Update to the Breast Cancer Guidelines-2016
Systemic Therapy

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Outline

- Preoperative endocrine rx
- Optimizing adjuvant endocrine rx in pre- and postmenopausal women
- Preoperative HER2 –directed therapy
- New partners for endocrine rx in MBC
- Fertility
Who is Suitable for Neoadjuvant Endocrine Therapy?

- Selection paramount
  - ER Rich Cancers (Allred 7+8)
  - Older postmenopausal women but also
  - Younger women with significant morbidities

Neoadjuvant chemotherapy +/- anti–HER2 rx is increasingly successful in producing pCRs, BUT only in ER- and HER2-positive cancers
ER vs Response to Neoadjuvant Chemotherapy

- 1731 patients neoadjuvant chemotherapy
- 1163 ER+; 556 ER-

Path CR Rate
- 24% for ER-
- 8% for ER+

p <0.001

Guarneri et al JCO 2006: 24; 1037-44

Effect of Phenotype on pCR to Neoadjuvant Chemotherapy - GeparTrio


Age <40 – black bars
Age ≥40 – blue bars
NeoSphere: Neoadjuvant Phase 2 Operable or Locally Advanced. >2cm (417pts)

4x3wkly cycles

![Diagram](image)

Adjuvant FEC given to Arms A, B, D; adjuvant docetaxel given to Arm C; 1 year adjuvant trastuzumab was given to all arms.


Not fully appreciated that pCR is not as important in predicting outcome of ER-positive cancers
ER status, pCR and prognosis in patients receiving neoadjuvant chemotherapy for early breast cancer

A E Ring, I E Smith, S Ashley, L G Fulford, and S R Lakhani


- 435 patients treated with neoadjuvant chemotherapy

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**DFS in Patients with ER– and ER+ Cancers vs pCR**

**ER Negative**

- Disease-free survival: ER –ve
  - Path CR (24)
  - Not CR (87)
  - *P*=0.001

**ER Positive**

- Disease-free survival: ER +ve
  - Path CR (22)
  - Not CR (240)
  - *P*=1.0

ACOSOG Z1031 Study Design
Cohort A

16 weeks
Postmenopausal
ER+, Allred 6-8, clinical stage 2 and 3

16 weeks
Continued AI therapy where possible.
Radiotherapy, chemotherapy discretionary

ACOSOG Z1031, Cohort A
Clinical Responses

<table>
<thead>
<tr>
<th>Clinical Response</th>
<th>EXE (n = 124)</th>
<th>LET (n = 127)</th>
<th>ANA (n = 123)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>25 (20%)</td>
<td>26 (21%)</td>
<td>20 (16%)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>49 (40%)</td>
<td>66 (52%)</td>
<td>63 (51%)</td>
</tr>
<tr>
<td>Clinical Response rate</td>
<td>74/124 (60%)</td>
<td>92/127 (72%)</td>
<td>83/123 (68%)</td>
</tr>
</tbody>
</table>

All were ER rich with Allred scores of 6-8.

**NCCN Guidelines Version 1.2016**

**Invasive Breast Cancer Updates**

Updates in Version 1.2016 of the NCCN Guidelines for Breast Cancer from Version 2.2015 include:

**BINV-H (1 of 2)**
- First paragraph, added the following “However, breast reconstruction should not interfere with the appropriate surgical management of the cancer or the scope of appropriate surgical treatment for this disease. Coordinating consultation and surgical treatment with a reconstructive surgeon should be executed within a reasonable time frame.”
- Modified “Oncoplastic techniques for breast conservation can extend breast-conserving surgical options in situations where the resection by itself would likely yield an unacceptable cosmetic outcome.”

**BINV-H (2 of 2)**
- Modified the statement “Evidence of nipple involvement such as Paget's disease or other nipple discharge associated with malignancy, and/or imaging findings suggesting malignant involvement of the nipple or subareolar tissues is a contraindication for nipple preservation.”

**BINV-J**
- This page has been reorganized and updated.

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**NCCN Guidelines Version 1.2016**

**Invasive Breast Cancer**

**ADJUVANT ENDOCRINE THERAPY**

- **Premenopausal at diagnosis** → Tamoxifen for 5 y (category 1) ± ovarian suppression or ablation (category 1) or Aromatase inhibitor for 5 y ± ovarian suppression or ablation (category 1)

  - **Postmenopausal** → Aromatase inhibitor for 5 y (category 1) or Consider tamoxifen for an additional 5 y to complete 10 y

  - **Premenopausal** → Consider tamoxifen for an additional 5 y to complete 10 y or No further endocrine therapy

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Early Stage Breast Cancer
Tamoxifen: 5 Years Vs. Not

- More than half of recurrences and deaths occur post-treatment

EBCTCG, Lancet 2005,365: 1687
Tamoxifen

Why did we stop at 5 years anyway?

Duration of Tamoxifen: NSABP B-14

Fisher, et al. JNCI 2001;
median f/u 7 years post-rerandomization

![Graph showing disease-free survival, relapse-free survival, and survival over time for Tamoxifen treatment.]
Duration of Adjuvant Endocrine Therapy: What Have ATLAS & aTTOM Taught Us?

Adj Tamoxifen To Offer More (aTTOM)
- Women with invasive tumors who received \( \geq 4 \) years of tamoxifen
  - N = 6934
- Discontinue Tamoxifen 20 mg PO qd
- Tamoxifen 20 mg PO qd × 5 additional years

Adj Tamoxifen Longer Ag Shorter (ATLAS)
- Pre and Postmenopausal women with invasive tumors
  - N = 10,543
- Tamoxifen 20 mg PO qd × 5 years
- Tamoxifen 20 mg PO qd × 10 years

Dent, R. 2013. ASCO Annual Meeting. Chicago, IL.
### Combined Outcomes in ATLAS and aTTom

<table>
<thead>
<tr>
<th></th>
<th>Breast Cancer Mortality</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years 5 - 9</td>
<td>0.97 (0.84-1.15)</td>
<td>0.99 (0.89-1.10)</td>
</tr>
<tr>
<td>Years 10+</td>
<td>0.75 (0.65-0.86)*</td>
<td>0.84 (0.77-0.93)*</td>
</tr>
<tr>
<td>All Years</td>
<td>0.85 (0.77-0.94)*</td>
<td>0.91 (0.84-0.97)*</td>
</tr>
</tbody>
</table>

*p < 0.05 favoring 10 years

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**Adjuvant Endocrine Therapy**

*Premenopausal Women*
Breast Cancer in Premenopausal Women: The Scope of the Problem

- Most frequent cancer diagnosis in women worldwide
- In the US
  - ~75,340 ≤ age 54
  - ~25,270 ≤ age 44
- Most common cause of cancer death

15 year Outcome with 5 Years of Tamoxifen in < 45 Year Old Women
EBCTCG Ovarian Suppression/Ablation

2006 EBCTCG
- OA/OS vs not
- No chemo
- Not selected for ER

SOFT: SUPPRESSION of OVARIAN FUNCTION TRIAL
Premenopausal ER+ve and/or PR+ve Breast Cancer

3047 Patients Randomized in ITT (Dec 2003 - Jan 2011)
Primary Analysis (n=2033)
Median follow-up=5.6 y

Two Patient Cohorts

- No Chemotherapy (47%)
  - Premenopausal, within 12 weeks of surgery
  - Median time since surgery = 1.8 months
  - Premenopausal or after completing chemotherapy
  - Randomization within 8 months of completion
  - Median time since surgery = 8.0 months

- Prior Chemotherapy (53%)

Tamoxifen x 5y (n=1018)
Tamoxifen+OFS x (n=1015) x 5y
Exemestane+OFS (n=1014) x 5y

*According to locally-determined E2 level in premenopausal range

OFS=ovarian function suppression (oophorectomy, triptorelin or XRT)

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SOFT Primary Analysis: Disease-free Survival

5.6 years median follow-up

Primary analysis in overall population not significant (p=0.10)
Multivariable Cox model HR=0.78 (95% CI 0.62-0.98) p=0.03


SOFT—Outcomes by Chemotherapy

No chemotherapy cohort selected for low risk features:
90% ≥ age 40yr, 91% node negative, 85% tumor ≤ 2cm, 41% grade 1

SOFT—Outcomes for Women < 35 yr

- 350 patients (11.5%) under age 35
- 94% received chemotherapy in this age group


TEXT and SOFT Joint Analysis

Enrolled: Nov03-Apr11
- Premenopausal
- ≤12 wk after surgery
- Planned OFS ± Planned chemo

Suppression of Ovarian Function Trial (N=3066)

Joint Analysis (N=4690)

Median follow-up 5.7yr

OFS=ovarian function suppression
Exemestane+OFS Improved DFS


Joint Analysis of TEXT and SOFT

Exemestane + OFS vs Tamoxifen + OFS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>0.72 (0.60-0.85)</td>
<td>0.0002</td>
</tr>
<tr>
<td>BCFI</td>
<td>0.66 (0.55-0.80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DDFI</td>
<td>0.78 (0.62-0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>OS</td>
<td>1.14 (0.86-1.51)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Median Follow-up of 5.7 years

Predictable Adverse Events Profile

<table>
<thead>
<tr>
<th>CTCAE V3.0 Grade 3-4</th>
<th>E + OFS</th>
<th>T + OFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal</td>
<td>11%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Fracture</td>
<td>1.3%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0.3%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Thrombosis/embolism</td>
<td>0.8%</td>
<td>1.9%</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>2.3%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Premature discontinuation</td>
<td>16%</td>
<td>11%</td>
</tr>
</tbody>
</table>


Patient Reported Outcomes in Joint Analysis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>OFS + Tamoxifen</th>
<th>OFS + Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot flashes/sweats</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Vaginal dryness</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Loss of sexual interest</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Difficulty with arousal</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Bone/joint pain</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

“Changes in global QOL were small and similar between treatments over the 5 years”

Bernhard et al, Lancet Oncol, 2015
Adjuvant Endocrine Therapy for Premenopausal Women

• Consider use of OFS+Tamoxifen or OFS+AI for higher risk women like:
  - Chemotherapy recipients who remain premenopausal
  - Multiple positive nodes
  - Age < 35 yrs

• Optimal duration of OFS-based therapy uncertain-suggest 3-5 years

• Long term follow-up of pivotal trials for adherence, toxicity & benefit critical

HER2+ Disease
Does improving pCR improve breast cancer outcomes?
Perfect scenario

Log(odds ratio of pCR)

Log(HR of EFS)

Individual trial

Association of pCR with EFS in Her2-positive Subtype

**HER2+**

- HR=0.39, P < 0.001
- pCR (n = 589)
- no pCR (n = 1403)

**HER2+ HR**

- HR=0.58, P = 0.001
- pCR (n = 247)
- no pCR (n = 839)

**HER2+ HR-**

- HR=0.25, P < 0.001
- pCR (n = 325)
- no pCR (n = 510)

pCR=ypT0/is ypN0

Nominal p-value

Cortazar, JCO, 2014.
Pathologic Response in Neo-ALTTO

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Path CR (breast only)</th>
<th>Path CR (breast + LN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib + Paclitaxel</td>
<td>25%</td>
<td>20%</td>
</tr>
<tr>
<td>Trastuzumab + Paclitaxel</td>
<td>29%</td>
<td>28%</td>
</tr>
<tr>
<td>Trast + Lap + Paclitaxel</td>
<td>51%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Baselga et al, Lancet 2012

ALTTO Trial: DFS Analysis

<table>
<thead>
<tr>
<th>Years since Randomisation</th>
<th>No. patients</th>
<th>No. events</th>
<th>4yr DFS rate</th>
<th>Hazard ratio c.f. Tras</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Lap+Tras</td>
<td>2093</td>
<td>254</td>
<td>88%</td>
<td>0.84 (0.70, 1.02)</td>
</tr>
<tr>
<td></td>
<td>Tras-&gt;Lap</td>
<td>2091</td>
<td>284</td>
<td>97%</td>
<td>0.96 (0.80, 1.15)</td>
</tr>
<tr>
<td></td>
<td>Tras</td>
<td>2097</td>
<td>301</td>
<td>86%</td>
<td>1.02 (0.79, 1.30)</td>
</tr>
</tbody>
</table>

Piccart et al, ASCO 2014

**p-value ≤ 0.025 required for statistical significance
**NeoSphere: Neoadjuvant Phase 2 Operable or Locally Advanced. >2cm (417pts)**

4x3wkly cycles

- trastuzumab + docetaxel (n = 107)
- trastuzumab + docetaxel + pertuzumab (n = 107)
- trastuzumab + pertuzumab (n = 107)
- pertuzumab + docetaxel (n = 96)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>pCR breast (%)</th>
<th>HR+ve</th>
<th>HR-ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>trastuzumab + docetaxel (n = 107)</td>
<td>31 (29%)</td>
<td>HR+ve 20%</td>
<td>HR-ve 37%</td>
</tr>
<tr>
<td>trastuzumab + docetaxel + pertuzumab (n = 107)</td>
<td>49 (45.8%)</td>
<td>HR+ve 26%</td>
<td>HR-ve 63%</td>
</tr>
<tr>
<td>trastuzumab + pertuzumab (n = 107)</td>
<td>18 (16.8%)</td>
<td>HR+ve 6%</td>
<td>HR-ve 27%</td>
</tr>
<tr>
<td>pertuzumab + docetaxel (n = 96)</td>
<td>23 (24%)</td>
<td>HR+ve 17%</td>
<td>HR-ve 30%</td>
</tr>
</tbody>
</table>

Adjuvant FEC given to Arms A, B, D; adjuvant docetaxel given to Arm C; 1 year adjuvant trastuzumab was given to all arms.


**Final OS Analysis of CLEOPATRA sets a new paradigm of treatment of HER2+ MBC**

- Ptz + T + D: median 56.5 months
- Pla + T + D: median 40.8 months

Δ 15.7 months

HR 0.68
95% CI = 0.56, 0.84
p = 0.0002

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APHINITY: Randomized Adjuvant Phase 3 Trial

N=3800 planned (4800 enrolled)

Arm A
ACCEC x 4 wks
Tx x 1 yr
Trastuzumab q 3 wks x 9 mo
Pertuzumab q 3 wks x 9 mo

Arm B
ACCEC x 4 wks
PEOPAC x 9 mo
Tx x 1 yr
Trastuzumab q 3 wks x 9 mo
Pertuzumab q 3 wks x 9 mo

Reason to be encouraged
NEOSPHERE: PFS by All Treatment Arms
ASCO 2015 Update

Kaplan-Meier curves are truncated at 60 months (the end of scheduled follow-up). However, summary statistics shown here take into account all follow-up.

Three late events occurred with PTD: two cases of progressive disease (PD) at 63 and 71 months, and one death due to an unrelated cerebrovascular accident without PD at 76 months.

Gianni et al ASCO 2015

Case #1

- A 67 yo WF presents with newly diagnosed bone metastases. She was originally dx with a 3 cm IDC of the left breast 4 years earlier and underwent mastectomy. The tumor was ER+/PR+/HER2- and SLN were negative. A recurrence score was low. Treatment with anastrozole was initiated.
Case #1

- She was doing well until recently when diffuse bone aches were noted not responding to NSAID
- Labs showed an elevated Alk Phos; a bone scan demonstrated several lytic lesions throughout the axial skeleton. CT CAP showed 2 suspicious 1 cm lesions in the liver
- A liver biopsy was consistent with the original dx and remained ER+

Audience Polling Results

Case #1

In addition to starting a bone agent (bisphosphonate or denosumab) and discontinuing anastrozole you would:

1. Start chemotherapy
2. Start an alternative AI
3. Start an alternative AI and add palbociclib
4. Start fulvestrant
5. Start fulvestrant and palbociclib

18%  4%  26%  8%  45%
Invasive Breast Cancer Updates

Updates in Version 1.2016 of the NCCN Guidelines for Breast Cancer from Version 2.2015 include:

BINV-K (1 of 7)
- Footnote 5 is new to the page. “The regimens listed for HER2-negative disease are all category 1 (except where indicated) when used in the adjuvant setting.”
- Removed FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide) and FEC/CEF (cyclophosphamide/epirubicin/fluorouracil) from the list of regimens for preoperative/adjuvant chemotherapy.

BINV-K (3 of 7)
- Under the regimen “FAC followed by weekly paclitaxel”, changed 6 to 4 cycles.
- BINV-K (4, 5, and 6 of 7)
- Replaced cardiac monitoring at baseline, 3, 6, and 9 mo with “Evaluate left ventricular ejection fraction (LVEF) prior to and during treatment.”
- Added the following footnote “The optimal frequency of LVEF assessment during adjuvant trastuzumab therapy is not known. The FDA label recommends LVEF measurements prior to initiation of trastuzumab and every 3 mo during therapy.”

BINV-L
- New page - Principles of Preoperative Systemic Therapy.

UPDATES-5

ENDOCRINE THERAPY FOR RECURRENT OR STAGE IV DISEASE

Premenopausal patients with hormone-receptor positive disease should have ovarian ablation/suppression and follow postmenopausal guidelines

Postmenopausal Patients
- Non-steroidal aromatase inhibitor (anastrozole, letrozole)
- Steroidal aromatase inactivator ( exemestane)
- Exemestane + everolimus
- Palbociclib + letrozole
- Palbociclib + fulvestrant (category 1)
- Fulvestrant
- Tamoxifen or toremifene
- Megestrol acetate
- Fluoxymesterone
- Ethinyl estradiol

BINV-N

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Phase II PALOMA-1/TRIO-18: Let +/- Palbociclib 1st line ER+ MBC

**Progression-Free Survival (ITT) PALOMA-1**

<table>
<thead>
<tr>
<th></th>
<th>PAL + LET (N=84)</th>
<th>LET (N=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Events (%)</td>
<td>41 (49)</td>
<td>59 (73)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>20.2 (13.8, 27.5)</td>
<td>10.2 (5.7, 12.6)</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.488 (0.319, 0.748)</td>
<td>0.0004</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0004</td>
<td></td>
</tr>
</tbody>
</table>

**Number of patients at risk**

<table>
<thead>
<tr>
<th></th>
<th>PAL + LET</th>
<th>LET</th>
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<tbody>
<tr>
<td>0</td>
<td>84</td>
<td>81</td>
</tr>
<tr>
<td>1</td>
<td>67</td>
<td>48</td>
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<td>2</td>
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<tr>
<td>12</td>
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<td>0</td>
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</table>

*Finn et al. The Lancet Oncology, Volume 16, Issue 1, 2015, 25-35*
PALOMA3: A Double-Blind, Phase III Trial of Fulvestrant with or without Palbociclib in Pre- and Post-Menopausal Women with Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer that Progressed on Prior Endocrine Therapy


**Phase III PALOMA-3: Fulvestrant +/- Palbociclib 2nd line ER+ MBC**

- HR+, HER2- ABC
- Pre-peri- or post-menopausal
- Progressed on prior endocrine therapy:
  - On or within 12 mo adjuvant
  - On therapy for ABC
- ≤1 prior chemotherapy regimen for advanced cancer

*All received gecevopox.*

<table>
<thead>
<tr>
<th>2:1 Randomization</th>
<th>N=521</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palbociclib (125 mg QD; 3 wks on/1 wk off)</td>
<td></td>
</tr>
<tr>
<td>Fulvestrant (500 mg IM q4w)</td>
<td></td>
</tr>
<tr>
<td>Placebo (3 wks on/1 wk off)</td>
<td></td>
</tr>
<tr>
<td>Fulvestrant (500 mg IM q4w)</td>
<td></td>
</tr>
</tbody>
</table>

Stratification:
- Visceral metastases
- Sensitivity to prior hormonal therapy
- Pre-peri- vs Post-menopausal

*Post-menopausal patients must have progressed on prior aromatase inhibitor therapy.*

Nicholas Turner at 2015 ASCO Annual Meeting

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Progression-free Survival.

B Central Assessment

- Palbociclib–fulvestrant (N=147)
  - Median progression-free survival, NE
- Placebo–fulvestrant (N=64)
  - Median progression-free survival, 3.7 mo (95% CI, 3.4–7.2)

Hazard ratio, 0.27 (95% CI, 0.16–0.46)
P<0.001

No. at Risk
Palbociclib–
fulvestrant
147 118 53 24 7 2
Placebo–
fulvestrant
64 37 12 4 1 1

Month


Invasive Breast Cancer Updates

UPDATES-4

BINV-D
- Fertility and birth control, modified the first bullet: “All premenopausal patients should be informed about the potential impact of chemotherapy on fertility and asked about their desire for potential future pregnancies. Patients who may desire future pregnancies should be referred to fertility specialists before chemotherapy and/or endocrine therapy, to discuss the options based on patient specifics, disease stage and biology, (which determine the urgency and type and sequence of treatment). Timing and duration allowed for fertility preservation, options inclusive of oocyte and embryo cryopreservation as well as evolving technologies, and the probability of successful pregnancies subsequent to completion of breast cancer therapy are also to be discussed.”

BINV-D
- Footnote 2: Removed the last sentence “However, only peritumoral injections map to the internal mammary lymph node(s).”

BINV-E
- Replaced “Sentinel lymph node biopsy is the preferred method of axillary lymph node staging if there is an experienced sentinel node team and the patient is an appropriate sentinel lymph node biopsy candidate (See BINV-G)” with “Sentinel lymph node biopsy should be performed and is the preferred method of axillary lymph node staging if the patient is an appropriate sentinel lymph node biopsy candidate.”

BINV-G
- Absolute contraindications: added “Diffusely positive pathologic margins” and removed “Positive pathologic margin.”
- Relative contraindications: added “Positive pathologic margin” and removed “Diffusely positive pathologic margins.”
- Added a link to NCCN Guidelines for Genetic/ Familial High-Risk Assessment Breast and Ovarian.
Many young women are diagnosed each year with breast cancer in the US.

Percent of new cases by age

>25,000 women < 45 years of age diagnosed each year

Treatment poses a risk of infertility

http://seer.cancer.gov/

Professional guidelines highlight the need for clinicians to address fertility

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Effect of Age on Ovarian Reserve

Adapted from Faddy et al 1992

Effects of Treatment on Fertility

Depletion of ovarian follicle pool

Adapted from Faddy et al 1992
Fertility Preservation Options

Cryopreservation

Reduction of Toxicity

Even a single treatment with gonadotoxic therapy can affect gamete quality and DNA integrity, so fertility preservation must be completed before treatment begins.

Ovarian Suppression

• GnRH agonists: leuprolide, goserelin, triptorelin
• Mechanism of action is unclear
  – Suppression of FSH $\rightarrow$ ↓ follicle recruitment and maturation $\rightarrow$ protection from chemo destruction?
• Administered as a monthly injection
  – Start 1-2 weeks before first chemotherapy
• Will cause menopausal symptoms

Blumenfeld et al 2015; Del Mastro et al 2011; Lambertini et al 2015; Moore et al 2015
Ovarian Suppression

• Results have been conflicting – investigational
  PROMISE (ER+)
    ↓ POF (8% vs 22%)  ↑ pregnancies (5.4% vs 3%)
  POEMS (ER-)
    ↓ POF (8.9% vs 25.9%)  ↑ pregnancies (21% vs 11%)

Blumenfeld et al 2015; Del Mastro et al 2011;
Lambertini et al 2015; Moore et al 2015

NCCN Guidelines Updates:
Breast Cancer

Kilian E. Salerno, MD
Director of Breast and Soft Tissue / Melanoma Radiation Oncology
Roswell Park Cancer Institute
NCCN Guidelines Updates: Breast Cancer

- All changes to guidelines summarized
  - pages UPDATES-1 through UPDATES-5

- Locoregional therapy manuscript published in current issue of JNCCN (March 2016 issue)
Locoregional Updates

• Outline
  – General principles of radiation
  – Guidelines updates
  – Regional nodal irradiation (RNI)
    • Which patients need RNI and to what extent?

Principles of Radiation Therapy

• Treatment options
  – Targets
  – Definitions
  – Techniques

• Optimizing treatment planning and delivery
Radiation Treatment Options

TARGETS:
Whole breast
Partial breast
Chest wall
Regional nodes
  SCV
  ICV
  Axilla at risk
  IMNs
Boost

DOSE and FRACTIONATION

– Conventional Fractionation
  • 1.8-2 Gy per fraction to total dose 45-50 Gy

– Hypofractionation
  • Shorter course utilizing larger doses per fraction
  • >2 Gy per fraction to lower total dose
    – 40 - 42.5 Gy given in daily fxs for whole breast
    – 34 - 38.5 Gy given twice daily fxs for partial breast

– Accelerated course
  • Treatment over shorter time course
Radiation Treatment Options

MODALITIES:

– External Beam
  • Photons
  • Electrons

– Brachytherapy
  • Radioactive source
  • Catheters/devices

– Intraoperative
  • Various means

PRINCIPLES OF RADIATION THERAPY

Whole Breast Radiation:
Target definition is the breast tissue in entirety. The whole breast should receive a dose of 46–50 Gy in 23–25 fractions or 40–42.5 Gy in 15–16 fractions (hypofractionation is preferred). All dose schedules are given 5 days per week. A boost to the tumor bed is recommended in patients at higher risk for recurrence. Typical boost doses are 10–16 Gy in 4–5 fractions.

Chest Wall Radiation (including breast reconstruction):
The target includes the ipsilateral chest wall, mastectomy scar, and drain sites when indicated. Depending on whether the patient has had breast reconstruction or not, several techniques using photons and/or electrons are appropriate. CT-based treatment planning is encouraged in order to identify lung and heart volumes and minimize exposure of these organs. Dose is 46–50 Gy in 23–25 fractions to the chest wall +/- scar boost at 2 Gy per fraction to a total dose of approximately 60 Gy. All dose schedules are given 5 days per week. Special consideration should be given to the use of bolus material to ensure that the skin dose is adequate.

Regional Nodal Radiation:
Target delineation is best achieved by the use of CT-based treatment planning. For the paracervical and axillary nodes, prescription depth varies based on the patient anatomy. For internal mammary node identification, the internal mammary artery and vein can be used as a surrogate for the nodal location (as the nodes themselves are not usually visible on planning imaging). Based on the post-mastectomy radiation randomized studies and recent trials, radiation therapy of the internal mammary lymph nodes should be strongly considered when delivering regional nodal irradiation. CT treatment planning should be utilized when treating the internal mammary lymph nodal volume to evaluate dose to normal tissues, especially the heart and lung, and dose constraints respected. Dose is 46–50 Gy in 23–25 fractions to the regional nodal fields. All dose schedules are given 5 days per week.
PRINCIPLES OF RADIATION THERAPY

Optimizing Delivery of Individual Therapy:
It is important to individualize radiation therapy planning and delivery. CT-based treatment planning is encouraged to delineate target volumes and adjacent organs at risk. Greater target dose homogeneity and sparing of normal tissues can be accomplished using compensators such as wedges, forward planning using segments, and intensity-modulated radiation therapy (IMRT). Respiratory control techniques including deep inspiration breath-hold and prone positioning may be used to try to further reduce dose to adjacent normal tissues, in particular heart and lung. Boost treatment in the setting of breast conservation can be delivered using enface electrons, photons, or brachytherapy. Chest wall scar boost when indicated is typically treated with electrons or photons. Verification of daily setup consistency is done with weekly imaging. In certain circumstances, more frequent imaging may be appropriate. Routine use of daily imaging is not recommended.

Radiation Treatment Options

TECHNIQUES:
- Positioning
  - Supine vs Prone
- CT based planning
- 3D conformal vs IMRT
- Respiratory control with deep inspiration breath hold technique
  - “respiratory gating”
Use of Prone Positioning

- Use of prone positioning
  - Use in select patients with early stage disease
  - Breast is target
  - Minimize normal tissue doses and treatment toxicity

Use of “Respiratory Gating”

- Breath hold technique
  - Moderate deep inspiration
  - Extra time, equipment, personnel, increased planning efforts and time for treatment
NCCN Guidelines Updates: Breast Cancer

- Adjuvant radiation options following breast conserving surgery
  - Hypofractionation
  - Accelerated Partial Breast Irradiation (APBI)
  - Omission of RT
Hypofractionation

- **Whole breast radiation: why is hypofractionation now preferred in the guidelines?**
  - Long term results from Ontario and UK trials

  Canadian 42.5 Gy in 16 fractions, no boost
  START B 40 Gy in 15 fractions, ± boost

- At least equivalent or better disease outcomes
- At least equivalent or better cosmesis
- At least equivalent or better side effects

Whelan et al, NEJM 2010
Haviland et al, Lancet Oncol 2013
Hypofractionation

- Who can be treated with hypofractionated whole breast irradiation?
- ASTRO Guidelines 2011 (following Ontario publication but prior to UK)

Table 1. Evidence supports the equivalence of hypofractionated whole breast irradiation with conventionally fractionated whole breast irradiation for patients who satisfy all of these criteria:

1. Patient is 50 years or older at diagnosis.
2. Pathologic stage is T1-2 N0 and patient has been treated with breast-conserving surgery.
3. Patient has not been treated with systemic chemotherapy.
4. Within the breast along the central axis, the minimum dose is no less than 95% and maximum dose is no greater than 107% of the prescription dose. (as calculated with 2-dimensional treatment planning without heterogeneity corrections).

* For patients who do not satisfy all of these criteria, the task force could not reach consensus and therefore chose not to render a recommendation for or against hypofractionated whole breast irradiation in this setting. Please see the text for a thorough discussion of tumor grade. Patients receiving any type of whole breast irradiation should generally be suitable for breast-conserving therapy with regard to standard selection rules (e.g., not pregnant, no evidence of multicentric disease, no prior radiotherapy to the breast, no history of certain collagen-vascular diseases).

- I treat more broadly than this since UK results
- ASTRO to update guidelines in 2017
- Not used routinely for nodal irradiation at this time

Smith et al, IJROBP 2011

Recent Publications: Hypofractionation

Hypofractionation for Early-Stage Breast Cancer
No More Excuses

JAMA Oncol 2015
Accelerated Partial Breast Irradiation (APBI)

- Different methods for delivery
  - IORT
  - Interstitial
  - Intracavitary
  - EBRT

- Different guidelines/consensus statements
  - ASTRO, ASBS, ABS, ESTRO
  - Inclusion/exclusion criteria for NSABP B39/ RTOG 0413

- ASTRO defines suitable, cautionary, unsuitable groups
- NCCN guidelines based on ASTRO suitable group

ASTRO APBI Consensus Statement

***Currently being updated***

New draft was open for public comment through March 2016

Table 2: Patients “suitable” for APBI if all criteria are present

<table>
<thead>
<tr>
<th>Factor</th>
<th>Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient factors</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>≥60 y</td>
</tr>
<tr>
<td>BRCA1/2 mutation</td>
<td>Not present</td>
</tr>
<tr>
<td>Pathologic factors</td>
<td></td>
</tr>
<tr>
<td>Tumor size</td>
<td>≤2 cm²</td>
</tr>
<tr>
<td>T-stage</td>
<td>T1</td>
</tr>
<tr>
<td>Margins</td>
<td>Negative by at least 2 mm</td>
</tr>
<tr>
<td>Grade</td>
<td>Any</td>
</tr>
<tr>
<td>ER status</td>
<td>Positive</td>
</tr>
<tr>
<td>Multicentricity</td>
<td>Uncentric only</td>
</tr>
<tr>
<td>Multifocality</td>
<td>Clinically unifocal with total size ≤2.0 cm²</td>
</tr>
<tr>
<td>Histology</td>
<td>Invasive ductal or other favorable subtypes</td>
</tr>
<tr>
<td>Pure DCIS</td>
<td>Not allowed</td>
</tr>
<tr>
<td>EIC</td>
<td>Not allowed</td>
</tr>
<tr>
<td>Associated LCIS</td>
<td>Allowed</td>
</tr>
<tr>
<td>Nodal factors</td>
<td></td>
</tr>
<tr>
<td>N-stage</td>
<td>pNO (c.T)</td>
</tr>
<tr>
<td>Nodal surgery</td>
<td>SN Br. or ALND</td>
</tr>
<tr>
<td>Treatment factors</td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant therapy</td>
<td>Not allowed</td>
</tr>
</tbody>
</table>

Smith et al, IJROBP 2009
Omission of Radiation

- In selected women with lower risk for recurrence
- No survival detriment
- CALGB 9343
  - 70 or older, small cancers, negative nodes, negative margins, ER/PR positive
  - BCS → Tamoxifen ± RT
  - 10% (no RT) vs 2% (RT) LRR at median 12.6 yrs
- PRIME II, Fyles et al, NSABP B-21

Adjuvant Radiation Options Following BCS: Summary

- Hypofractionated Whole Breast Irradiation
  - PREFERRED

- Accelerated Partial Breast Irradiation (APBI)
  - ASTRO suitable criteria

- Omission of RT
  - YES in select patients
NCCN Guidelines Updates: Breast Cancer

- Post Mastectomy Radiation Therapy (PMRT)
- Regional nodal irradiation (RNI)
  - Either in setting of BCT or PMRT
  - $\geq 4$ LNs +
  - 1-3 LNs +
- Treatment of recurrence

### Historical PMRT Indications

<table>
<thead>
<tr>
<th>Classic Indications</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>- $\geq 4$ positive axillary lymph nodes</td>
<td>- 1-3 positive lymph nodes</td>
</tr>
<tr>
<td>- Positive margins</td>
<td>- pT3N0</td>
</tr>
<tr>
<td>- Tumor &gt; 5 cm</td>
<td>- Close margins</td>
</tr>
<tr>
<td><strong>No radiation</strong></td>
<td>- High risk features</td>
</tr>
<tr>
<td>- Tumor &lt; 5 cm</td>
<td>- Age</td>
</tr>
<tr>
<td>- Negative lymph nodes</td>
<td>- Extracapsular extension</td>
</tr>
<tr>
<td>- No high risk features</td>
<td>- Lymphovascular invasion</td>
</tr>
<tr>
<td></td>
<td>- Certain phenotypes</td>
</tr>
</tbody>
</table>
Adjuvant Radiation Recommendations

• After neoadjuvant systemic therapy?

  • RT recommended as per maximal stage of either clinical staging pre-systemic therapy or pathologic staging
Adjuvant Radiation Recommendations

- Treatment of inoperable or locally advanced breast cancer?
  - Neoadjuvant systemic therapy
  - Either BCT or PMRT with AxLND
  - RT to breast +/- boost or chest wall
  - RNI: SCV, ICV, axillary bed at risk, IMNs
Treatment of Recurrence

• Importance of multi-disciplinary approach for optimal outcomes
• Management of recurrence depends on extent of disease and prior therapies received
  – Prior surgery
  – Prior axillary staging
  – Prior systemic therapy
  – Prior radiation therapy
Locoregional Updates

• Outline
  – General principles of radiation
  – Guidelines updates
  – Regional nodal irradiation (RNI)
    • Which patients need RNI and to what extent?

NCCN Guidelines Updates: Breast Cancer

• Who needs RNI?

• What influence of surgical resection and axillary surgical staging?

• What about in setting of neoadjuvant chemotherapy?

• What extent of RNI?
Which patients need regional nodal irradiation (or not)?

TARGETS:
Whole breast
  • Standard Tangents
  • High Tangents
Chest wall
  ±
Regional nodes
  • SCV
  • ICV
  • Axilla at risk
  • IMNs

Which patients need regional nodal irradiation (or not)?

• In setting of BCT?
  – ACOSOG Z11: cT1-2N0, 1-2 +SLNs, tangents
  – IBCSG 23-01: N1mic
  – MA 20: higher risk patients
  – EORTC 22922: higher risk patients

Giuliano et al, JAMA 2011; Galimberti et al, Lancet Oncol 2013;
Whelan et al, NEJM 2015; Poortmans et al, NEJM 2015;
Which patients need regional nodal irradiation (or not)?

- In post mastectomy setting?
  - B-04, Danish 82b and 82c, British Columbia
  - ECOG and NSABP pooled analyses
  - Patients on more recent trials?
    - Few on IBCSG and some on EORTC
    - SUPREMO
  - EBCTCG: benefit to RT

  Fisher et al, NEJM 2002; Overgaard et al, Radiother Oncol. 2007; Ragaz et al, JNCI 2005;

Which patients need regional nodal irradiation (or not)?

- AxLND vs Axillary RT?
  - AMAROS
  - In setting of neoadjuvant chemo?
  - Currently based on maximal disease stage
  - SENTINA: axillary staging options
  - Current open trials
    - NSABP B51 / RTOG 1304
    - Alliance A011202

  Donker et al, Lancet Oncol 2014
ACOSOG Z11

- RCT of ALND vs observation for women with 1-2 positive SLNs
- 891 pts, cT1-2N0
- ~40% of +SLNs were micromets
- On AxLND, 27.4% of patients had additional +LNs
- Whole breast RT via tangents, no nodal
  - QARC analysis showed variation with 3rd field, high tangents use
- Median 6.3 yrs, no difference and low rates of LR / LRR (<5%), less lymphedema with SLN alone

Giuliano et al, JAMA 2011
Jagsi et al, JCO 2014
EBCTCG Meta-Analysis 2014

- “Effects of RT after Mastectomy and Axillary Surgery on 10 yr Recurrence and 20 yr Breast Cancer Mortality”
- 8,135 women, 22 randomized trials, 1964-1986
- In women with 1-3 N+ and ≥4 N+ (not N0)
  - RT reduced LRR, OR, and breast cancer mortality
- Are the risks for recurrence the same now?
- Does this mean everyone should be treated?
Recent Publications: Regional Nodal Irradiation

**Regional Nodal Irradiation in Early-Stage Breast Cancer**


**Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer**

Regional Nodal Irradiation

• MA.20:
  – 1832 pN+ (85% N1) or high risk N- pts (10%)
  – BCS and ALND, adjuvant systemic tx
  – WBI ± RNI
    • RNI = IMNs, SCV, ICV, ± Ax

• EORTC 22922:
  – 4000 pN+ (44% N1) or high risk N- pts (43%)
  – BCS (76%) or M and ALND, adjuvant systemic tx
  – WBI or CW ± RNI
    • RNI = IMNs, SCV, ICV, ± Ax

* definitions of high risk N- differed as types did use of chemotherapy/endocrine therapy

Whelan et al, NEJM 2015
Poortmans et al, NEJM 2015

MA.20 Radiation

• WBI
  • 50/25 +/- 10 Gy boost

• WBI + RNI (45/25)
  • IMNs
  • SCV/Level III

Whelan et al, NEJM 2015
Regional Nodal Irradiation

- Results from MA 20 and EORTC 22922:
  - 10 yr median follow up
  - Primary endpoint was OS
  - RNI improved locoregional DFS, distant DFS, and death from breast cancer, but did not improve OS

Whelan et al, NEJM 2015
Poortmans et al, NEJM 2015

MA.20 Results

- OS
  82.8% vs 81.8%
  p=0.38
  ER-
  81.3% vs 73.9%
  p=0.05

- DFS
  5% at 10 yrs
  82% vs 77%
  p=0.01

- Isolated LR DFS
  95.2% vs 92.2%
  p=0.009

- Distant DFS
  86.3% vs 82.1%
  p=0.03

Figure 1: (a) Ten Kaplan-Meier Estimates of Survival. (b) Five-year disease-free survival estimates: (Panel A) overall survival, (Panel B) local-regional disease-free survival, (Panel C) isolated locoregional disease-free survival, and (Panel D) distant disease-free survival: Among patients who underwent whole-breast irradiation plus regional nodal irradiation (RNI) and those who underwent whole breast irradiation alone (WBI), local-regional group.

Whelan et al, NEJM 2015
How do we interpret and reconcile the differences between these studies in determining the role for regional nodal irradiation?

Which patients need regional nodal irradiation?

• Consider whether a given study is applicable and whether an individual patient met the study eligibility.

• Assess individual risk for recurrence.

• Nomograms may be helpful.
Which patients need regional nodal irradiation?

• Questions and answers regarding the extent of lymph node surgery (SLN Bx vs Ax LND) are not the same as question and answers regarding the need for, type of, and extent of regional nodal radiation.

Clinical Case

48 year old premenopausal female with a cT2N1M0 (bx proven N+) left breast invasive carcinoma NST, grade 3, ER/PR negative, Her2 positive receives neoadjuvant chemotherapy with significant clinical response.

She is desirous of BCT and proceeds with WLE and SLN biopsy.
Clinical Case

Pathology returns ypT1aN1a(sn) with 4 mm residual disease, associated DCIS, negative margins, and 1/2 lymph nodes positive with 3 mm involvement and no ECE.

What are your recommendations for next therapies?

Audience Response Question

1. Axillary LND before any RT recommendation
2. Whole breast RT using high tangents with boost
3. Whole breast RT with boost + RNI to SCV, ICV and axilla, no IMNs
4. Whole breast RT with boost + RNI to SCV, ICV, axilla, and IMNs
5. Clinical trial
Regional Nodal Irradiation Recommendations: Summary

• ≥4 LNs +
  Following either BCT or PMRT

  *RT to breast +/- boost or chest wall +RNI*

  (category 1)

Regional Nodal Irradiation Recommendations: Summary

• 1-3 LNs +
  BCT
  – RT to breast +/- boost (category 1)
  – *Strongly consider RNI*

  PMRT
  – *Strongly consider RT to chest wall +/- boost and RNI*
Regional Nodal Irradiation Recommendations: Summary

- Which nodal volumes treated?
  - SCV
  - ICV
  - Axillary bed at risk
  - IMNs

- Attention to normal tissue dose constraints
  - In particular heart and lung

Areas of Ongoing Study

- Concomitant boost with hypofractionation
  - RTOG 1005
- cN+ disease receiving neoadjuvant chemotherapy
  - Extent of axillary surgery and/or radiation
  - SLN bx negative → NSABP B51 / RTOG 1304
  - SLN bx positive → Alliance A011202
- Hypofractionation for nodal RT / PMRT?
- Use of biologic parameters to guide local therapy options
cN1 $\rightarrow$ ypN0(sn) Extent of RNI: NSABP B51 / RTOG 1304

A Randomized Phase III Clinical Trial Evaluating Post-Mastectomy Chest Wall 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

NSABP B-51/RTOG 1304 Trial Phase III
- Clinical T1-3N1M0 breast cancer
- Pathology positive axillary node (FNA/Core)
- Neoadjuvant CT + anti HER2
  
  ypN0 at definitive Breast Surgery + AND or SNB

Randomization

Arm 1
No Regional Nodal XRT
A. Lumpectomy: Breast XRT.
B. Mastectomy: Observation

Arm 2
Regional Nodal XRT
A. Lump.: Breast/Nodal XRT
B. Mast: Chestwall/ Nodal XRT

Targeted accrual = 1636

Stratification: Type of Surgery (Mast v. Lump) , ER-Status (+ v. -), HER2 Status (+ v. -), pCR in Breast (yes v. no)

Courtesy of Dr. Julia White
cN1 $\rightarrow$ ypN+(sn) Extent of Axillary Sx: Alliance A011202

A Randomized Phase III Trial Comparing Axillary Lymph Node Dissection to Axillary Radiation in Breast Cancer Patients (cT1-3 N1) who have Positive Sentinel Lymph Node Disease After Neoadjuvant Chemotherapy
Questions?

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