AROI

ICRO PRE-CONFERENCE WORKSHOP - IMPACT MANGALORE
28th NOVEMBER 2024

44th Annual Conference of Association of Radiation Oncologists of India

AROCON 2024

New Horizons in Radiation Oncology : Biology to Imaging to Therapeutics

28th November- 1st December 2024

Dr. TMA Pai International Convention Centre, Mangaluru, Karnataka

ADJUVANT RADIOTHERAPY IN BREAST CONSERVATION SURGERY

Moderator: Dr. Shagun Misra, Additional Professor, SGPGIMS, Lucknow

Panelists:

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Case Capsule

- 49 years aged lady
- P1L1, postmenopausal
- No known comorbidities or past surgeries
- No significant family history
- No addictions
- Presented with complaints of
  - Lump in right axilla x 1 month
- No other significant history elicited

Points of Discussion

1. **Risk Factors for Ca Breast?**
2. **Negative history?**

Risk Factors	Category at Risk	Comparison Category
Established Risk Factors		
Older age	Older than 50	Younger than 50
Country of residence	North America or Northern Europe	Asia or Africa
Germline mutation	With *BRCA1* or *BRCA2* mutations	Without *BRCA1* or *BRCA2* mutations
Personal history of breast cancer	With history of invasive breast carcinoma	No history of invasive breast carcinoma
High radiation exposure to chest area	With high radiation exposure to chest	Without radiation exposure
Atypical hyperplasia in breast biopsy	With atypical hyperplasia	Without hyperplasia
Cytologic findings (fine needle aspiration; nipple aspiration fluid)	Proliferation with atypia	No abnormality detected
Family history of breast cancer	With one or more close relatives with breast cancer	No close relatives with breast cancer
Early menarche	Menarche before age 12	Menarche after age 14
Late menopause	Menopause after age 55	Menopause before age 55
Older age at 1st full-term birth	Older than 30 years when first child was born	Younger than 20 years when first child was born
Not having children	Without children	With one or more children
Using menopausal hormone therapy	With hormone treatment after menopause	Without hormone treatment after menopause
Obesity after menopause	Obese after menopause	Not obese after menopause

On Examination

ECOG PS - 1

Wt: 64kg, Ht: 162cm, BMI:24.4

No pallor, icterus, pedal edema

Systemic examination

- **Respiratory system: No added sounds**
- **Per Abdomen - Soft, non tender, No organomegaly**
- **No bony tenderness**

On Examination

Local examination

- **Right breast: 2 x 1 cm lump palpable in the upper outer quadrant**
- **Right axilla: 5 x 5 cm hard, matted.**
- **Left breast and axilla - normal**
- **B/L SCF - normal**

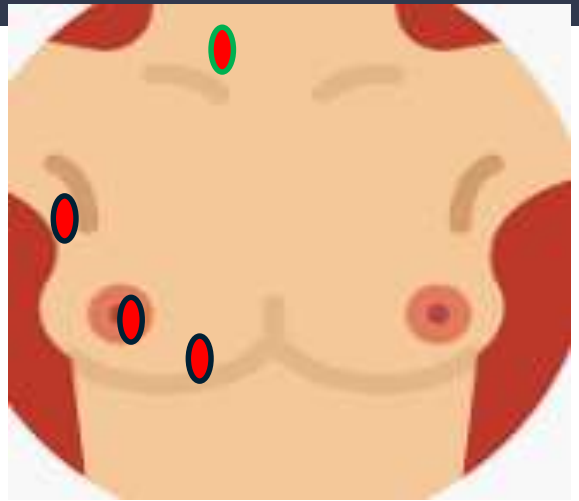
Points of Discussion

1. **Breast and Axillary Examination: Important points.**

Inspection/Palpation

Skin thickening

Breast, axilla lump



Symmetry

Nipple inversion

Nipple discharge

Location, consistency, size, mobility, tenderness

Probable diagnosis

49yr aged female no comorbidities with

- **Locally Advanced ?Carcinoma Right breast**

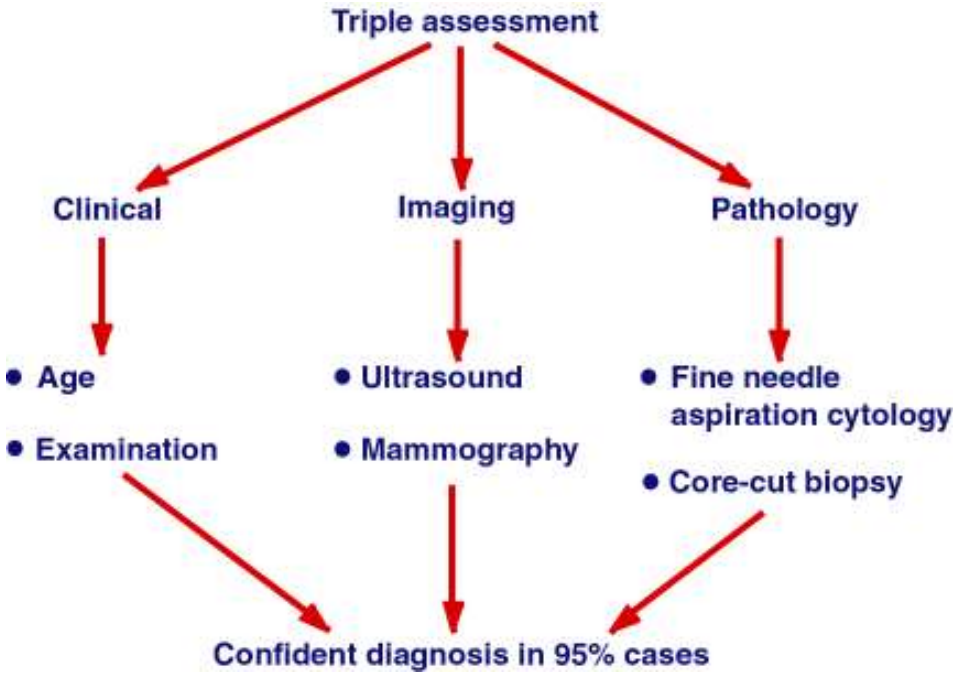
Points of Discussion

How will you investigate the case?

What is Triple Assessment

- **TRIPLE ASSESSMENT.**
- **CORE NEEDLE BIOPSY -** histology and receptor status studies
- **MAMMOGRAPHY** to the contralateral breast
- **METASTATIC WORK UP -**
  - Chest X Ray
  - USG abdomen pelvis,
  - Liver function tests
  - CT chest,
  - Skeletal survey by Bone scan or X-rays
  - CT brain - only if symptoms suggestive.
- **ROUTINE EVALUATION**

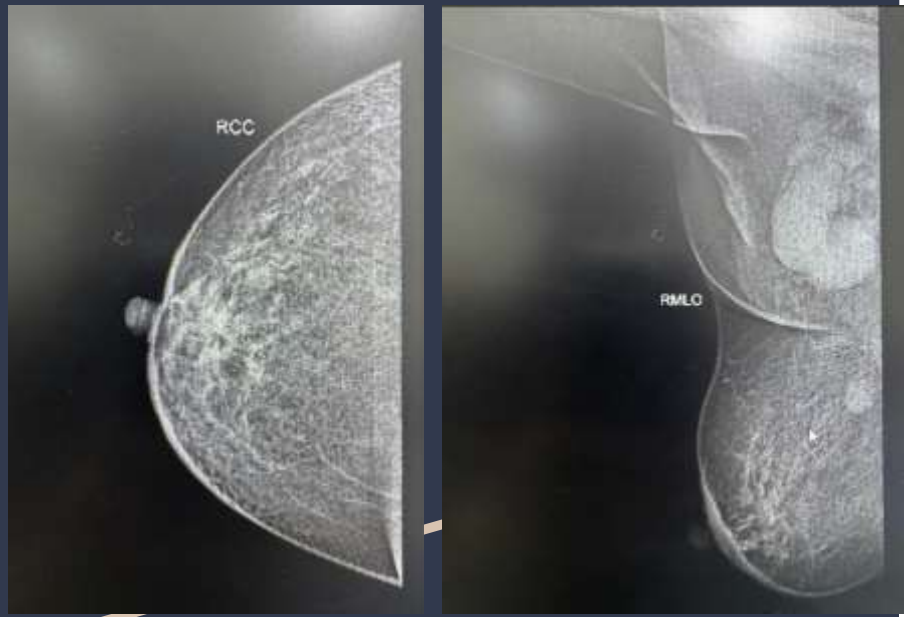
Triple Assessment



Most large series report a false-negative rate of 0.1 - 0.7%

The false-positive rate is 0.4%

Diagnostic Work up



Bilateral Sonomammography

- Well defined hypoechoic lesion in the right upper quadrant at 12 o'clock position in the periareolar region
- 12 x 7 x 10 mm
- Multiple enlarged right axillary LN, largest 44 x 28 mm continuous with another 27 x 19 mm node
- Few left axillary LN with maintained hilum
- BIRADS 4A

Points of Discussion: Radiology

1. Mammography views
2. Features of malignant mass
3. BIRADS Scoring
4. Problems in this mammogram
5. Dense breast
6. Indications of MRI
7. Problems of MRI

Positioning for Mammography

A. MLO view. The MLO view is obtained with the tube angled at 45° to the horizontal, with compression applied obliquely across the chest wall, perpendicular to the long axis of the pectoralis major muscle.

B. CC view. Positioning is achieved by pulling the breast up and forward, away from the chest wall, with compression applied from above.

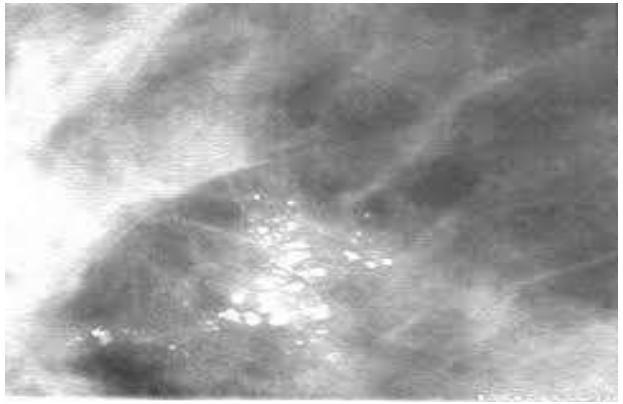
Calcifications, Mass, Asymmetry, Density

Characteristics of a malignant lesion: irregular, indistinct spiculated margins with microcalcifications, architectural distortion

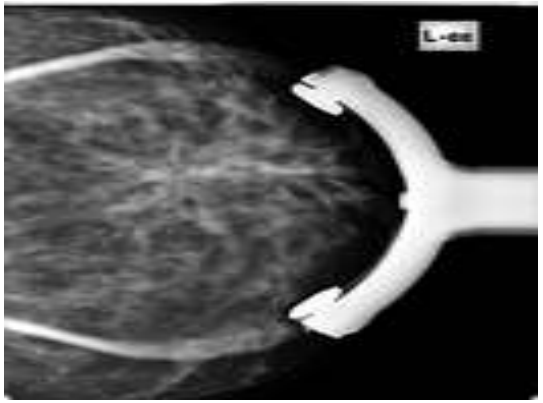
Bilateral synchronous cancers are reported in 3% of cases

Spot Compression / Magnification Views

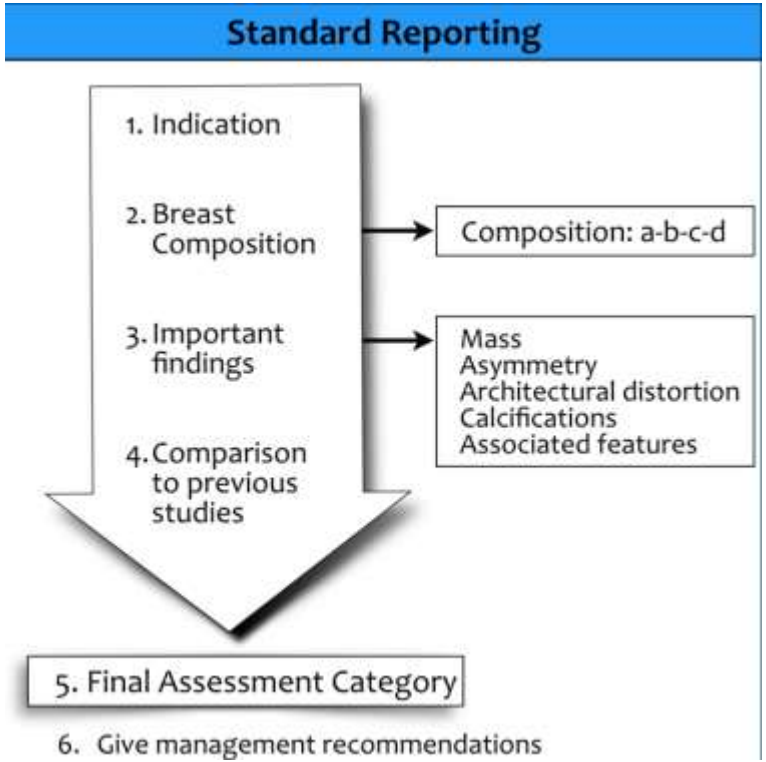
Magnification View



Spot Compression View



Components of Mammogram Report



The sensitivity of diagnostic mammography is around 90%, and the specificity up to 88%.

The known false negative rate of mammography is between 8% and 10%.

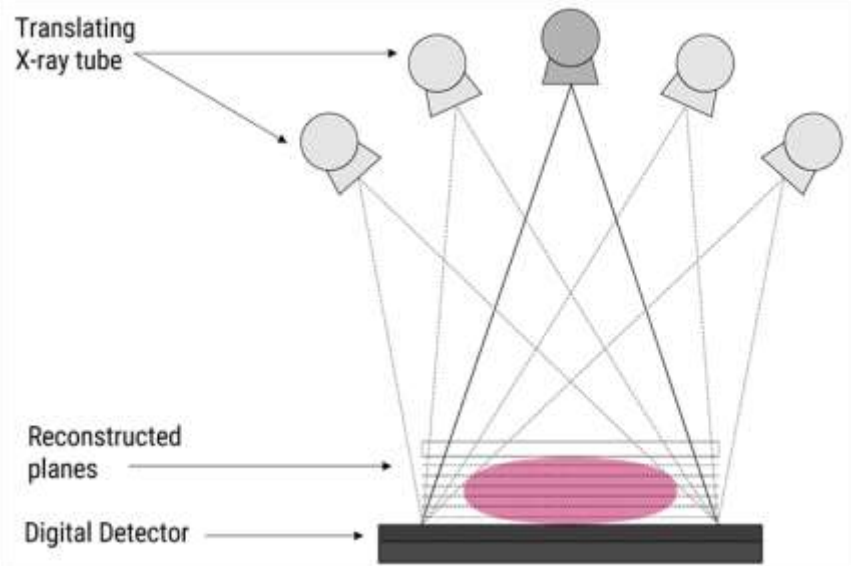
BIRADS (Breast Imaging Reporting & Data System)

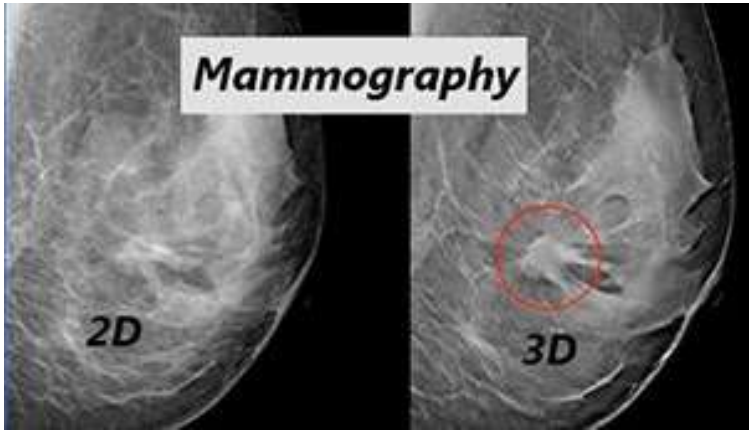
Final Assessment Categories			
	Category	Management	Likelihood of cancer
0	Need additional imaging or prior examinations	Recall for additional imaging and/or await prior examinations	n/a
1	Negative	Routine screening	Essentially 0%
2	Benign	Routine screening	Essentially 0%
3	Probably Benign	Short interval-follow-up (6 month) or continued	>0 % but ≤ 2%
4	Suspicious	Tissue diagnosis	4a. low suspicion for malignancy (>2% to ≤ 10%) 4b. moderate suspicion for malignancy (>10% to ≤ 50%) 4c. high suspicion for malignancy (>50% to <95%)
5	Highly suggestive of malignancy	Tissue diagnosis	≥95%
6	Known biopsy-proven	Surgical excision when clinical appropriate	n/a

BIRADS 0---is not benign—it needs further work up

Dense Breasts: breast tomosynthesis or digital breast tomosynthesis (DBT)

Three-dimensional (3D) mammography:{machine takes many low-dose x-rays as it moves in a small arc around the breast. A computer then puts the images together into a series of thin slices





Ultrasound Breast : Dense Breasts

In young women < 40 Yrs with dense breast

Increase the accuracy by up to 7.4% in dense breast

Differentiate cysts from solid lesions

Role in localizing occult lesions preoperative preparations and in percutaneous biopsy

In screening axilla for staging purposes and guiding FNA and Biopsies.

Indications for breast MRI

For screening, in BRCA 1, 2 positive women and other high-risk patients.
Unknown primary source of cancer(negative mammography and sonography)
Invasive lobular carcinoma
Multi-focal or multi-centric disease
Breast implants

MRI should be performed at high volume center with dedicated breast coil and breast imaging radiologists

Problems with MRI

Sensitivity 98%, makes MRI useful in specific clinical situation

Moderately low specificity of 47 - 67%, may increase the number of false positive test results

Can not visualize micro-calcification that typically occurs in DCIS.

Expensive

Diagnostic Workup: Biopsy

HPE - Core needle biopsy

s/o Infiltrative ductal carcinoma, NOS, Grade 3

IHC -

- ER/PR negative
- Her 2 negative
- Ki 67 60%

Points of Discussion: Pathology

1. **HPE FNAC vs Core needle biopsy?**
2. **What Scoring system for grading**
3. **What is the scoring system for ER/PR status?**
4. **Pathological Risk Stratification: Luminal subtypes and Her2 Neu testing**

FNAC

Highly operator dependent Procedure

Requires special training by a pathologist

Appreciable false-negative rate of 9.6%.

Inability to distinguish invasive from non-invasive carcinomas and to accurately diagnose lobular carcinomas.

During pregnancy is of low sensitivity

ER, PR and other test can not be done

Biopsy

Provides cores of tissue by 14-gauge manual or automated core biopsy needle.

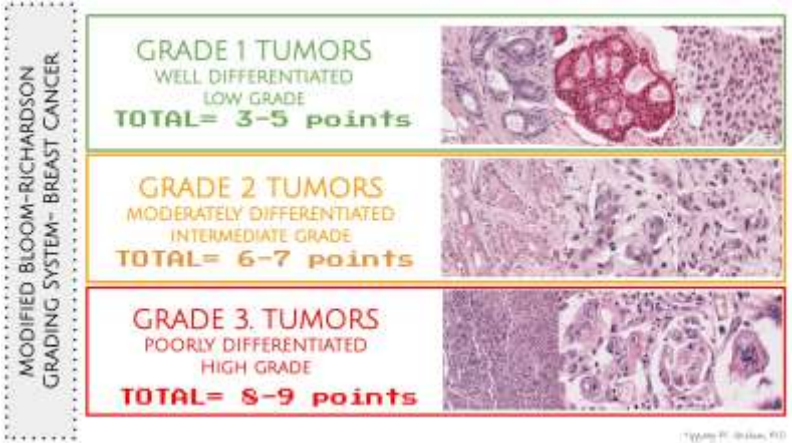
The procedure has a specificity of 85 - 100% and a sensitivity of 80 - 95%.

The sensitivity increases when the procedure is performed under image guidance.

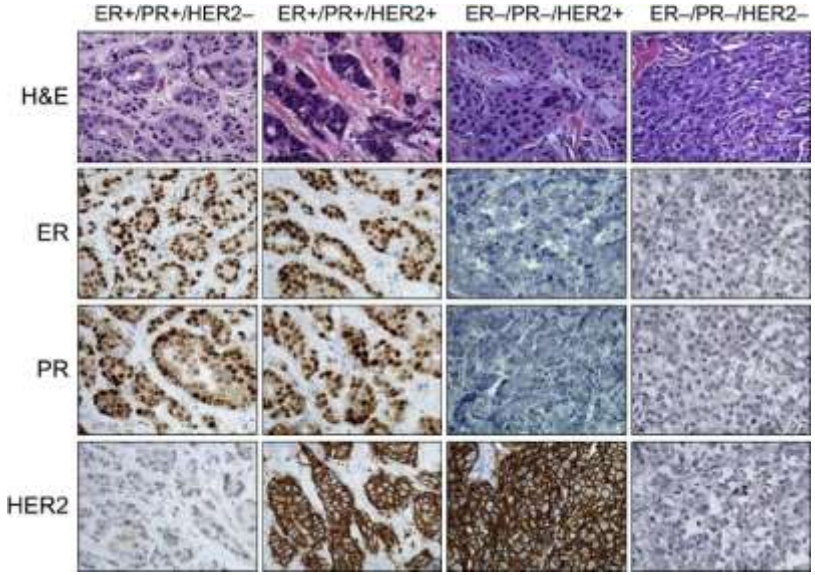
A minimum of 4 - 5 cores are advised to achieve greater accuracy.

Modified Scarff-Bloom-Richardson Histologic Grading

Features		Score
Tubule and gland formation	Majority of tumour (>75%)	1
	Moderate degree (10–75%)	2
	Little or none (< 10%)	3
Nuclear pleomorphism	Small, regular uniform cells	1
	Moderate increase in size and variability	2
	Marked variation	3
Mitotic count (dependent on microscopic field area, e.g. for field area 0.264 mm^2 with field diameter 0.58 mm)	0–9	1
	10–19	2
	>20	3



Allred Scoring



Proportion Score	
Score	*Percentage of stained cells*
0	No cells are ER positive
1	≤1% cells are ER positive
2	1-10% cells are ER positive
3	11-33% cells are ER positive
4	34-66% cells are ER positive
5	67-100% cells are ER positive
Intensity Score	
Score	*Intensity of staining*
0	Negative
1	Weak
2	Intermediate
3	Strong
Allred Score (Allred score=Proportion Score + Intensity Score)	
Allred score	*Effect of hormone therapy*
0-1	No effect
2-3	Small (20%) chance of benefit
4-6	Moderate (50%) chance of benefit
7-8	Good (75%) chance of benefit

ER: Estrogen receptor; PR: Progesterone receptor

Table 1

Classification of molecular subtypes and correlation with biomarker staining on immunohistochemistry

Molecular subtype	ER		PR		HER 2
Luminal A	positive	and/or	positive		negative
Luminal B	positive	and/or	positive negative*	or	negative
Luminal B	positive	and/or	positive negative**	or	positive
HER2	negative		negative		positive
Triple negative or basal-like	negative		negative		negative

*(PR<20% + Ki 67>14%)
**(Any PR + any Ki 67)

ER – estrogen receptor; HER2 – human epidermal growth factor receptor 2; PR – progesterone receptor

HER 2 assessment –ASCO-CAP guidelines

HER2	IHC Positive if > 10% complete membrane straining (3+) ISH • Single probe if HER2 ≥ 6 copies • Dual probe Positive if HER2/CEP17 ≥ 2 and HER2 copies ≥ 4 or HER2/CEP17 < 2 and HER2 copies ≥ 6	Essential to the characterization of: • HER2-enriched (ER-negative) • Luminal B-like, HER2-positive Pro… Pre… Ma… tre…

Biomarker	Method	Use
Ki67	IHC No final consensus on cut-off but values below 10% are considered low and above 30% are considered high*	Absence of international consensus for scoring and threshold Prognostic value in ER-positive, HER2-negative tumours (primary tumours and post-neoadjuvant residual tumour) Absence of prognostic value in HER2-positive or triple-negative tumours Predictive of response to neoadjuvant ET† Predictive of response to neoadjuvant ChT If elevated, ChT is often prescribed in ER-positive, HER2-negative tumours Part of the IHC definition of luminal-like tumours • Ki67 low, luminal A-like • Ki67 high, luminal B-like

Final Diagnosis

Local examination

- **Right breast: 2 x 1 cm lump palpable in the upper outer quadrant**
- **Right axilla: 5 x 5 cm hard, matted.**
- **Left breast and axilla - normal**
- **B/L SCF - normal**

49yr aged female, no comorbidities with

- Locally Advanced Carcinoma Right breast
- Infiltrative Ductal carcinoma, poorly differentiated, Grade 3

- Stage??

Points of Discussion: Staging and Genetic testing

What Staging System?

Metastatic work up?

Would you offer Genetic testing?

What are the components of Genetic testing?

AJCC 8th Staging

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)	Ductal carcinoma in situ
Tis (Paget)	Paget disease not associated with inv
T1	Tumor size ≤ 20 mm
T1mi	Tumor size ≤ 1 mm
T1a	Tumor size > 1 mm but ≤ 5 mm
T1b	Tumor size > 5 mm but ≤ 10 mm
T1c	Tumor size > 10 mm but ≤ 20 mm
T2	Tumor size > 20 mm but ≤ 50 mm
T3	Tumor size > 50 mm
T4	Tumor with direct extension to the c with macroscopic changes
T4a	Tumor with chest wall invasion
T4b	Tumor with macroscopic skin chang and/or satellite skin nodules and/o
T4c	Tumor with criteria of both T4a and
T4d	Inflammatory carcinoma

Stage	TNM
Stage 0	Tis, N0, M0
Stage IA	T1, N0, M0
Stage IB	T0, N1mi, M0
	T1, N1mi, M0
Stage IIA	T0, N1, M0
	T1, N1, M0
	T2, N0, M0
Stage IIB	T2, N1, M0
	T3, N0, M0
Stage IIIA	T0, N2, M0
	T1, N2, M0
	T2, N2, M0
	T3, N1, M0
	T3, N2, M0
Stage IIIB	T4, N0, M0
	T4, N1, M0
	T4, N2, M0
Stage IIIC	Any T, N3, M0
Stage IV	Any T, Any N, M1

cN Criteria
al nodes cannot be assessed (previously removed)
ional nodal metastases
ases to movable ipsilateral level I and/or level II axillary nodes metastases
ases to fixed or matted ipsilateral level I and/or level II axillary es; or metastases to ipsilateral internal mammary nodes without ary metastases
ases to fixed or matted ipsilateral level I and/or level II axillary es
ases to ipsilateral internal mammary nodes without axillary astases
ases to ipsilateral level III axillary nodes with or without level I or level II axillary metastases; or metastases to ipsilateral internal mmary nodes with level I and/or level II axillary metastases; or astases to ipsilateral supraclavicular nodes
ases to ipsilateral level III axillary nodes with or without level I or level II axillary metastases
ases to ipsilateral internal mammary nodes with level I and/or II axillary metastases
ases to ipsilateral supraclavicular nodes

Metastatic Workup:
Role of bone scanning/USG abdomen

A computed tomography (CT) scan of the chest, abdominal imaging (US, CT) and a bone scan:

- clinically positive axillary nodes;
- large tumours (e.g. 5 cm)
- clinical signs, symptoms or laboratory values suggesting the presence of metastases

(PET) CT scanning may be an option for high-risk patients and when conventional CT/bone scan methods are inconclusive.

ESMO Pan Asian Guidelines,2024

Genetic Testing

Testing for high penetrance genes beyond BRCA1/2, including PALB2, TP53, PTEN, STK11, andCDH1

Individuals with a diagnosis of breast[†], ovarian[‡], prostate[§], or pancreatic cancer meeting one or more of:

- Criteria based on diagnostic characteristics only
  - Breast cancer diagnosed at age ≤45 years
  - Triple negative breast cancer diagnosed at age ≤60 years
  - Two primary breast cancer diagnoses with one diagnosed at age ≤50 years
  - Male breast cancer
  - Ovarian cancer
- Criteria based on combinations of diagnosis with personal characteristics or family history[‖]
  - Breast cancer and Ashkenazi Jewish decent
  - Breast cancer diagnosed at age ≤50 years and ≥1 close biological relative with breast, pancreatic, or prostate cancer
  - Breast cancer diagnosed at age ≤50 years and an unknown or limited family history
  - Breast cancer and ≥1 close biological relative with breast cancer diagnosed at age ≤50 years
  - Breast cancer and ≥1 close biological relative with ovarian cancer
  - Breast cancer and ≥2 close biological relatives breast, pancreatic, or prostate cancer
  - Breast cancer and a male close biological relative with breast cancer
  - Pancreatic cancer and Ashkenazi Jewish decent
  - Prostate cancer and ≥1 close biological relative with breast cancer diagnosed at age ≤50 years and/or ovarian cancer and/or pancreatic cancer and/or prostate cancer
  - Pancreatic cancer and ≥1 close biological relative with breast cancer diagnosed at age ≤50 years and/or ovarian cancer and/or pancreatic cancer and/or prostate cancer

Unaffected[¶] individuals based on family history of cancer

- Known deleterious *BRCA1/2* mutation in family
- First or second degree relative with a breast or ovarian cancer diagnosis meeting testing criteria
- Third-degree blood relative with breast cancer and/or ovarian cancer with ≥2 close blood relatives with breast cancer (at least one diagnosed at age ≤ 50y) and/or ovarian cancer

* Based on National Comprehensive Cancer Network criteria, version 2.2015

† Breast cancer includes ductal cancer in situ and invasive; see Supplemental Table 1 for site and histology codes.

‡ Ovarian cancer includes epithelial ovarian cancer, primary peritoneal cancer, or fallopian tube cancer, see Supplemental Table 1 for site and histology codes.

§ Prostate cancer with Gleason's score ≥7

‖ Family history of a close biological relative (first, second, or third degree) on the same side

¶ Individuals with no personal diagnosis of cancer meeting testing criteria included among "unaffected".

Genetic Testing

Testing for moderate penetrance breast cancer genes currently offers no benefits.

Patients undergoing genetic testing should be given sufficient information before testing to provide informed consent.

Patients with pathogenic variants should be provided with individualized post-test genetic counseling and offered referral to a provider experienced in clinical cancer genetics

Workup of Carcinoma Breast: Summary

Assessment of general health status	• History • Menopausal status • Physical examination • Full blood count • Liver, renal and cardiac (in patients planned for anthracycline and/or trastuzumab treatment) function tests, alkaline phosphatase and calcium
Assessment of primary tumour	• Physical examination • Mammography • Breast US • Breast MRI in selected cases • Core biopsy with pathology determination of histology, grade, ER, PgR, HER2 and Ki67
Assessment of regional lymph nodes	• Physical examination • US • US-guided biopsy if suspicious
Assessment of metastatic disease	• Physical examination • Other tests are not routinely recommended, unless high tumour burden, aggressive biology or when symptoms suggestive of metastases are present

Final Diagnosis

49yr aged female, with no comorbidities with

- **Locally Advanced Carcinoma Right breast**
- **Infiltrative ductal carcinoma, poorly differentiated, Grade 3**
- **c T1 N2a M0**
- **Stage IIIA**
- **TNBC**
- **gBRCA1/2 Negative**

Treatment options?

Multidisciplinary discussion

Upfront surgery or NACT?

Systemic therapy

Radiotherapy

Treatment Plan cT1N2aM0,TNBC

1. **Neoadjuvant chemotherapy**
2. **Surgery**
3. **Adjuvant Radiotherapy**

Discussion: Chemotherapy

Why Neoadjuvant Chemotherapy?

What is the preferred Chemotherapy Backbone in this case?

Role of Carboplatin?

Any inputs from the Surgical team before NACT?

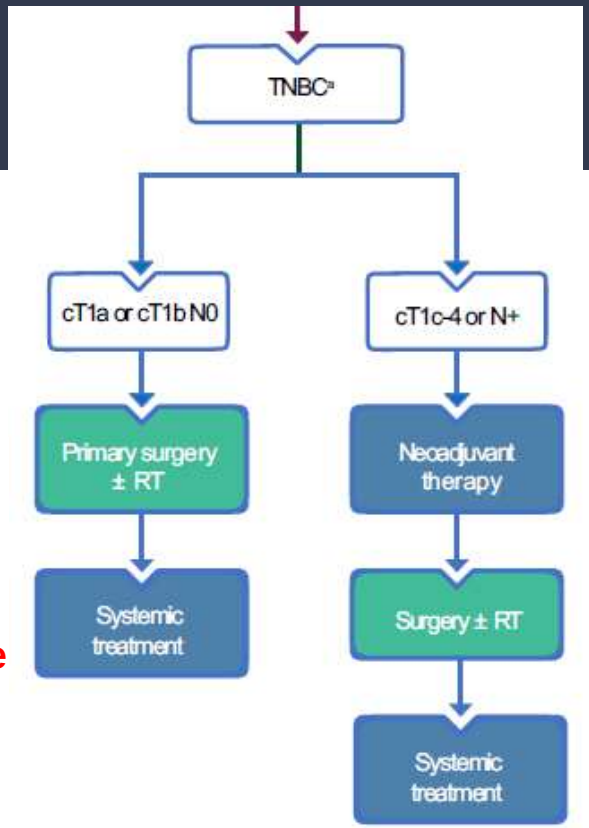
Benefit of Neoadjuvant CT

1. Downsize the disease to facilitate Surgery:

Neoadjuvant systemic therapy may be offered to reduce the extent of surgery

2. In Vivo Assessment of Response Recommendation 1.3

- **Neoadjuvant systemic therapy should be offered to triple negative breast cancer (TNBC) in** whom the finding of residual disease would guide recommendations related to adjuvant therapy.



ESMO Guidelines

Chemotherapy Backbone: Sequential Anthracycline and Taxanes

- **Dose-dense AC followed by paclitaxel**[2]
  - Doxorubicin 60 mg/m^2 IV day 1
  - Cyclophosphamide 600 mg/m^2 IV day 1
    - Cycled every 14 days for 4 cycles.
    - Followed by:
  - Paclitaxel 175 mg/m^2 by 3 h IV infusion day 1
    - Cycled every 14 days for 4 cycles.
- **Dose-dense AC followed by weekly paclitaxel**[2]
  - Doxorubicin 60 mg/m^2 IV day 1
  - Cyclophosphamide 600 mg/m^2 IV day 1
    - Cycled every 14 days for 4 cycles.
    - Followed by:
  - Paclitaxel 80 mg/m^2 by 1 h IV infusion weekly for 12 weeks.

Benefit of Carboplatin in TNBC: Phase III Study TMH

Adding weekly carboplatin to the Anthracycline-Taxane regimen resulted in an absolute increase of 6.6% in 5-year event-free survival.

12.5% absolute increase in event-free survival and 11.2% increase in overall survival in patients aged ≤ 50 years.

No benefit was observed in patients older than age 50.

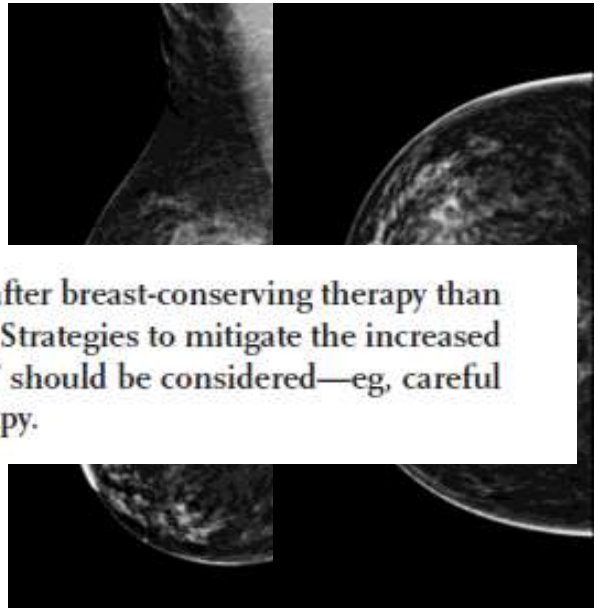
Gupta S et al SABCS 2023

Tumor Mapping before NACT

Placement of Clips before starting NACT

Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of

Interpretation Tumours downsized by NACT might have higher local recurrence after breast-conserving therapy than might tumours of the same dimensions in women who have not received NACT. Strategies to mitigate the increased local recurrence after breast-conserving therapy in tumours downsized by NACT should be considered—eg, careful tumour localisation, detailed pathological assessment, and appropriate radiotherapy.



Neoadjuvant CT cT1N2aM0,TNBC

Patient Received

4 cycles of (AC) Adriamycin with cyclophosphamide 3 weekly followed 12 cycles of Paclitaxel with carboplatin weekly.

Discussion Chemotherapy

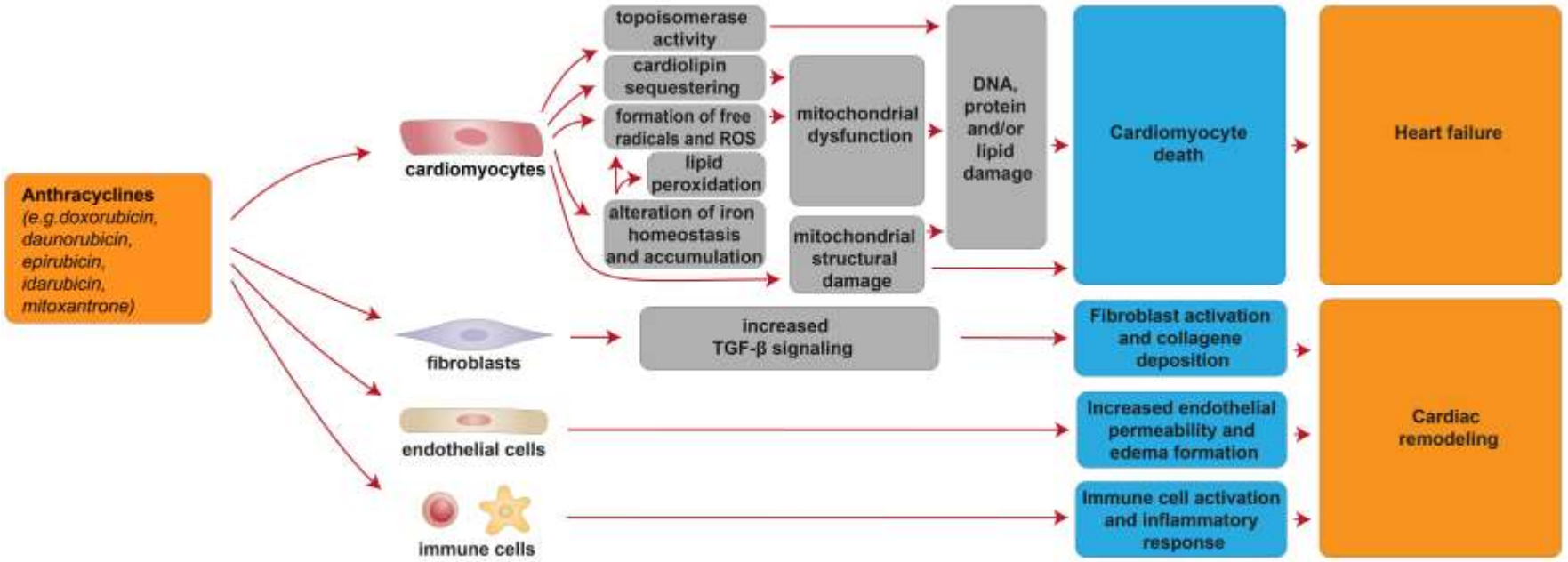
How do you monitor the response to NACT

Toxicity of Anthracyclines?

Adriamycin vs Epirubicin

Ceiling Doses of anthracyclines?

Monitoring Response to NACT and Toxicity of Anthracyclines



Monitoring Response to NACT and Toxicity of Anthracyclines

The recommended maximum **lifetime cumulative dose for doxorubicin is 400–550 mg/m^2**

LV function should be assessed with **2D/3D Echo**

- Baseline
- patients attain a cumulative dose of 200-250 mg/m^2 of doxorubicin
- Subsequently, after every additional 100 mg/m^2

Drug	Relative cardiotoxicity	Incidence of HF rises to >5% when cumulative dose exceeds (mg/m^2)
Doxorubicin rapid infusion	1	400
Epirubicin	0.7	900
Daunorubicin	~0.75	800
Idarubicin	0.53	150

Decline of LVEF 10% from the Baseline
Decline of GLS 15% from baseline

The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC)

Surgery

Post NACT patient had complete clinical response in the breast and axilla.

Options for Surgery

- **Breast conservative surgery with right axillary lymph node dissection**
- **Modified radical mastectomy with axillary lymph node dissection**

Discussion Surgery

The preferred choice of surgery
BCS vs MRM
SLNB vs AxLND

Absolute Contraindications to BCS

Role of Surgical clips during BCS?

MRM Vs BCT(Sx+RT)

Randomized trials

Meta-analysis

Comparable local control, Overall survival

Better cosmetic outcome

Comparative Study > World J Surg. 2016 Jul;40(7):1583-9. doi: 10.1007/s00268-015-3222-2.

A Comparative Validation of Primary Surgical Versus Post-neo-adjuvant Chemotherapy Sentinel Lymph Node Biopsy for Stage III Breast Cancers

Gaurav Agarwal [1], Sendhil Rajan [2], Sanjay Gambhir [3], Punita Lal [4], Narendra Krishnani [5], Subhash Kheruka [3]

Affiliations + expand

PMID: 26324160 DOI: 10.1007/s00268-015-3222-2

Full text links | Cite

Abstract

Introduction: Sentinel lymph node biopsy (SLNB) is the standard of care for staging N0 primary early breast cancers (EBC). Patients in developing countries mostly present with large (LOBC) or locally advanced cancers (LABC) and are treated with neo-adjuvant chemotherapy (NACT). Accuracy of SLNB in staging stage III N0 and post-NACT N0 patients is uncertain. This prospective validation study on LOBC/LABC patients compared the accuracy of SLNB between primary versus post-NACT surgery.

Materials and methods: Fifty T3/T4, N0 patients undergoing primary surgery (Group I) and 70 LOBC/LABC (index stage) treated with NACT and N0 at the time of surgery (Group II) were inducted. Validation SLNB was performed using low-cost methylene-blue and (99m)Tc-Antimony colloid. SLN identification (IR) and false-negative (FNR) rates were compared between the groups. Sub-group analysis was done in Group II per index tumor and nodal stage to identify factors predicting SLN IR and FNR in post-NACT patients. SLN IR and FNR in both groups were compared with those in previously published SLN validation study and meta-analysis in EBC.

Results: Using combination of blue-dye and radio-colloid, post-NACT SLN IR and FNR (82.9, 13.5 %) were far inferior to T3/T4 primary surgery group (94, 7.7 %; p values 0.034, 0.041) and in EBC. SLN IR using blue-dye alone was dismally low in post-NACT LABCs. Factors predicting unidentified post-NACT SLN and false-negative SLNB included young age, LVI, skin infiltration, extra-nodal spread or N2a stage, and UOQ tumors.

Conclusions: Accuracy of SLNB in T3, N0 tumors undergoing primary surgery is comparable to that of SLNB for N0 EBC. In post-NACT patients, SLNB IR are lower and FNR are higher. Factors predictive of non-identification and false-negative SLNB include pre-NACT skin involvement (T4b), N2a stage or extra-nodal invasion and LVI, and to a lesser extent, young age and UOQ location of the tumor.

Decision Making: Patient

- The absence of a long-term survival difference between treatments
- The possibility and consequences of LR with both approaches
- Psychological adjustment (including the fear of cancer recurrence), cosmetic outcome, sexual adaptation, and functional competence

Absolute Contraindication to BCS

- Diffuse suspicious microcalcifications
- Persistent, positive margins after “reasonable” surgical attempts.
- Inflammatory breast cancer (IBC).
- Requirement to deliver of RT during pregnancy
- Widespread disease that can not be incorporated by local single incision that achieve negative margin.

Placement of Surgical Clips during BCS

Surgical clips should be placed intraoperatively to assist in
tumour bed delineation and postoperative radiation planning.

The optimal number of surgical clips to be placed is at least 4, with 1 clip placed on each
of the cavity side walls (medial, lateral, superior, inferior) at the level where the tumour was initially situated.

Clips in pairs

Avoid the use of clips anywhere else in the breast or axilla except for the purposes of tumour bed delineation

Common Language

Post NACT Surgery BCS+ AxLND

Post op histopathology

Complete response to therapy

No residual viable tumor

0/25 LN

ypT0N0 (AJCC 8th edition)

Discussion Adjuvant Radiotherapy

Indications of postoperative RT in BCS

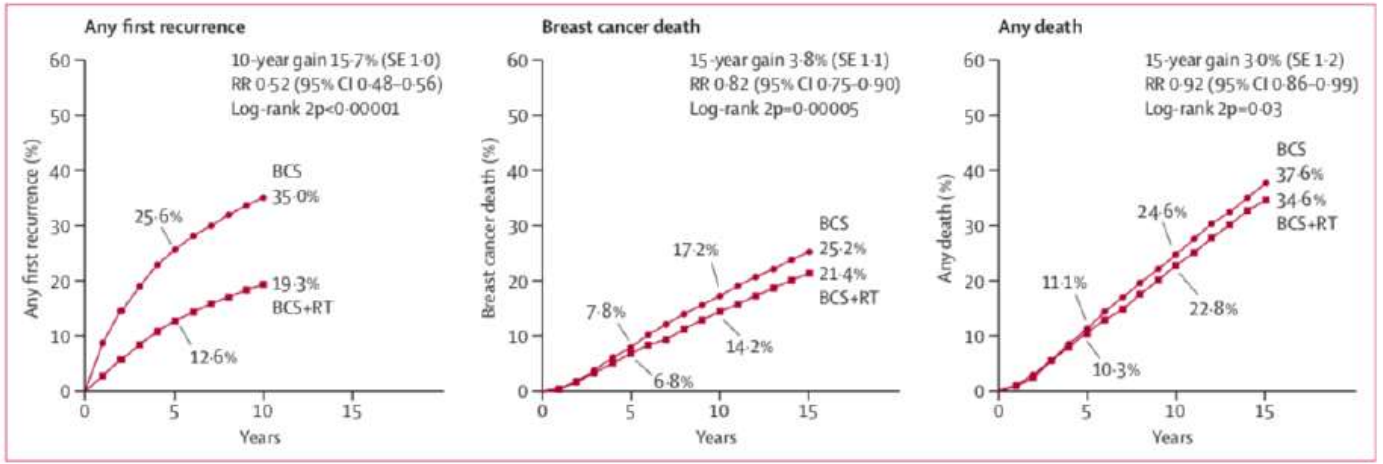
What Dose Schedules

Rationale of Hypofractionated RT

What Nodal Regions

Indications for boost?

Breast Conserving Therapy: Whole breast radiation-Why?



16% **4%** **3%**

Radiotherapy reduces risk of any recurrence by 50%
4:1 ratio for breast cancer death

EBCTCG Lancet 378: 1707–16,2011

Dose Of Radiotherapy : Whole Breast

- Conventional fractionation:
  - 45 - 50Gy/25# @ 1.8 – 2 Gy/#, 5 fractions per week.

- Hypofractionation:
  - 40 - 42.5 Gy/15-16# @ 2.66 Gy/#, 5 fractions per week.

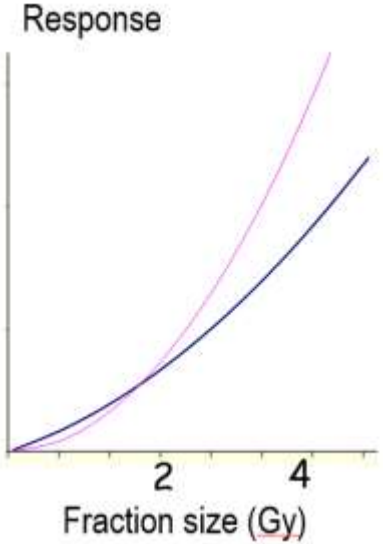
Hypofractionation in Breast Cancer

Breast cancer is as sensitive to fraction size as normal tissues.

α/β for breast is much lower (~3).

2Gy fractions spare breast tumour cells as much as they spare normal tissues.

Total dose must be reduced to allow for the increasing rate of late adverse effects per unit increase in fraction size.



Breast cancer α/β<10Gy

Other tumours α/β≥10Gy

Hypofractionated RT: Evidence

	Patients	FU (years)	RT standard	RT hypofx	Reference
UK Start trial B	2,215 T1-3a, N0-1	10	25 x 2 Gy 5 weeks	15 x 2.67 Gy (40 Gy) 3 weeks	Haviland, Lancet Oncol, 2013
Results			**5.5%**	**4.3%**	
Canadian trial	1,234 T1-2, N0	10	25 x 2 Gy 5 weeks	16 x 2.67 Gy (42.5 Gy) 3.1 weeks	Whelan, NEJM, 2010
Results			**6.7%**	**6.2%**	
DBCG HYPO trial	1,854 T1-2, N0-1 or DCIS	9	25 x 2 Gy 5 weeks	15 x 2.67 Gy (40 Gy) 3 weeks	Offerson, JCO, 2020
Results			**3%**	**3%**	

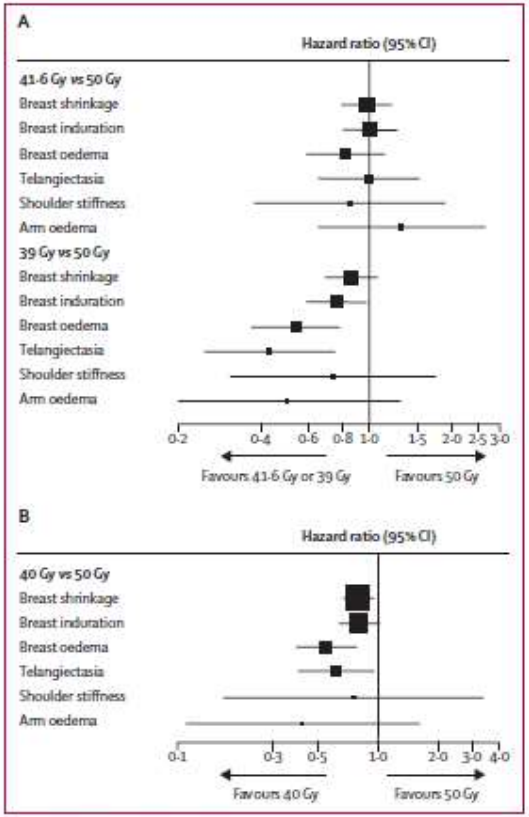
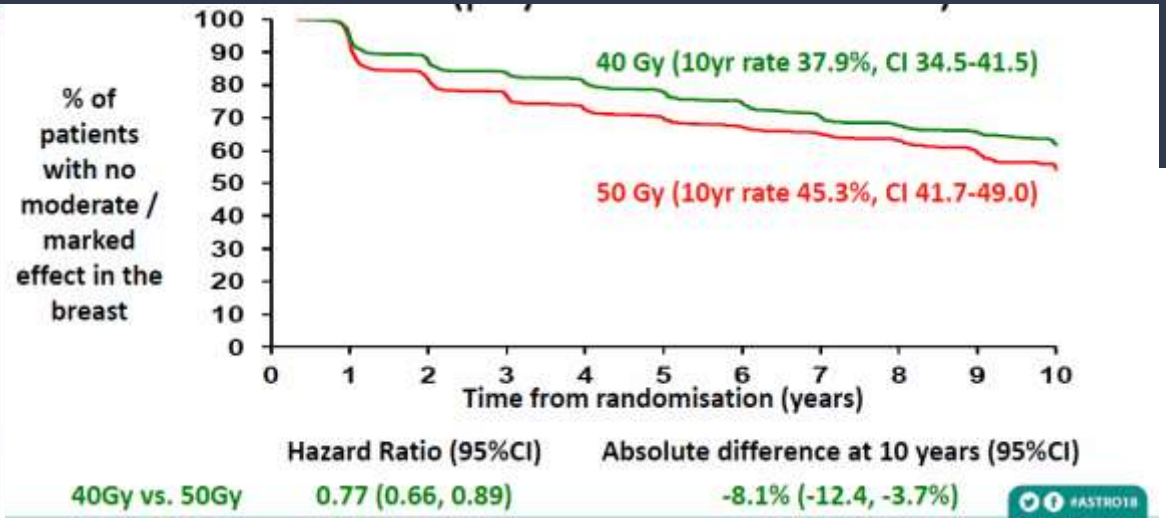


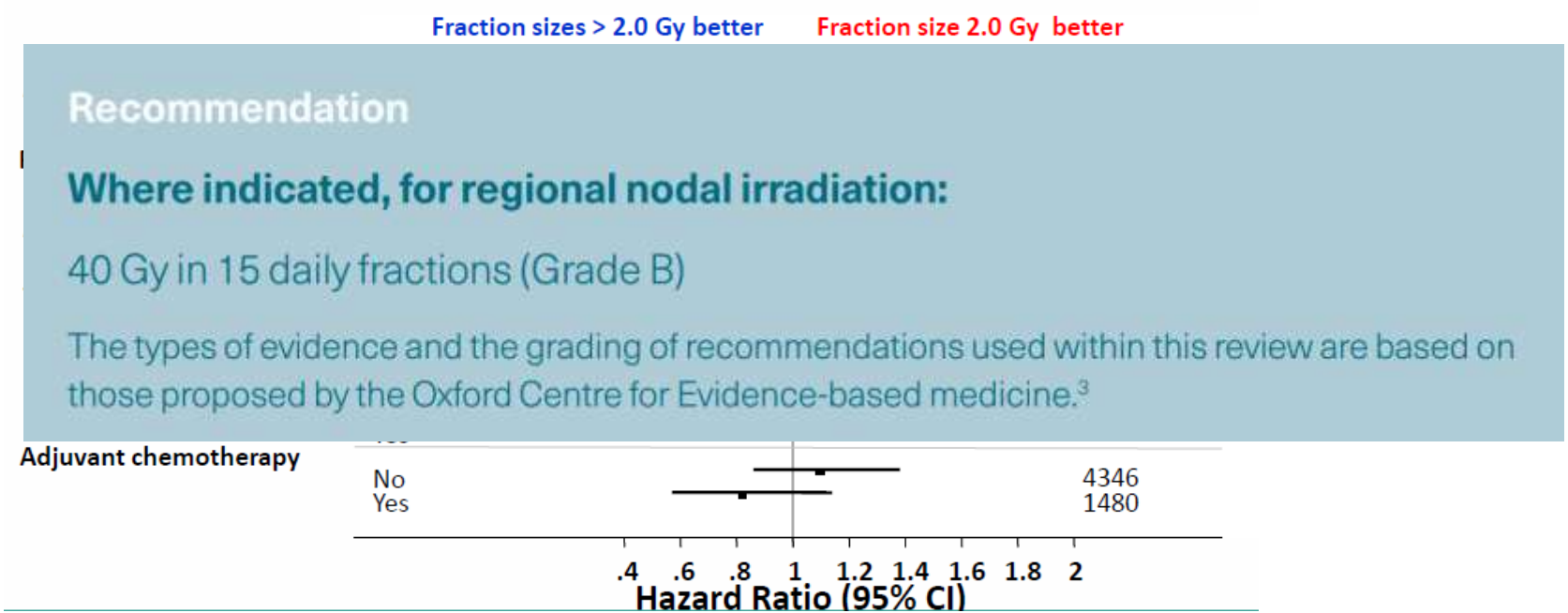
Figure 3: **Late normal tissue effects**
In START-A (A) and START-B (B). Assessed as moderate or marked by physicians.



Lower side effects with 40Gy/15 #

Haviland et al Lancet Oncol 2014; 14:1086-94.

Meta-analysis of START pilot & START A & B: Subgroup analyses of LR relapse (n=5861)



Haviland et al Lancet Oncol 2014; 14:1086-94

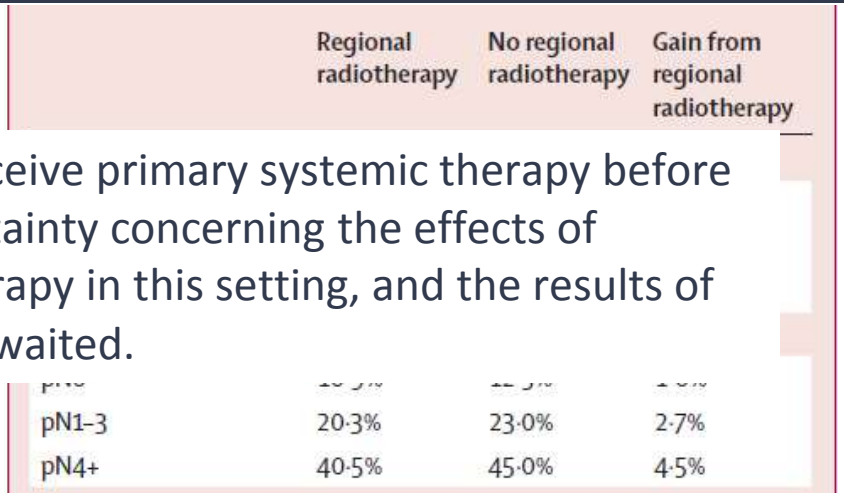
Regional Nodal Radiation: Supraclavicular Fossa

Indications of Supraclavicular Radiation

- Absolute
  - cN2/3 disease
  - pN2 or pN3 dise
    lymph nodes af

Many women today receive primary systemic therapy before surgery. There is uncertainty concerning the effects of regional node radiotherapy in this setting, and the results of randomised trials are awaited.

- Relative:
  - 1-3 positive lymph nodes
  - Positive sentinel lymph node with no axillary dissection



	Regional radiotherapy	No regional radiotherapy	Gain from regional radiotherapy
pN1–3	20·3%	23·0%	2·7%
pN4+	40·5%	45·0%	4·5%

Absolute effect of regional node radiotherapy on 15-year risk of any recurrence and breast cancer mortality

EBCTCG 2023

Internal Mammary Nodal Radiation Evidence

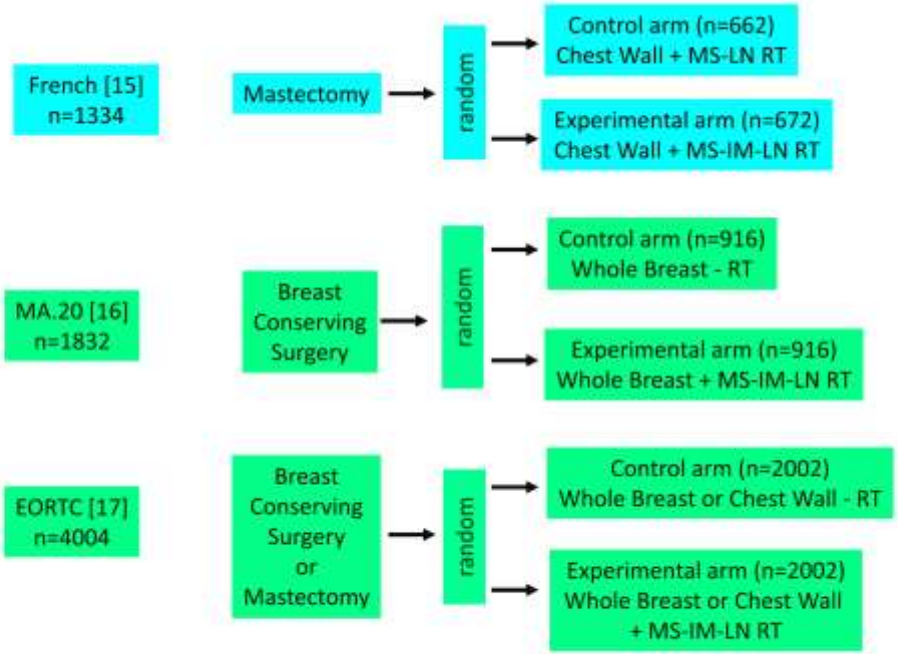
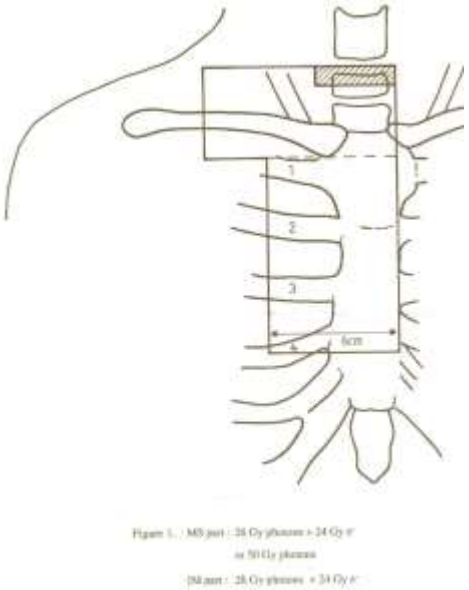
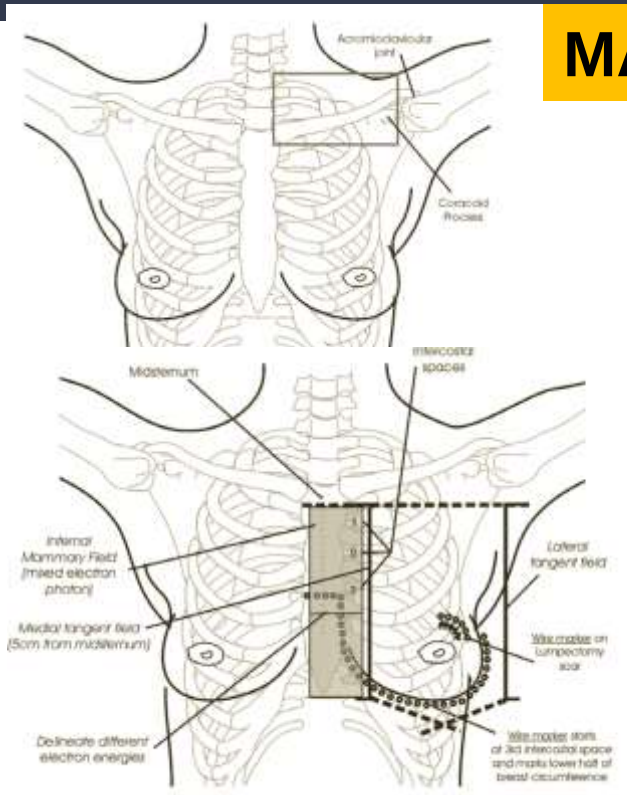


Figure 1 Trial designs. Random = randomization. RT = radiotherapy. MS-LN-RT = radiotherapy of medial supraclavicular lymph nodes. MS-IM-RT = radiotherapy of medial supraclavicular and internal mammary lymph nodes.

Regional Nodal Radiation: IMN Radiation



EORTC22921



MA20

	NCIC MA.20 RNI vs. Control	EORTC 22922 RNI vs. Control
Median follow up (years)	9.5	10.9
10-yr OS	82.8% vs. 81.8% (P =0.38) 1%	82.3% vs. 80.7% (P =0.06) 2.4%
10-yr DFS	82% vs. 77% (P = 0.01) 5%	72.1% vs. 69.1% (p=0.044 3%
10-yr Distant DFS	86.3% vs. 82.4% (P = 0.03) 4%	78% vs. 75%P=0.02 3%
10-yr Breast cancer mortality	10.3% vs. 12.3% (P = 0.011) 2%	12.5% vs. 14.4% (P=0.02) 3%

Regional Nodal Radiation: Internal Mammary Nodes

- Neither showed survival benefit. EORTC – nearly significant!
- MA20 – HR(-) benefits with RNI
- **Exact impact of IMN & SCF can't be ascertained**
- **Risk – benefit for patient selection**

Overall risk/benefit ratio for IMLN RT RNI is quite ambiguous

Undoubtedly one of the reasons IMLN RT RNI has been (and will likely continue to be) individualized.

Rationale and Evidence for Boost

Most of the local recurrences occur in the index quadrant

Boost radiotherapy improves local control significantly in younger patients.

Increased price: severe fibrosis but less so in young patients.

Absolute gain of a boost dose is largest in patients younger than 50 years.

No impact on OS

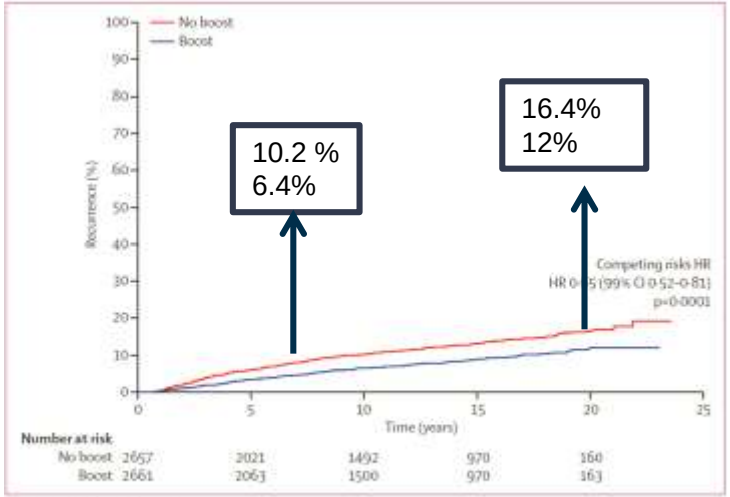


Figure 3: **Ipsilateral breast tumour recurrence**
HR=hazard ratio.

EORTC 22881-10882 Bartelink H,Lancet Oncol. 2015 Jan;16(1):47-56

Indications and Dose for Boost Radiation

Patients below 50 years of age

Patients above 50 years in case of

- Presence of extensive intraductal component
- Grade 3 tumour
- T3/T4 tumor
- Pleomorphic lobular carcinoma
- Triple negative tumour
- Multicentric tumour
- Residual tumor after neo-adjuvant chemotherapy

Recommended Dose: 10 Gy in 4-5 fractions

Combination of risk factors for LR such as young age and close margins 12.5- 16Gy in 5-8 fractions

ASTRO 2018 Guideline

RT planning

Planned for Radiotherapy

Right Breast and SCF: 40Gy/15#
Tumor Bed Boost: 12.5Gy/5#

Discussion: RT planning

Patient positioning

Target delineation of Breast and Cavity

Cardiac delineation and avoidance

Dose homogeneity (including planning approaches)

Boost planning approaches

Patient Positioning: Supine with hands over head

Primary goals:-

1. Reproducibility and patient comfort
2. Minimize positioning errors

Positioning Device

1. Wing board
2. Breast board

Wires Localisation
Breast/ Lumpectomy scar
No contrast

Target Delineation

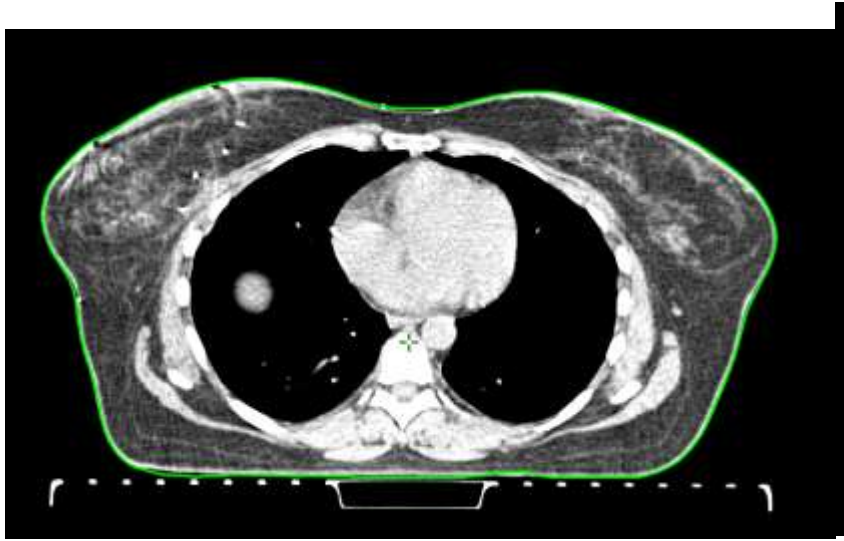
- **Contouring lumpectomy site and nodes necessary to ensure coverage.**

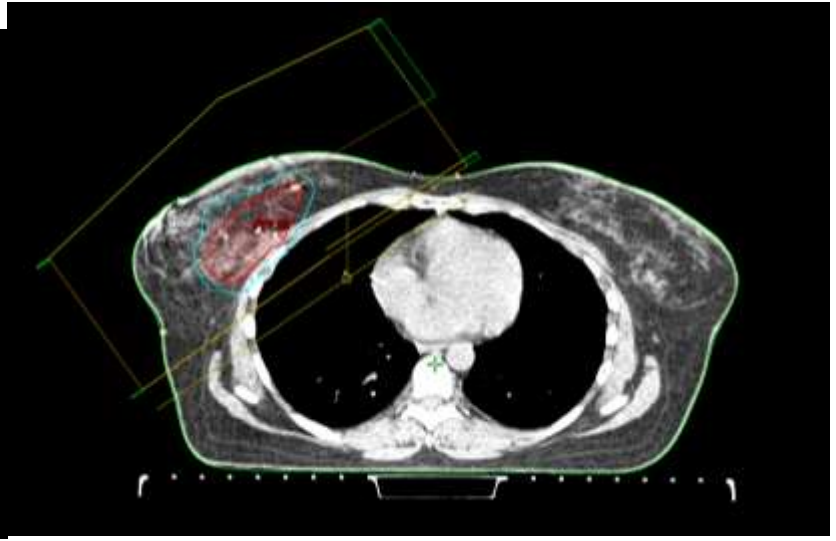
- **Clearly necessary for IMRT/VMAT, protons, APBI, where it is easy to miss undefined targets**
  - Provides uniformity across centers

Target Delineation: Whole Breast and Cavity

The whole breast volume may be contoured on the treatment planning CT or identified using radio-opaque wire at the time of planning.

Cavity: Combination of initial examination, mammogram, seroma, scar, clips





Targ

- **RTO**
- **EST**
- **Rad**

Innc
Atla

	RTOG guidelines	ESTRO guidelines
CTVp_Breast		
Cranial	Clinical reference + second rib insertion	Upper border of palpable/visible breast tissue; maximally up to the inferior edge of the sternoclavicular joint
Caudal	Clinical reference + loss of CT apparent breast	Most caudal slice with visible breast
Anterior	Skin	5 mm under skin surface
Posterior	Excludes pectoralis muscle, Chest wall muscles, ribs	Pectoralis major or costal and intercostal muscles where no muscle
Lateral	Clinical reference and mid-axillary line, typically excludes latissimus dorsi muscle	Lateral breast fold; anterior to the lateral thoracic artery
Medial	Sternal–rib junction	Lateral to the medial perforating mammary vessels; maximally to the edge of the sternal bone

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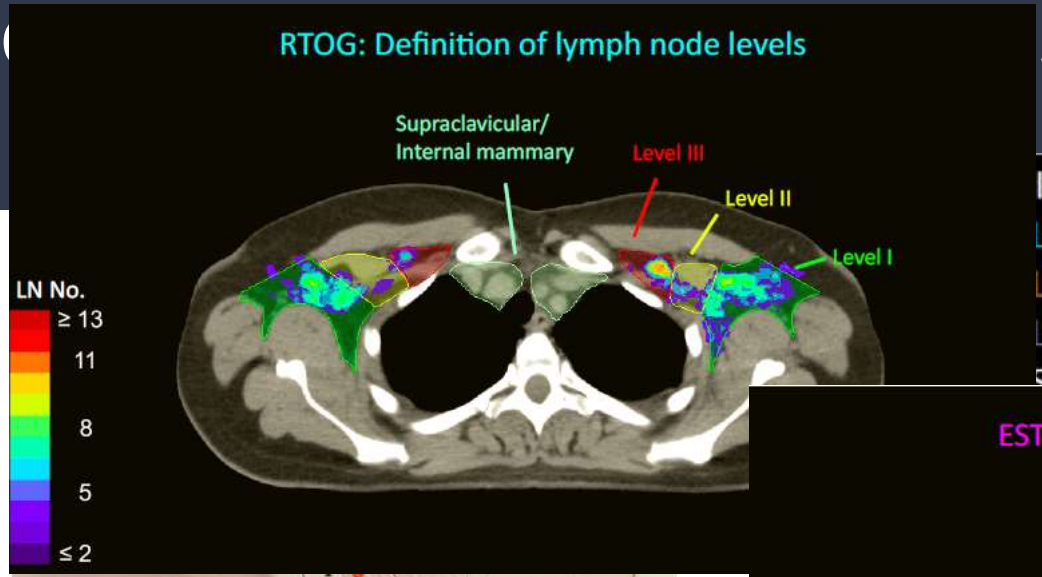
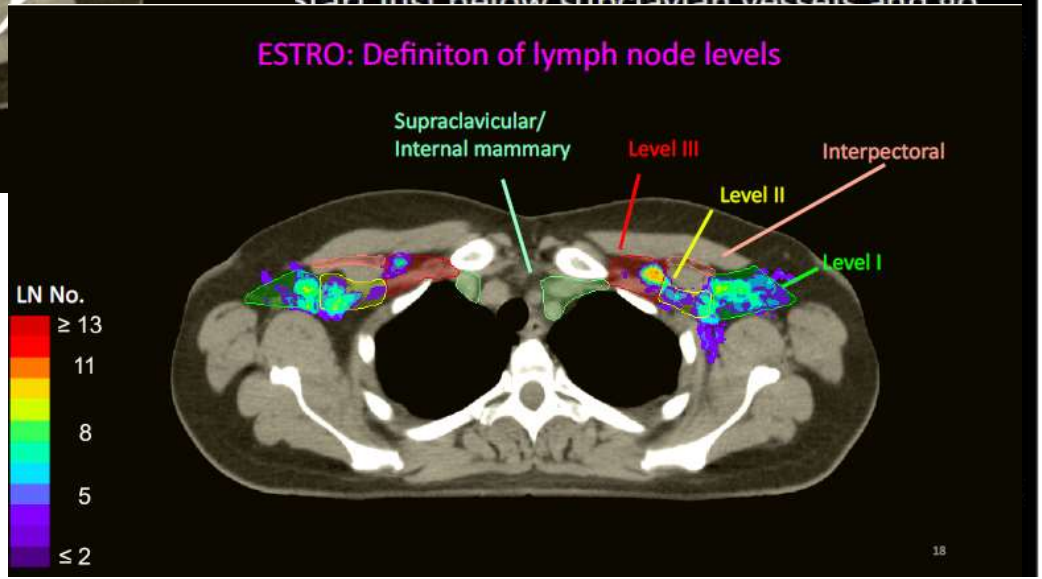
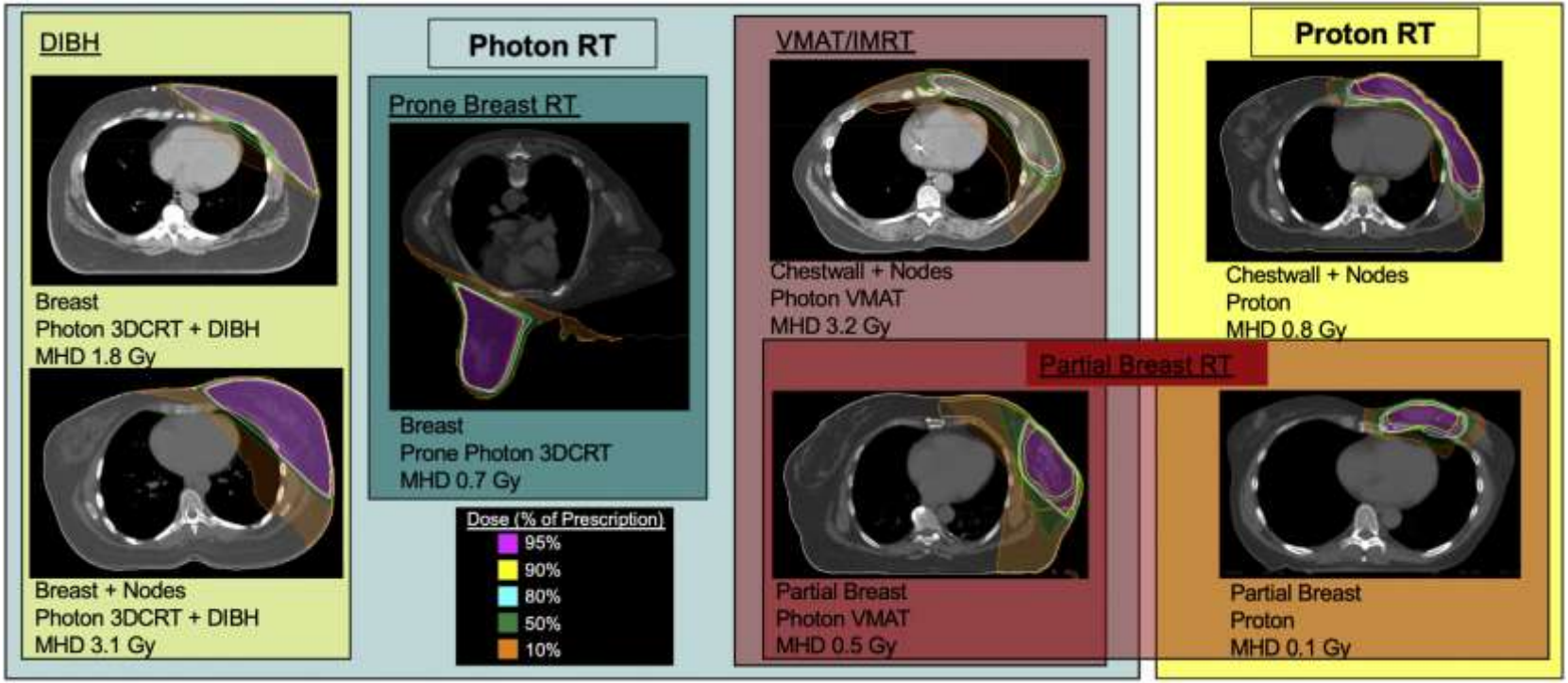


lary levels – Relative to **pec. minor:**
Level I: lateral
Level II: post./ant. (contour first!)
Level III: medial
Start just below subclavian vessels and go



Heart Sparing Techniques



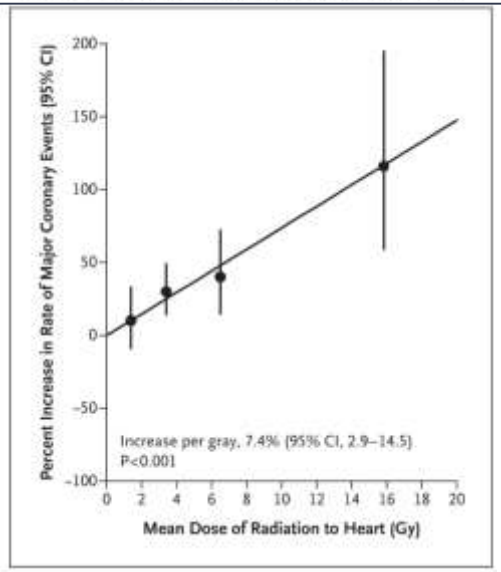
UK Heart Spare Study

RCT comparing Visual DIBH to Active Breath Control DIBH

23 patients were randomized to receive one technique for fractions 1-7 and the other for fractions 8-15.
Comparable dosimetry, positioning accuracy and reproducibility

Visual DIBH: shorter treatment and set-up time *(p=0.04;p=0.02)*
Visual DIBH: preferred by patients and RTTs *(both p=0.007)*

Bartlett et al. Radiother Oncol 2013;108:242-7

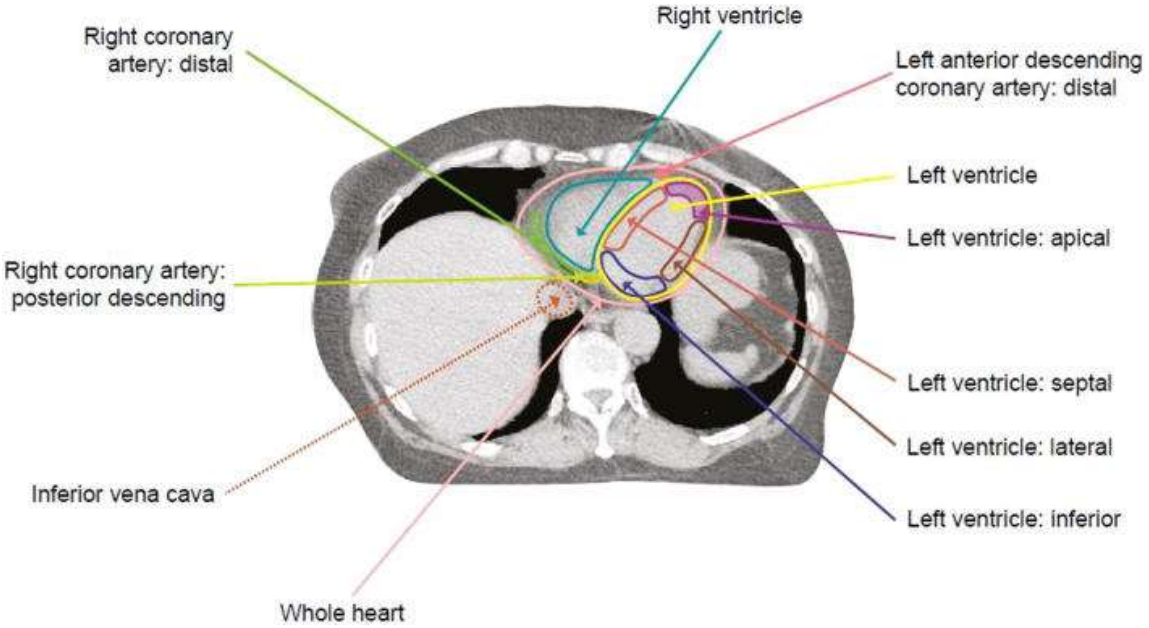


Mean heart dose associated linearly with major coronary events in breast cancer (~4-16% increased risk per Gy ; relative risk)

No threshold below which there was no risk.

Darby SC, N Engl J Med. 2013 Mar 14;368(11):987-98

Contouring cardiac Substructures



- More difficult with non-contrast CT
- Atlases available
- Autosegmentation methods published by a number of groups

Duane F, Radiother Oncol. 2017 Mar;122(3):416-422
Feng M, Int J Radiat Oncol Biol Phys. 2011 Jan 1;79(1):10-8
Milo MLH, Acta Oncol. 2022 Feb;61(2):247-254

Dose Constraints

Heart: MHD<2.5 Gy

Ipsilateral Lung V12< 30%

LV: Dmean < 3 Gy, V5 (volume of receiving ≥5 Gy) <17%; V23 (volume receiving ≥23 Gy) <5%

LAD: Dmean < 10 Gy; V30 (volume receiving ≥30 Gy) <2%; V40 (volume receiving ≥40 Gy) <1%

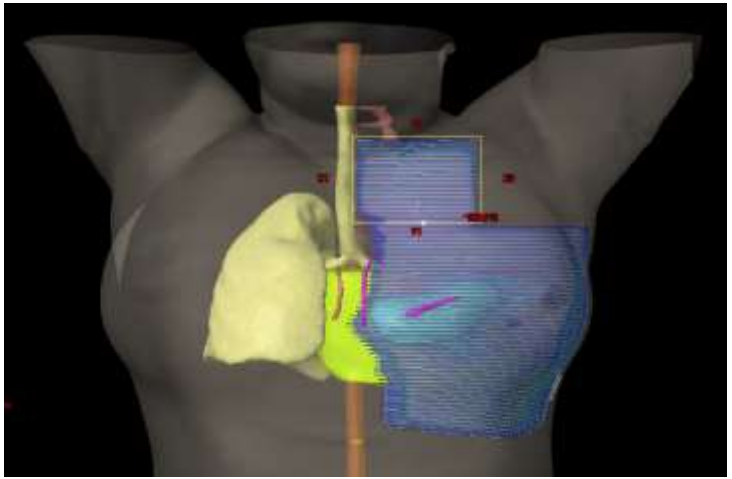
Contralateral Breast Mean<1Gy

Piroth et al. Strahlenther Onkol 2019

Planning Considerations

Matching Supraclavicular Fossa and Tangents

Monoisocentric technique
Casebow’s technique



Planning Considerations

The volume of breast tissue receiving greater than 105% of the prescription dose should be minimized.

3-D CRT treatment planning with a “field-in-field” technique is recommended as the initial treatment planning approach

No more than 200cc >105% and 2cc >107%

The goal for tumour bed coverage should be at least 95% of the prescription dose.

In addition, not fully covering the entire medial or lateral extent of breast tissue may be necessary to decrease the dose to the heart and/or lung.

Completed Adjuvant RT to Right Breast+ SCF

Any Adjuvant treatment

Follow up

- Follow up schedule

Summary of recommendations
Regular follow-up visits are recommended: • every 3–4 months in the first 2 years (every 6 months for low-risk and DCIS patients) • every 6–8 months from years 3–5 • annually thereafter
Annual bilateral* and/or a contralateral mammography** and US are recommended
Regular bone density evaluation is recommended for patients receiving AIs or undergoing OFS