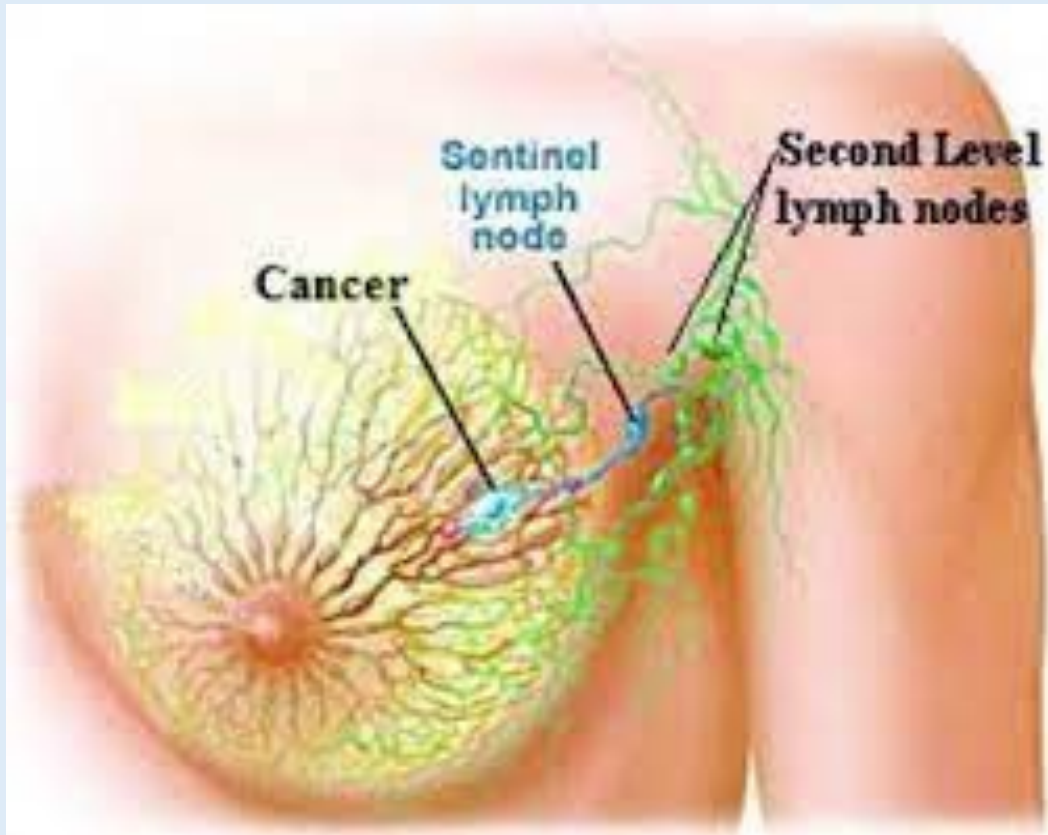


Axillary managements in Breast cancer



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- Globally, breast cancer is the most frequently diagnosed and the leading cause of cancer death in women.
- In the last few years, the treatment is improving due to:

New surgical techniques

New options in systemic therapy

A better understanding of the biology

Advances in the field of radiation oncology

- The status of the axillary lymph nodes is one of the most important prognostic factors in women with early stage breast cancer.
- Histologic examination of removed lymph nodes is the most accurate method for assessing spread of disease to these nodes.

RISK FACTORS FOR LYMPH NODE INVOLVEMENT IN BREAST CANCER

- **Tumor size and margins**
- **Histologic features (G1 ...G2,3!) , interinsic Biology, LVI,...**
- **Time at presentation**
- **Tumor location**

In a series of **2282** women with invasive breast cancer or DCIS, the incidence of ALN involvement was as follows :

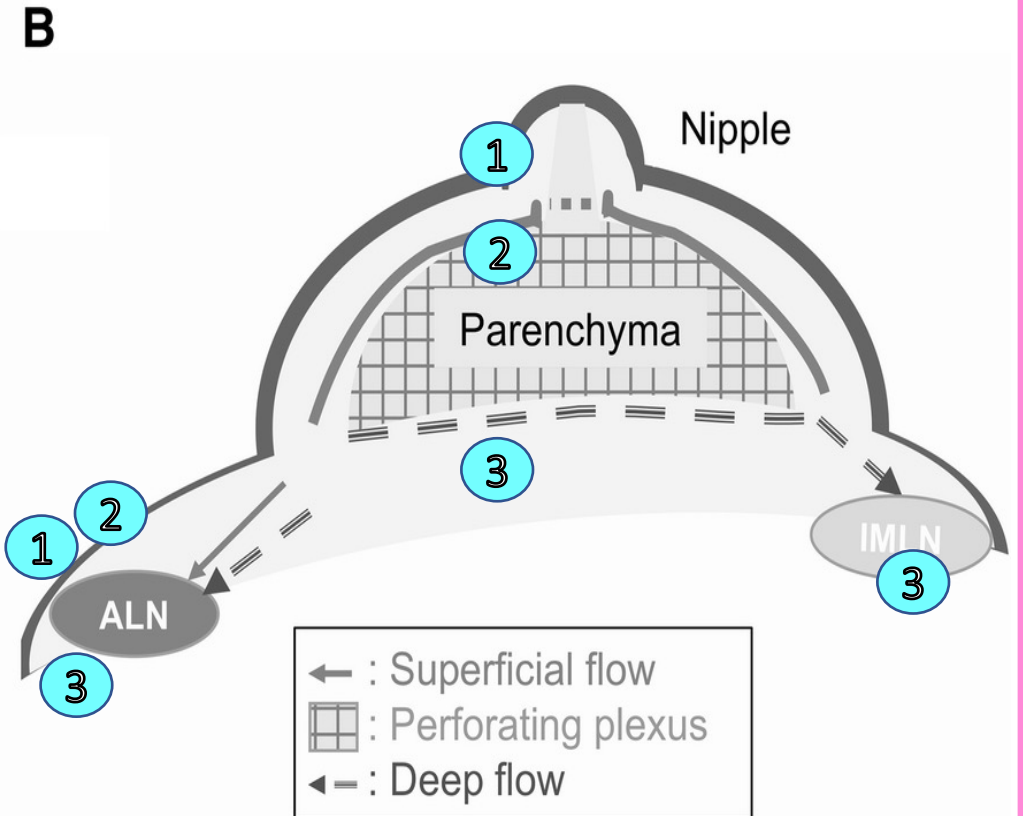
- Tis – 0.8 percent
- T1a – 5 percent
- T1b – 16 percent
- T1c – 28 percent
- T2 – 47 percent
- T3 – 68 percent
- T4 – 86 percent

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Breast Lymph drainage

- The Breast parenchyma has superficial, perforating, and deep drainage flows.
- ✓ The superficial and perforating plexuses drain almost exclusively into ALN through the sub areolar lymphatic network.
- ✓ The deep system drains into ALN and IMN.
- ✓ The intermediate perforating plexus is connected to the deep plexus.



Axillary management in different clinical settings

Early BC

Locally Advanced

After Neoadjuvant

The Z0011 study (ACOSOG group)

- Patients with **T1-2** lesions, breast-conserving surgery (**BCS**), whole breast radiotherapy (**WBRT**) and had **1 to 2 positive sentinel nodes** (micro or macroscopic disease).
- 446 cases were randomized to SLNB-only and 445 cases to completion ALND.
- Median follow-up of **6.3 years**:

no statistically significant differences in **local recurrence** ($p = 0.11$), regional recurrence ($p = 0.45$), disease-free survival ($p = 0.14$), and overall survival ($p = 0.25$) between the two groups

Update of the Z0011/ 2016-2017

- Median follow-up of **9.25 years** confirms positive results on locoregional disease control.
- The **cumulative incidence of regional recurrences** at 10 years in the ipsilateral axilla was similar in both arms with **(0.5%)** in the ALND group compared with **(1.5%)** patients in the SLNB-only group ($p = 0.28$).
- **Ten-year** locoregional recurrence was **6.2%** with ALND and **5.3%** with SLNB-only ($p = 0.36$).
- After multivariable analyses adjusted for treatment arm; **hormone receptor** status, pathologic **tumor size** and **tumor grade** were associated with locoregional recurrences

Update of the Z0011/ 2016-2017

- The 10-year **OS** was 86.3% in the SLND-only group and 83.6% in the ALND group (Non-inferiority $p = 0.02$).
- The 10-year **DFS was 80.2%** in the SLND-only group and **78.2%** in the ALND group ($p = 0.32$)
- The first phase of trial was closed with 891 cases before reaching the planned accrual size of 1900 patients), and limited follow-up (6.3 years), because the event rate was much lower than anticipated in both arms

updated reports with longer median follow-up of 9.25 and 9.3 years, respectively, **have confirmed its findings**

The AMAROS Trial

- (After Mapping of the Axilla: Radiotherapy Or Surgery?) trial from the EORTC selected patients with **similar criteria to Z011, but also included cases operated with mastectomy.**
- Patients were randomized to completion ALND (744) or axillary radiotherapy (681).
- After a median **follow-up of 10 years**, there were no significant differences in 10-year axillary recurrence, **10y-DMFS** (Distant metastasis-free survival) and **10y-OS** between the two groups.
- **More second primaries** were observed after axillary radiotherapy: 75/681 contralateral breast) as compared to ALND: 57/744 (11 contralateral breast) ($p = 0.035$).

The AMAROS Trial

- The 5 year report showed a statistically significant difference in the 5-year incidence of measured **arm lymphedema**, with 13% after ALND and 5% in the radiotherapy group (p= 0.0009)
- Approximately 80% of lesions were < 2 cm with a resulting **82% of cases being treated with BCS** and approximately 18% with mastectomy in both arms

Some New Trials

SOUND

Sentinel node vs. Observation after axillary UltrasouND

- cT1 cN0, for BCS +WBRT
- Randomized to **No axillary surgery** vs. **SLNB**
- **1560 ps**
- Primary EP: **Distant dfs**

INSEMA

(Intergroup Sentinel Mamma)

- cT1-2 cN0, for BCS + WBRT randomized to **No axillary surgery vs. SLNB** (1:4 allocation)
- **a second randomization of cases with 1-3 positive SLNs to either no further surgery or completion ALND 1:1)** (macrometastasis only)
- Outcome: **DFS-Non-inferiority**

Completion axillary dissection may not benefit:

ER positive

T1 or T2 tumors

clinically node negative

with **fewer than three** positive sentinel nodes

who will be treated with whole breast irradiation.

The clinical approach to such patients **is best resolved on a case-by-case** basis, taking into account all of the other risk factors and comorbidities for each patient to determine whether or not to complete the ALND. **Patient autonomy** should be incorporated in the decision-making process.

In Neoadjuvant patients



PATIENT SELECTION

- **Locally advanced breast cancer** – **stage III disease, T3, or T4 lesions**, no matter the subtype, are ideal candidates for neoadjuvant therapy because their cancers are often not amenable to upfront resection, much less breast conservation, and because their risk of distant recurrence warrants systemic treatment.
- **Select patients with early-stage breast cancer** – Patients with **stage I or II breast cancer** are appropriate candidates for neoadjuvant therapy **if breast-conserving surgery is not possible** due to a high tumor-to-breast ratio, or if their anticipated cosmetic outcome would be suboptimal due to tumor location.

Additionally, neoadjuvant therapy is often recommended to patients with **T2 tumors and even T1c triple-negative or HER2-positive** breast cancers, in part to identify patients who might benefit from additional treatments in the adjuvant setting if a pathologic complete response (pCR) is not achieved

For women who have received neoadjuvant therapy, approach to the axilla depends on

- the presence of **suspicious nodes prior** to neoadjuvant therapy (either on exam or axillary US), the results of a **FNA or CNB** of such nodes prior to treatment, and **clinical node status following neoadjuvant therapy**

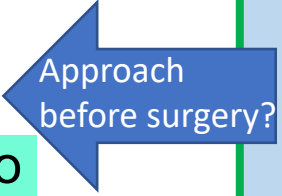
Clinically negative axilla prior to treatment

SLNB following completion of neoadjuvant therapy

- If SLNB is negative (ypN0), no further axillary treatment is required.
- If the SLNB is positive (ypN+), suggest proceeding with ALND.
- Patients in whom sentinel node mapping is not technically successful require an ALND.

Positive axilla prior to treatment

- Management involves Sentinel node surgery, ALND, and/or axillary radiation.
- A choice between them depends on the extent of nodal involvement prior to neoadjuvant therapy and, for those with limited involvement (cN1), response to treatment.
- For cN2, cN3, an ALND should be performed following neoadjuvant therapy, independent of the clinical response to treatment, with subsequent regional nodal irradiation.



Approach
before surgery?

After Neoadjuvant therapy



- In BCS patients, postoperative WBRT regardless of response to treatment
- for patients with residual nodal disease and for those who presented with stage III disease (regardless of response) is to treat the regional nodes
- For patients presenting with stage II disease who have a complete response to therapy, consider an individualized approach regarding the radiation of the regional nodes, weighing risk factors of the presenting tumor

Awaiting for **NSABP B-51/ RTOG 1304 trial**

NRG Oncology/ NSABP B-51 /RTOG 1304

- A Randomized **Phase III** Clinical Trial
- Post-Mastectomy Chestwall and **Regional** Nodal XRT and Post-**Lumpectomy** Regional Nodal XRT in Patients With Positive Axillary Nodes Before Neoadjuvant Chemotherapy Who Convert to Pathologically Negative Axillary Nodes After Neoadjuvant Chemotherapy
- 1636 cases, ongoing (to....July 2023)

Patients treated with mastectomy

Who received neoadjuvant therapy:

- any degree of residual macroscopic nodal disease
- stage III disease at presentation (regardless of response)
- stage II considering pretreatment risk factors as well as the patient's response to N/A, with a lower threshold to omit treatment for those patients who have a complete response.

Radiotherapy



The **objective** of adjuvant radiation therapy (RT)

is to eradicate any tumor deposits remaining following surgery for patients treated by either breast-conserving surgery or mastectomy.

- reduces risk of **locoregional recurrence** (LRR)
- improves **breast cancer-specific** and **overall survivals**

After Breast-Conserving Surgery (BCS)

After Mastectomy (MRM)

Indications



Breast-Conserving Surgery (BCS)

- After BCS we administer whole-breast radiation therapy (WBRT)
- This includes women treated with neoadjuvant therapy even if they experienced a complete pathologic response (CPR) to treatment

Any Exceptions



✓ For **older** women (typically defined as ≥ 70 years) with **node-negative**, **T<3** cm and **HR+** who are treated with endocrine therapy.....

exclusion of radiation therapy (RT) may be an option, depending on the values and preferences of the patient.

Regional nodal irradiation

- **Lymph node involvement**
- **T3 or T4 primary lesion**
- **T2 lesion with other high-risk features** (high-grade histology, ER negativity, or lymphovascular invasion, young age, ...)

- **MA.20 trial and EORTC 22922:**

- significantly prolonged disease-free survival
- trend toward OS (no statistical significance)

- **Recent meta-analyses that were well-powered with a larger number of patients:**

- improved OS with the addition of RNI to whole breast radiation in node-positive and high-risk node-negative patients who underwent upfront surgery

Regional nodal irradiation



- For women who have had breast-conserving therapy and have any number of macroscopically involved lymph nodes, suggests addition of RT to the regional nodes to standard WBRT
- RT to the regional nodes typically includes treatment of the supraclavicular and infraclavicular nodes +/- internal mammary , and if axillary dissection has not been performed, also to the axilla
- For women with extensive involvement of the lymph nodes (eg, extensive extracapsular extension, large number of involved lymph nodes, perinodal fat invasion, offers axillary radiation, even if lymph node dissection has been performed

Contraversy



Regional nodal irradiation



Some controversy exists for patients with **one to three involved lymph nodes** because of some studies that suggest good outcomes in these patients without RT

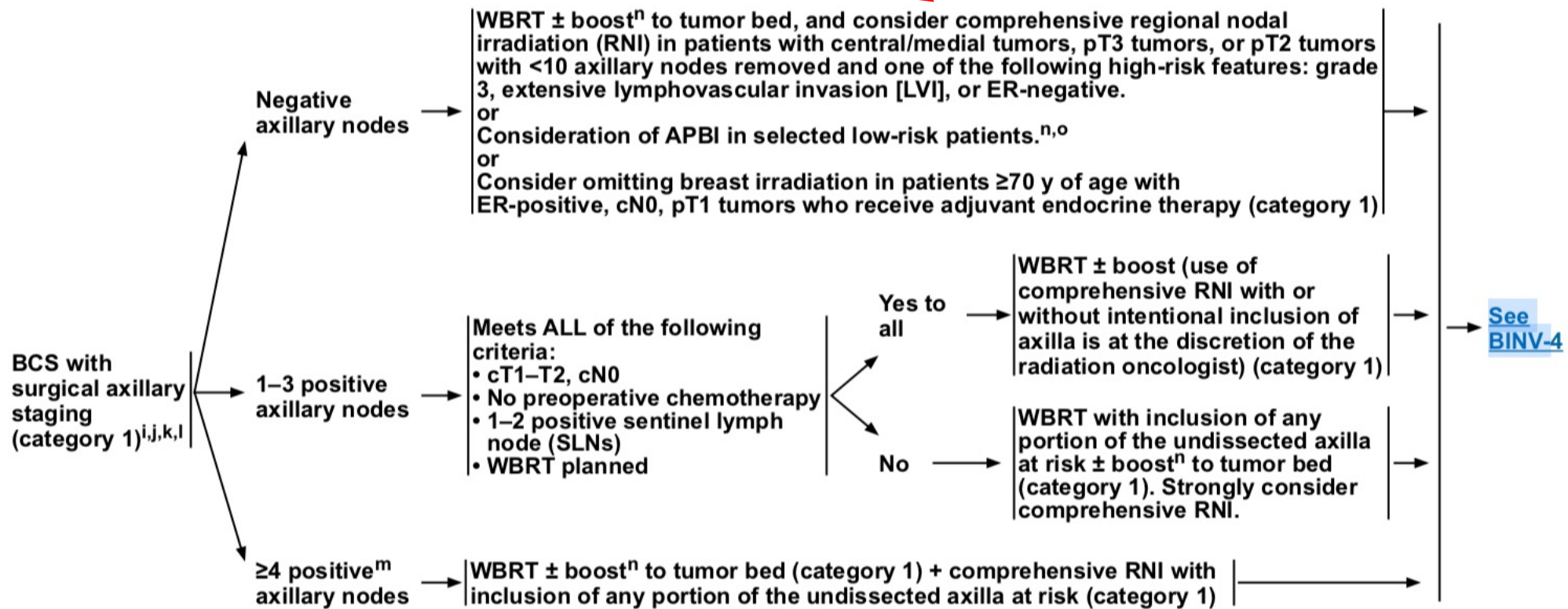
However, for this population, recommends locoregional RT in order to maximize the opportunity to reduce the risk of recurrence and potentially improve disease-specific survival.

((NCIC-CTG) MA.20 and EORTC 22922 trials: Both of these trials show decreased risk of recurrence, and better dfs although OS is not improved statistically)



LOCOREGIONAL TREATMENT OF cT1–3, cN0 or cN+, M0 DISEASE:^a BREAST-CONSERVING SURGERY (BCS) FOLLOWED BY RT

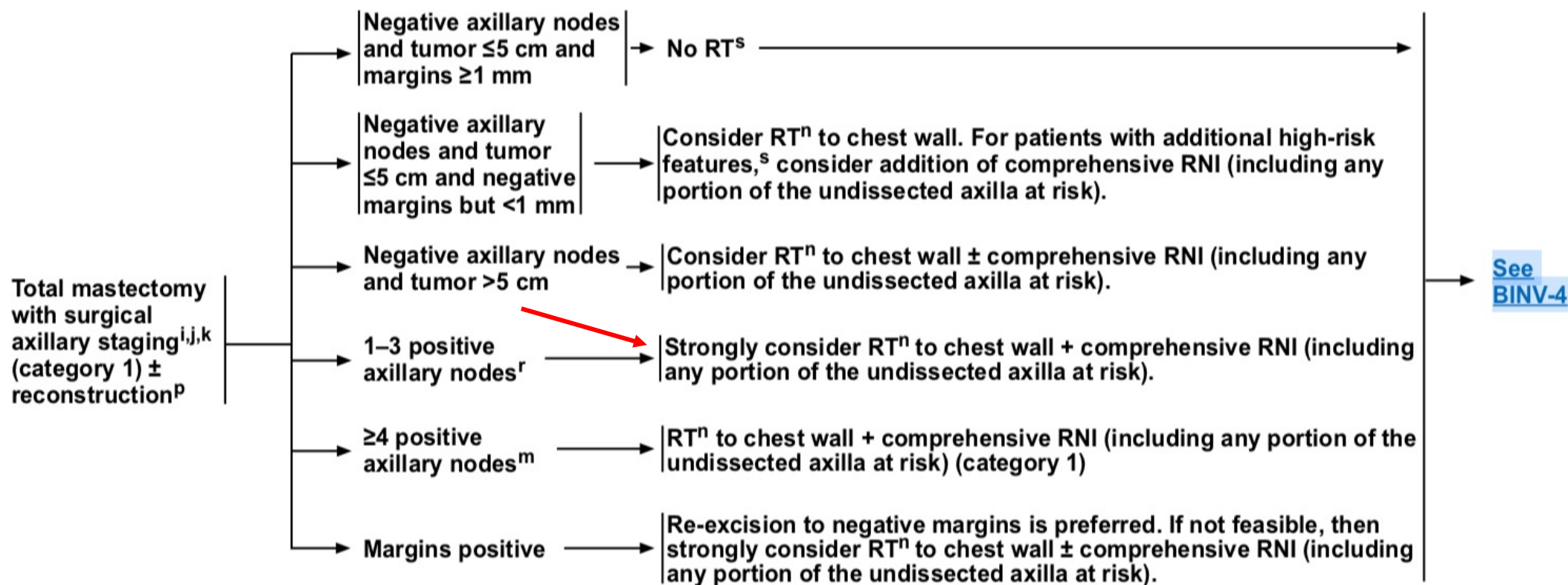
RT AFTER COMPLETION OF BCS AND AXILLARY STAGING





LOCOREGIONAL TREATMENT OF cT1-3, cN0 or cN+, M0 DISEASE:^{a,q} MASTECTOMY FOLLOWED BY RT

RT AFTER COMPLETION OF MASTECTOMY AND AXILLARY STAGING



Accelerated partial-breast irradiation (APBI)

delivers a higher dose of RT per day to a limited volume of tissue, encompassing the lumpectomy bed with margin over a shorter period of time.

34 Gy /10 fr twice per day with brachytherapy

Or

38,5 Gy/10 twice per day with EBRT

American Society for Radiation Oncology (ASTRO)
American Society of Breast Surgeons (ASBS)
American Brachytherapy Society (ABS)

- ≥50 years of age
- Diagnosed with a small (≤ 2 cm), node-negative breast cancer
- Tumor excised to negative surgical margins (2mm in IDC and 3mm low-int grade DCIS)

against APBI due to limited outcomes data

- Multicentric breast cancer
- Evidence of pathologic involvement of lymph nodes
- Primary tumor >3 cm
- The presence of lymphovascular space invasion

may also make patients less than optimal candidates

- Invasive lobular carcinoma (ILC) or grade III DCIS
- Triple-negative breast cancers
- HER2 positive breast cancers
- Hereditary breast cancer (*BRCA1/2* mutation)

Micrometastatic nodal disease

If 1-2 lymph nodes involved with micrometastatic disease, regional RT in the absence of other high-risk features could be omitted.

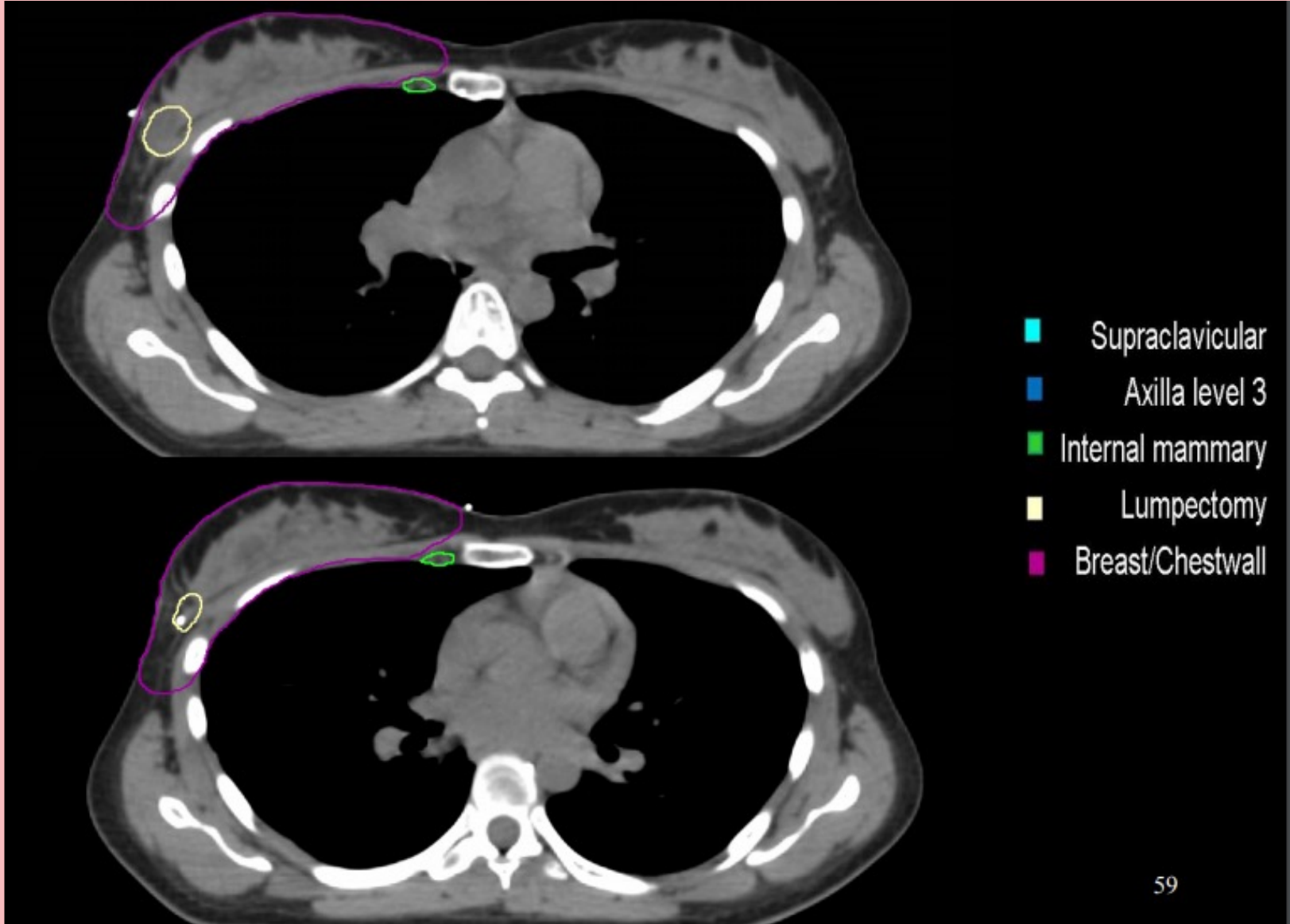
- irrespective of whether the lymph nodes were removed via sentinel or axillary nodal dissection
- High risk features include: T3 or T4 disease, T2 tumors with limited axillary dissection and also have other risk factors, including high-grade histology, ER negativity, or lymphovascular invasion

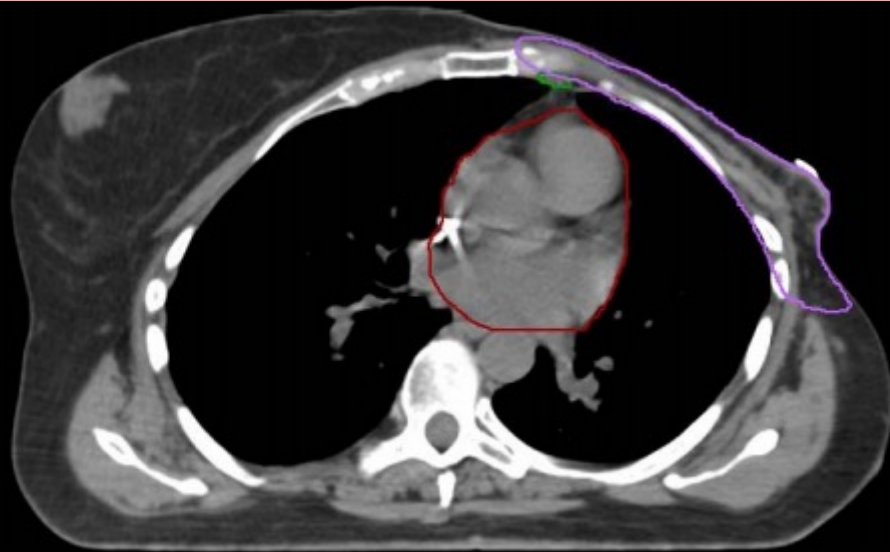
RADIATION OF INTERNAL MAMMARY NODES

- whether the IMNs should be included in the RT field is controversial, as data are limited and conflicting.
- However, the sum of the data suggests a benefit of IMNRT in patients with a high risk of recurrence
- Radiation of internal mammary nodes is associated with greater toxicity, for example cardiotoxicity, particularly when used in conjunction with anthracyclines

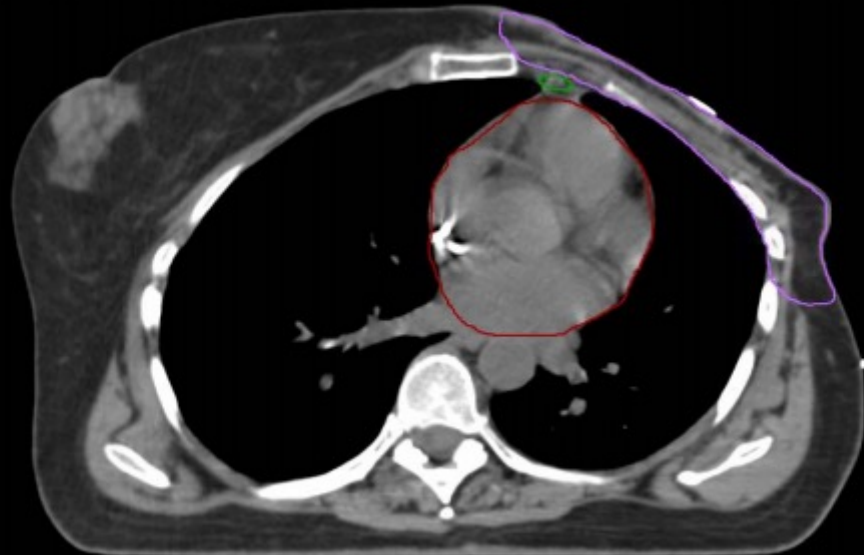
Timing of radiation relative to systemic therapy

- In patients with adjuvant chemotherapy, RT is generally administered following the completion of chemotherapy
- In case of endocrine therapy it is acceptable to initiate endocrine therapy either concomitantly with RT or following completion of RT
- In patients with breast cancers that overexpress HER2 receptor, RT is administered concomitantly with adjuvant trastuzumab and pertuzumab





- Supraclavicular
- Axilla level 3
- Axilla level 2
- Axilla level 1
- Internal mammary
- Chestwall
- Heart



Take home messages

- Adjuvant radiotherapy is an essential part of treatment in most breast cancers, reducing the risk of LRR and improving DSS and OS.
- After BCS we administer whole-breast radiation therapy (WBRT) even in PCR after neoadjuvant therapy.
- APBI may be an option in ≥ 50 yrs, luminal type, LN negative, small tumors resected with adequate negative margins.
- Lung and abd pelvic CT scan, WBBS, or PET CT In $\geq T3N1$ or if Alp elevated in routin biochemisty tests

- For patients who have clinically negative axillary lymph nodes, sentinel lymph node biopsy reliably identifies patients without axillary node involvement, thereby obviating the need for more extensive surgery.
- Regional nodal irradiation..... LN positives, T3-T4 tumors, and some T2 tumors with high risk features.
- For women with extensive involvement of the lymph nodes (eg, extensive extracapsular extension, large number of involved lymph nodes, perinodal fat invasion, offers axillary radiation, even if lymph node dissection has been performed
- In micrometastatic involvements, regional RT in the absence of other high-risk features could be omitted.
- In patients with mastectomy after N/A therapy, adjuvant RT is considered in any degree of residual macroscopic nodal disease, stage III disease at presentation (regardless of response), some stage II cases considering pretreatment risk factors.

Thanks!

