Breast Cancer Case-based Learning Session

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Panelists:
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Learning Objectives

1. Understand the role of pathologic and molecular predictors of in-breast tumor recurrence for the treatment of DCIS.
2. Define the current role and risks of partial breast irradiation in primary and recurrent early stage breast cancer.
3. Specify basic constraints and associated toxicities for IMRT/VMAT for breast/chest wall radiotherapy.
4. Understand the potential efficacy of hypofractionated post-mastectomy radiotherapy.
5. Discuss the role of radiotherapy after complete response to neoadjuvant chemotherapy and review enrollment criteria for ongoing trials.

Case 1 – DCIS

- 60 yo woman, otherwise healthy
- Gyn Hx
  - Age at menarche: 13
  - Age at menopause: 50
  - Gravida/Para: G3P2
  - Age at first delivery: 27
- Family Hx:
  - Mother with breast CA and recurrence after Tamoxifen x5 years (died of other causes)

Work-up

- Bilateral screening mammogram followed by left diagnostic mammogram; No palpable finding.
- Fine pleomorphic calcifications in the upper outer left breast, spanning 3 cm (BI-RADS 4)
- Stereotactic core biopsy
  - Intermediate-high grade DCIS
  - Post-biopsy mammogram showed clip displaced by 0.7 cm
Artificial Intelligence/Machine Learning in Breast Cancer Screening

**Discussion**

- What is the current role of AI/ML in breast cancer screening?
- How can AI best be incorporated into the Diagnostic Radiology workflow?

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**AI System for Breast Cancer Screening**


- USA: False positive reduction 5.7%, False negative reduction 2.7%
- UK: AI reduced workload of second reader by 88%

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**Breast MRI for DCIS - example**

**Discussion**

- How do you approach the interpretation of breast MRI for DCIS?
Surgery

- Left lumpectomy #1, wire-localized:
  - 4.5 x 2.0 x 6.5 cm specimen.
  - Intraop specimen imaging showed the wire, but no biopsy clip.
  - Pathology negative. Biopsy site change was not identified.

- Left lumpectomy #2, Magseed-guided:
  - High grade DCIS, measuring 0.6 cm.
  - Comedonecrosis present.
  - Margin within 0.1 cm medially.
  - ER+ (strong >90%), PR+ (weak to strong, 80%)
  - Her2 negative by FISH (1.2 Avg ratio Her2:Cent17)

Post-op complications

- Post-operative course was complicated by recurrent hematoma requiring drainage, packing, and ultimately wound-vac.

- She re-presented for radiotherapy 2 months post-operatively.

SACME1: For completely resected (margins >2 mm) high grade DCIS, <1 cm in size, what would you cite as the 12-year risk of any in-breast tumor recurrence without adjuvant therapy?

A. <5%
B. 10-15%
C. 20-30%
D. 50%
E. 75%
Predictors of invasive recurrence after DCIS
- Race (African American)
- Premenopausal
- Palpable
- High grade
- Necrosis
- p16 high
- Her2+


Prognostic nomograms/calculators
- Van Nuys Prognostic Index
- MSKCC Nomogram
  - Age, Family Hx, palpability, grade, necrosis, margins, re-excision, era of surgery.

Omission of Radiotherapy for DCIS
  - Single arm trial (lumpectomy w/o RT)
  - 2 cohorts (tamoxifen used by ~30%)
  - DCIS G1-2, size <= 2.5cm, margins >=3mm (12 year IBTR 14%)
  - DCIS G3, size <= 3cm, margin >=3mm (12 year IBTR 23%)

- RTOG 9804 (2015)
  - RCT lumpectomy +/- RT (tamoxifen in ~60%)
  - DCIS G1-2, size <=2.5cm, margins >=3mm
  - Closed due to poor accrual (n=836 of 1790 planned)
  - 12-year IBTR (11% vs 3%)

DCIS - EBCTCG
Oncotype DCIS

- 12 gene assay
- Developed from DCIS cases from NSABP B14, NSABP B20, Kaiser, Genomic Health, Marin General
- Applied to ECOG E5194 patients, validated on Ontario DCIS cohort
- 10-year risk of ipsilateral breast event
  - Low grade – 19.6%
  - Intermediate grade – 29.7%
  - High grade – 28.3%


Gene expression assays in DCIS

Discussion

- How do you currently incorporate gene expression assays (e.g., OncotypeDCIS) into treatment decisions for DCIS?
- Does the use of gene expression assays and recurrence risk scores have a role in risk-adapted imaging surveillance of DCIS?
- Do gene expression assays add value to a Medomics profile, beyond clinicopathologic information, to help predict outcomes and adapt management?

Combining Oncotype DCIS and Clinicopathologic Features

- Combined analysis of ECOG E5194 and Ontario DCIS cohort (N=773)
- Excluded positive margins and multifocality

60 yo with left upper outer high grade DCIS (0.6 cm) with close margin and post-op wound complications

**Discussion**
- What are her best treatment options?
  - Observation
  - Endocrine therapy alone
  - Traditionally fractionated whole breast RT (50 Gy in 25 fx) +/- endocrine therapy
  - Hypofractionated whole breast RT (40.05 Gy in 15 fx) +/- endocrine therapy
  - Hypofractionated partial breast RT (40.05 Gy in 15 fx) +/- endocrine therapy
  - Accelerated partial breast radiotherapy (38.5 Gy in 10 fx BID) +/- endocrine therapy

SACME2: When comparing accelerated external beam partial breast irradiation (38.5 Gy in 10 fractions BID) and hypofractionated whole breast irradiation (42.5 Gy in 16 fractions), APBI has ______ acute grade 2+ toxicity and ______ late grade 2+ toxicity.

A. similar, similar
B. lower, lower
C. higher, higher
D. lower, higher
E. higher, lower

DCIS - EBCTCG

**IMPORT LOW** (Lancet 2017)

- Multicenter, phase 3 RCT, non-inferiority design
- >50 yo, IDC <3 cm, 0-3 nodes (97% pN0) [N=674]
- Arms (all in 15 fx)
  - 40 Gy whole-breast
  - 36 Gy whole breast and 40 Gy partial breast
  - 40 Gy partial breast
- Partial breast: Tumor bed + 1.5 cm (CTV + 1.0 cm PTV)
- 5-year outcomes
  - Cumulative incidence of IBTR (1.1%, 0.2%, 0.5%)
- 5-year toxicity (patient reported) favors PBI
  - Appearance changes (47.7%, 36.7%, 35.1%)
  - Firmness (35.3%, 21.0%, 15.3%)

Non-inferiority confirmed.

**Accelerated Partial Breast Irradiation – RAPID Trial**

- Multicenter, randomized, non-inferiority trial
- <3.0 cm, node negative (micromets allowed) [N=2135]
- Arms
  - Traditionally fractionated whole breast (50 Gy/25 fx OR 42.5 Gy/16 fx) +/- boost
  - APBI (38.5 Gy/10 fx bid, brachy or EBRT)
- 82% invasive, 70% <1.5 cm, 99% pN0, 90% ER+
- 8 year outcomes
  - Cumulative incidence of IBTR (3.0% APBI vs 2.8% WBI)
  - No difference in DFS or OS
- Toxicity
  - Acute grade 2+ (28% APBI vs 45% WBI)
  - Late grade 2+ (32% APBI vs 13% WBI)
  - 7-year, nurse-reported fair-poor cosmesis more common with APBI (36% vs 19%)

Non-inferiority confirmed.

**Accelerated Partial Breast Irradiation – NSABP B-39**

- Phase III RCT, equivalence trial
- <3.0 cm, 0-3 nodes (DCIS allowed) [N=4216]
- Arms
  - Traditionally fractionated whole breast (30-35 Gy/15-20 fx)
    - APBI (34-38.5 Gy/10-12 fx bid, brachy or EBRT)
- 24% DCIS, 65% pN0, 10% pN1
- 10 year outcomes favor WBI
  - Cumulative incidence of IBTR (4.6% vs 3.9%)
  - Recurrence-free interval (93.4% vs 91.9%, p=0.02)
  - No difference in DDFS or OS
- Toxicity
  - Any grade 3 toxicity (10% APBI vs 7% WBI)

Equivalence CANNOT be concluded.

**ASTRO APBI Consensus Guidelines**


Equivalence CANNOT be concluded.
60 yo with left upper outer high grade DCIS (0.6 cm) with close margin and post-op wound complications

**Discussion**
- When delivering partial breast irradiation what techniques can help with target delineation?
- How do you account for tissue rearrangement after reconstruction?

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**Ongoing DCIS Trials**

- **LORIS DCIS trial (UK)**
  - Randomized non-inferiority trial
  - Women age 44 or greater
  - Histopathological low-intermediate grade DCIS or resected
  - Arms: Active surveillance (every 12 mo) vs RT, HT, or both

- **LORD (Low-Risk DCIS) trial (EORTC)**
  - Randomized non-inferiority trial
  - Women age 45 or greater
  - Pure low grade DCIS
  - Arms: Active surveillance vs conventional treatment (WLE, WLE+RT, mastectomy, endocrine therapy)

- **COMET trial (US)**
  - Women age 45 or older
  - Low-intermediate grade DCIS
  - Arms: Active surveillance + HT vs Local therapy (surgery + radiation) + HT

- **Observational studies incorporating Oncotype DCIS**

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**Case 2 – Recurrence**

- Our patient undergoes adjuvant left whole breast radiotherapy (50 Gy in 25 fractions) with tangent fields
- She returns 4 years later with screen-detected in-breast tumor recurrence
- Diagnostic mammogram and ultrasound
  - 1.1 cm spiculated mass
  - Axilla negative
- Ultrasound-guided core biopsy
  - Invasive ductal carcinoma, 1.1 cm, grade 2, ER+PR+Her2-, Ki67 5%

**Discussion**
- What are her best treatment options?
  - Lumpectomy and observation
  - Mastectomy
  - Lumpectomy and whole breast re-irradiation
  - Lumpectomy and partial breast re-irradiation

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64 yo with prior left whole breast RT for high grade DCIS, now with in-breast invasive recurrence, cT1cN0, ER+PR+Her2-, Ki67 5%

**Discussion**
- What are her best treatment options?
  - Lumpectomy and observation
  - Mastectomy
  - Lumpectomy and whole breast re-irradiation
  - Lumpectomy and partial breast re-irradiation
RTOG 1014 – PBI for reirradiation

- Phase 2, single arm, prospective trial
- Recurrence >1 year after RT, <3 cm in size, 0-3 nodes, margin negative resection [N=58]
- Prior RT: 50 Gy/25 fx
- Reirradiation
  - Dose: 45 Gy in 30 fx (1.5 Gy BID)
  - Target: Cavity + 1.5 cm CTV + 1.0 cm PTV (avoid 5 mm from skin)
- 5-year cum incidence of recurrence: 5.2%
- Toxicity: 26.3% Grade 2, 7% Grade 3


Case 3 - Locally advanced

- 60 yo woman with palpable mass in left axilla
- Ultrasound left axilla: 3.1 x 2.2 x 1.8 cm lymph node.
- US-guided core biopsy of the left axillary node:
  - Mammary carcinoma with mucinous and neuroendocrine differentiation, ER+(>95%), PR+(75%), Her2-, Ki67 30%.
- Diagnostic left mammogram
  - Heterogeneously dense breast tissue.
  - Pleomorphic calcifications in a linear segmental distribution in the upper central left breast spanning 6 cm, extending to the sub-nipple area.
- MR breast
  - 7.5 cm broad swath of non-mass enhancement throughout the inferolateral quadrant of the left breast.
- MRI-guided vacuum-assisted core biopsy
  - IDC, grade 2, ER+PR+, Her2-, Ki67 5%.
- PET/CT
  - Multiple foci in the left breast (SUV 3.67).
  - Axillary lymph nodes in axilla (SUV 12.09)
  - Internal mammary node (SUV 7.17).
- No distant metastases.
- Stage: cT3N3bM0, grade 2, ER+/PR-/Her2-, Stage IIIB
- Received neoadjuvant AC-T

Discussion

- How do you recommend monitoring response during neoadjuvant treatment?
  - Modality?
  - Frequency of imaging?
  - Quantification?
If radiographic CR, can biopsy identify those with pCR to avoid surgery?

- **MICRA TRIAL**
  - Multi-center observational prospective cohort study [n=167]
  - After neoadjuvant systemic therapy with radiographic CR or PR (≥30% size reduction) on MRI [79% rCR, 21% rPR]
  - US-guided core biopsies near prior clip: 4 central (<0.5 cm) and 4 peripheral biopsies (0.5-1.5 cm).
  - False negative rate of biopsy: 45% in rCR, 13% in rPR
  - Radiographic CR plus biopsy does not accurately assess for pCR.

Mastectomy

- Left breast mastectomy and axillary lymph node dissection
  - 6.6 cm residual invasive carcinoma with neuroendocrine differentiation
  - Extensive lymphovascular invasion
  - Residual intermediate grade DCIS
  - All margins were negative
  - 4/17 nodes involved (3 macromets, 1 micromet, 1 ITC), up to 1.6 cm
  - ypT3N2a
  - IHC: ER+ (>98%), PR+ (10%), Her2-, Ki67 5%.

60 yo woman with IDC of the left breast, cT3N3M0, grade 2, ER+ PR+ Her2-, s/p neoadjuvant AC-T, mastectomy and ALND, ypT3N2M0.

**Discussion**

- How would you deliver PMRT?
  - 3-field or IMRT/VMAT?
  - Which nodal regions would you cover?
  - Boost to involved undissected nodes?
  - Traditionally fractionated or hypofractionated?

SACME3: When delivering intensity modulated post-mastectomy radiotherapy with regional nodal irradiation (axillary, supraclavicular, and internal mammary), what do you cite as the risk of grade 3 radiation pneumonitis?

- **A.** 1%
- **B.** 5%
- **C.** 10%
- **D.** 20%
- **E.** 33%
SACME3: When delivering intensity modulated post-mastectomy radiotherapy with regional nodal irradiation (axillary, supraclavicular, and internal mammary), what do you cite as the risk of grade 3 radiation pneumonitis?

A. 1%
B. 5%
C. 10%
D. 20%
E. 33%

VMAT PMRT Simulation
- Supine, arms above head, head turned right
- Breast board at 5 degree incline
- 3-5 mm custom wax bolus
- Wire breast borders and scars

Breast IMRT/VMAT OAR Constraints

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SACME4: As compared to conventional post-mastectomy radiotherapy (50 Gy in 25 fractions), hypofractionated PMRT (43.5 Gy in 15 fractions) to the chest wall and supraclavicular region results in:

A. Inferior locoregional control and similar acute skin toxicity
B. Inferior locoregional control and less acute skin toxicity
C. Non-inferior locoregional control and similar acute skin toxicity
D. Non-inferior locoregional control and more acute skin toxicity
E. Non-inferior locoregional control and less acute skin toxicity

MSKCC Prospective Breast IMRT Experience

- N=113
- Median follow-up 53.4 months
- Technique
  - 50 Gy in 25 fractions
  - 8-12 coplanar beams, 6 MV
  - 3-5 mm bolus
- Dosimetry
  - Median lung V20Gy=29%
  - Median lung V5Gy=100%
- Respiratory Toxicity
  - Grade 1: 6.7%
  - Grade 2: 2.9%
  - Grade 3: 1%
  - Grade 4/5: 0%
- 5-year Clinical Outcomes
  - LRRF: 93.2%
  - DFS: 63.6%
  - OS: 80.3%
Hypofractionated PMRT – Chinese trial

- Randomized, non-inferiority trial
- Post-mastectomy, T3-4N2-3 (N=820)
- 6-9 MeV, 5 mm bolus
- Arms
  - Conventional (50 Gy / 25 fx)
  - Hypofx (43.5 Gy / 15 fx)
- Median follow-up 58.5 months
- 5-year local recurrence (8.3 vs 8.1%)
- No difference in overall toxicity
  - Except less acute grade 3 skin toxicity (8 vs 3%)

FABREC trial – hypofractionated PMRT after reconstruction

- T1-3N+ s/p mastectomy with immediate expander/implant reconstruction
- Arms; Post-mastectomy RT +/- IMNs
  - Conventional: 50 Gy / 25 fx
  - Hypofx: 42.56 Gy / 16 fx (39.9 Gy / 15 fx to SCV)
- Outcome measures
  - Primary: patient reported, 6 month physical well being
  - Secondary: Oncologic, clinical, and cosmetic

60 yo woman with IDC of the left breast, cT3N3M0, grade 2, ER+ PR+ Her2-, s/p neoadjuvant AC-T, mastectomy and ALND, ypT0N0M0.

Discussion

- How can radiographic and Medomics be used to predict who will have a pCR?
- What adjuvant treatment do you recommend if our patient achieved a complete pathologic response with neoadjuvant systemic therapy?

SACME: NSABP B-51 includes all of the following EXCEPT:

A. T1-3
B. N1
C. Adjuvant chemotherapy
D. Post-mastectomy RT to the chest wall only (without regional nodal irradiation)
E. Sentinel node biopsy or axillary dissection
SACME: NSABP B-51 includes all of the following EXCEPT:

A. T1-3
B. N1
C. Adjuvant chemotherapy
D. Post-mastectomy RT to the chest wall only (without regional nodal irradiation)
E. Sentinel node biopsy or axillary dissection


ASTRO Consensus guidelines

- ypN+ → PMRT
- ypNO → pre-chemo decision making

NSABP B-51
Questions?