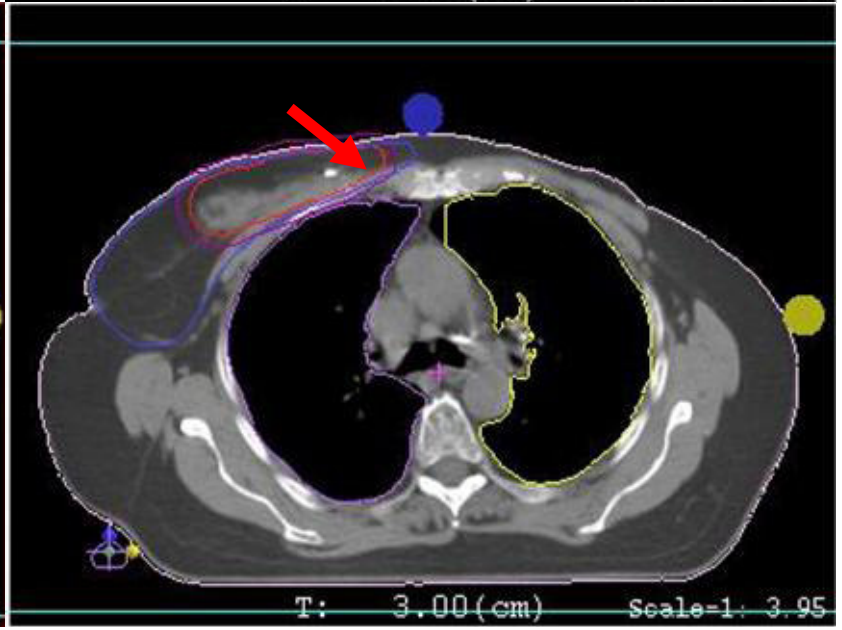
CTV + 1 cm 3D expansion

(limiting to 3 mm from skin and to 4 mm intrusion in homolateral lung)

TARGET IDENTIFICATION







VOLUMES CONTOURING

Target is contoured in each CT slice

<u>OARs</u>

HOMOLATERAL BREAST

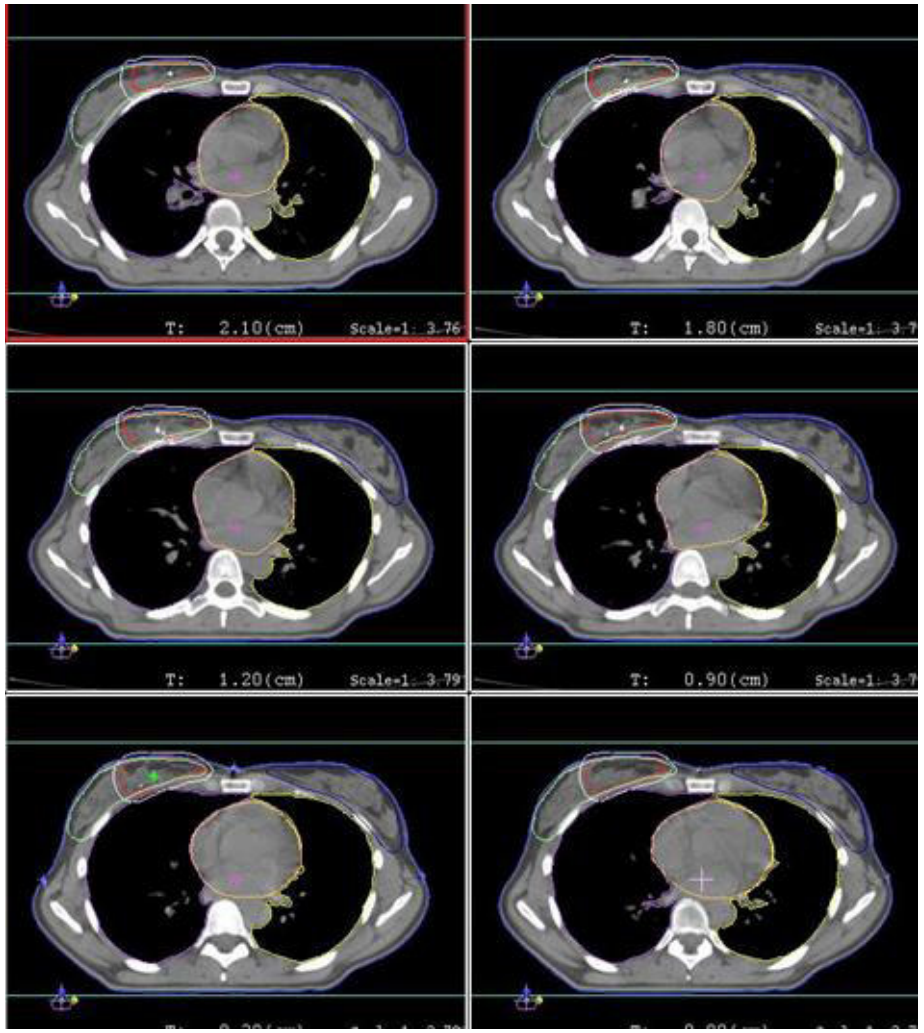
CONTRALATERAL BREAST

RIGHT LUNG

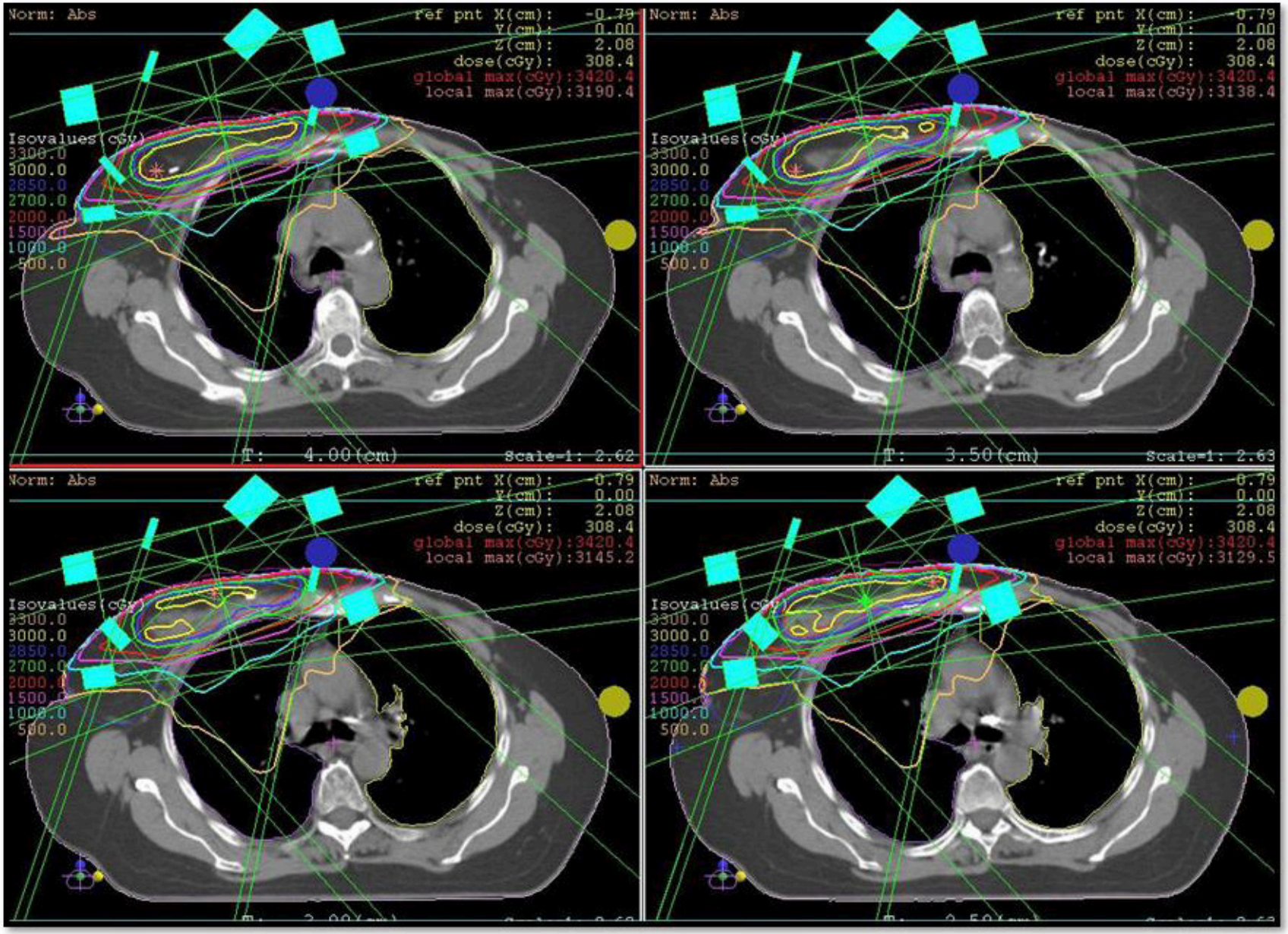
LEFT LUNG

HEART

SPINAL CORD

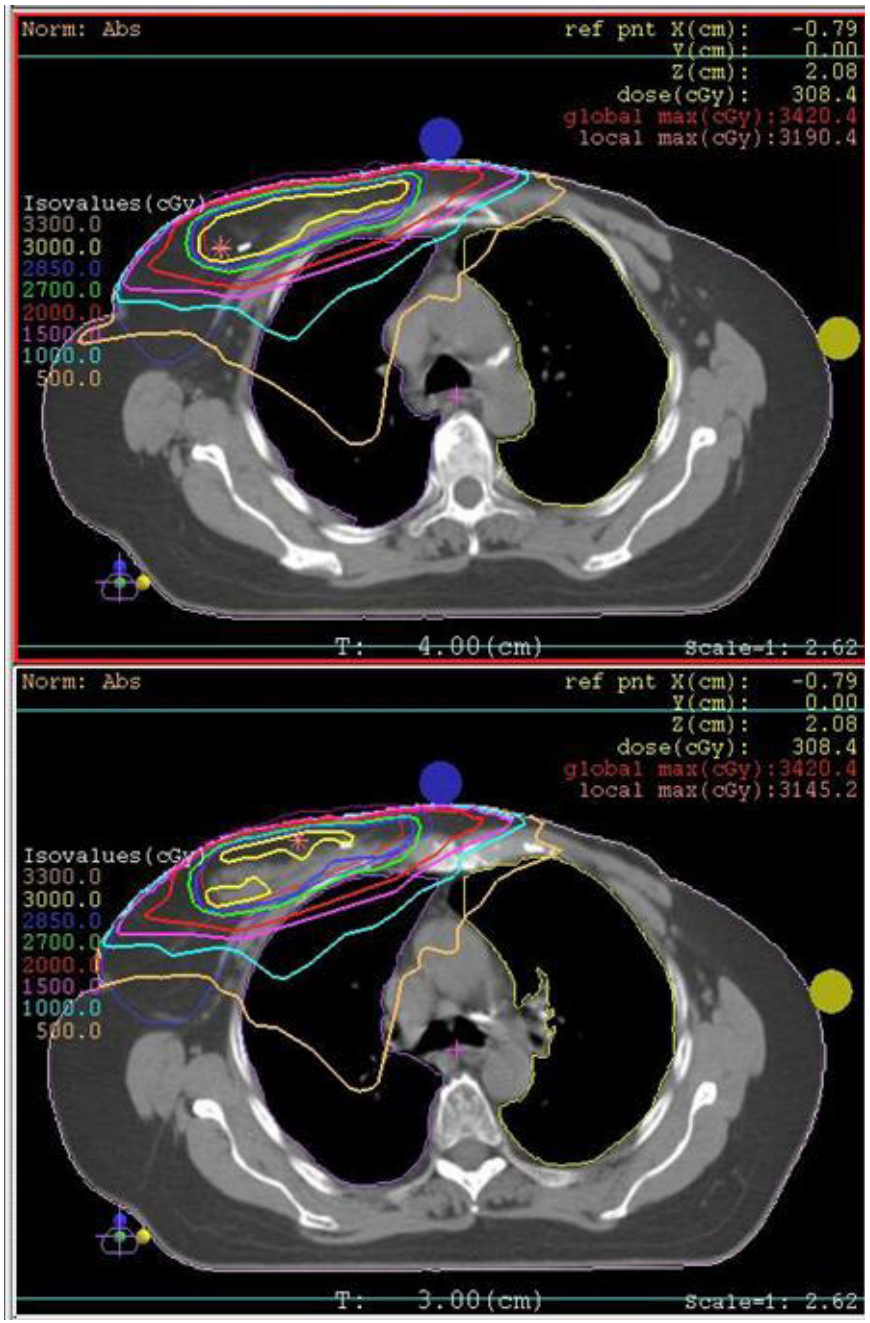


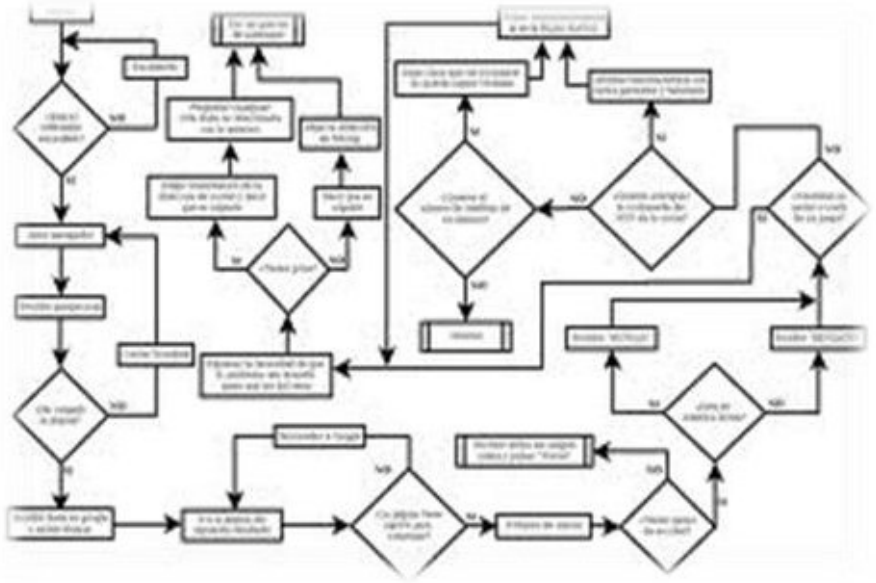
BEAMS PLANNING



DOSE CONSTRAINTS

OARs	Constraints
Contralateral Lung	V5<10%
Homolateral Lung	V10<20%
Heart	V3<10%
Homolateral breast (uninvolved tissue)	V15<50%
Contralateral Breast	Max 1Gy in each point





RADIOTHERAPY: SMALLER VOLUMES FOR SHORTER TIMES

WHY? HOW? **WHEN?**

PARTIAL BREAST IRRADIATION: WHEN

The necessity of giving Whole Breast Irradiation (WBI) for all patients after Breast Conserving Surgery has been questioned, and several centres have evaluated the feasibility and efficacy of accelerated partial-breast irradiation (APBI).

The results of these clinical trials showed that APBI **with proper patient selection and quality assurance** yields similar results to those achieved with standard WBI.

Despite **the 5-year results** of several Phase III randomized trials will be **available only in the next 5–10 years** for the radiation oncology community, and American and European experts **encouraged the use of APBI in the context of prospective phase III trials**, during the past few years the concept of APBI has been widely accepted by patients and treating physicians and **more than 30 000 patients have been treated outside clinical trials worldwide**.

ESTRO Recommendations, Radiotherapy and Oncology, 2010

Radiotherapy and Oncology 94 (2010) 264–273

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

GEC-ESTRO Recommendations

Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: Recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009)

Csaba Polgár [a,*], Erik Van Limbergen [b], Richard Pötter [c], György Kovács [d], Alfredo Polo [e], Jaroslaw Lyczek [f], Guido Hildebrandt [g], Peter Niehoff [h], Jose Luis Guinot [i], Ferran Guedea [j], Bengt Johansson [k], Oliver J. Ott [l], Tibor Major [a], Vratislav Strnad [l], On behalf of the GEC-ESTRO breast cancer working group

• 3 randomized and 19 prospective non randomized studies with a minimum median follow-up time of 4 years were identified.

(1)a low-risk group for whom APBI outside the context of a clinical trial is an acceptable treatment option;

(1)a high-risk group, for whom APBI is considered contraindicated;

(1)an intermediate-risk group, for whom APBI is considered acceptable only in the context of prospective clinical trials

ESTRO Recommendations

1. Low-risk group:

- Patients ageing **at least 50 years** with unicentric, unifocal, **pT1–2 (<30 mm) pN0**, non-lobular invasive breast cancer without the presence of an extensive intraductal component (EIC) and lympho-vascular invasion (LVI) and with negative surgical margins of at least 2 mm.

2. High-risk group:

- Patients ageing <40 years; having positive margins, and/or multicentric or large (>30 mm) tumours, and/or EIC positive or LVI positive tumours, and/or 4 or more positive lymph nodes or unknown axillary status (pNx).

3. Intermediate-risk group:

- Only patients enrolled in clinical trials.

Polgar C, Radiother Oncol, 2010

Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 4, pp. 987–1001, 2009

Printed in the USA.
0360-3016/09/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.02.031

CONSENSUS STATEMENT

ACCELERATED PARTIAL BREAST IRRADIATION CONSENSUS STATEMENT FROM THE AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO)

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AND JAY R. HARRIS, M.D.¶¶

- 4 randomized trials and 38 prospective single-arm studies were identified.

- The Task Force proposed three patient groups:

(1) a ‘‘suitable’’ group, for whom APBI outside of a clinical trial is acceptable.

(1) a ‘‘cautionary’’ group, for whom caution and concern should be applied when considering APBI outside of a clinical trial.

(1) an ‘‘unsuitable’’ group, for whom APBI outside of a clinical trial is not generally considered warranted.

ASTRO Consensus Statement

Suitable group

Factor	Criterion
Patient factors	
Age	≥60 y
BRCA1/2 mutation	Not present
Pathologic factors	
Tumor size	≤2 cm*
T stage	T1
Margins	Negative by at least 2 mm
Grade	Any
LVSI	No†
ER status	Positive
Multicentricity	Unicentric only
Multifocality	Clinically unifocal with total size ≤2.0 cm‡
Histology	Invasive ductal or other favorable subtypes§
Pure DCIS	Not allowed
EIC	Not allowed
Associated LCIS	Allowed
Nodal factors	
N stage	pN0 (i^-, i^+)
Nodal surgery	SN Bx or ALND‖
Treatment factors	
Neoadjuvant therapy	Not allowed

Cautionary group

Factor	Criterion
Patient factors	
Age	50–59 y
Pathologic factors	
Tumor size	2.1–3.0 cm*
T stage	T0 or T2
Margins	Close (<2 mm)
LVSI	Limited/focal
ER status	Negative†
Multifocality	Clinically unifocal with total size 2.1–3.0 cm‡
Histology	Invasive lobular
Pure DCIS	≤3 cm
EIC	≤3 cm

Unsuitable group

Factor	Criterion
Patient factors	
Age	<50 y
BRCA1/2 mutation	Present
Pathologic factors	
Tumor size*	>3 cm
T stage	T3-4
Margins	Positive
LVSI	Extensive
Multicentricity	Present
Multifocality	If microscopically multifocal >3 cm in total size or if clinically multifocal
Pure DCIS	If >3 cm in size
EIC	If >3 cm in size
Nodal factors	
N stage	pN1, pN2, pN3
Nodal surgery	None performed
Treatment factors	
Neoadjuvant therapy	If used

Smith BD, IJROBP, 2009

APBI and IMRT - Patient Selection
Phase III ongoing randomized Florence Trial

Inclusion Criteria

- Verified carcinoma of the breast
- tumour ≤ 25 mm with positive or negative axillary lymph-nodes
- Surgical margins (> 5 mm)
- Age at presentation ≥ 40 year
- Surgical clips in the tumour bed

Exclusion Criteria

- Heart dysfunction (EF < 50%)
- Pulmonary dysfunction (FEV1 <1 L/min)
- Massive intraductal invasion and/or Multifocal lesions
- Breast reconstruction
- Impossibility to attend regular follow-up
- Absence of clips in the tumour bed

Conclusions

- IMRT provides acceptable coverage of target volumes and an associated reduction of dose delivery to normal breast.

- IMRT reduces the incidence of acute and late toxicity related to breast, skin, and lungs.

- The advantage of IMRT is greatest in patients with more challenging anatomy, such as smaller breast size, a larger PTV/Homolateral Breast ratio, or tumours in the vicinity of the heart.

- IMRT deliver APBI using non-invasive modality.

Conclusions

- Many experiences reported APBI can be safely and effectively delivered via an IMRT technique for selected breast cancer patients.

- **Usefulness of Phase III trials in adjuvant setting of breast cancer?**

- Patients enrolled in our Phase III randomized study: 450.

- Minimal acute toxicity in IMRT APBI group. **100% of patients had G0 acute skin toxicity**; **2 patients had local breast relapse** *(0.8% IMRT group)* at **4 years** of median follow-up.

- APBI with IMRT may reach excellent results in terms of **local control** of disease, treatment **toxicity** and **Quality of Life**

Thanks for your attention...