2023 Free, Live Streamed Webinar
Highlights of the 2023 International Invasive Lobular Carcinoma (ILC) Symposium

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Lobular Breast Cancer Alliance (LBCA)

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UPMC Hillman Cancer Center
University of Pittsburgh School of Medicine

Matt Covington
University of Utah and Huntsman Cancer Institute
Today’s Agenda

Welcome and Agenda Review – Laurie and Claire
Basic Science - Patrick Derksen, PhD and Peter Simpson, PhD
Translational Science - Bhuvaneswari Ramaswamy, MD
Imaging Science - Matthew Covington, MD
Clinical Science - Priscilla McAuliffe, MD, PhD
Moderated Q&A – All panelists
Our Panelists

Patrick Derksen, PhD
Peter Simpson, PhD
Bhuvaneswari Ramaswamy, MD
Matt Covington, MD
Priscilla McAuliffe, MD, PhD
Jason Mouabbi, MD
Session 1: Pathology, Diagnosis, ILC Variants and Lobular Neoplasia

Session 2: E-cadherin and the ILC Tumor Microenvironment

Session 3: Modelling ILC
Stuart Schnitt, MD (Dana-Farber Cancer Institute, Boston, MA)  
– The Leigh Pate Memorial Lectureship on Lobular Breast Cancer  
Invasive Lobular Carcinoma: Where Have We Been and Where Are We Going?

Tari King, MD (Dana-Farber Cancer Institute, Boston, MA)  
Lobular Carcinoma In Situ – Current Concepts and Challenges

Maxim De Schepper, MD, PhD (KU Leuven, Belgium)  
Homogenization of Pathological Diagnosis of ILC

Lounes Djerroudi, MD (Institut Curie, Paris)  
E-cadherin inactivation shapes tumor microenvironment specificities in ILC

Osama Shah, PhD (UPMC Hillman Cancer Center)  
Spatial profiling of mixed invasive ductal-lobular carcinoma reveals intrinsic molecular subtype and oncogenic signaling heterogeneity
Normal → Atypical Lobular Hyperplasia (ALH) → Lobular carcinoma in situ (LCIS) → Classic ILC

- E-Cadherin
- PIK3CA/AKT1/PTEN
- -16q +1q

Stuart Schnitt
- history of ILC
- ‘Rogue’ variants

Tari King
- LCIS

Maxim De Schepper
- classification/diagnosis

Lounes Djerroudi
- biology of ‘stroma’

Osama Shah
- biology of mixed ductal-lobular carcinomas

Classic ILC
- Grade 2
- ER+
- HER2-
- Low Ki67

Mixed
More complex than this:

- Not all LCIS progress to ILC – how to predict? How to manage?
- Some LCIS have variable morphological features – how to manage them?

- ILC can be difficult to classify at diagnosis – what tools can help?
- Not all ILC are ‘classic’ type – what are ‘Rogue’ variants, how do we define/identify them?
- Risk of upgrade / progression to inv ca ~2%/yr
- Risk is for lobular and ductal types (ILC and DCIS/IDC)
- Risk for ipsilateral but also contralateral breast
  -> LCIS is a risk lesion for both breasts

- LCIS and ILC are genetically very similar
  -> LCIS is a non-obligate precursor to cancer

- Challenge - what to do if LCIS identified in a biopsy
  - bilateral mastectomy, mastectomy, wide local excision or observe??!!

- cLCIS
  - selective excision only
  - observation with imaging
  - chemoprevention possible

- PLCIS
  - natural history less clear, but upgrade rate higher
  - excision and clear margins
  - ie treat like DCIS

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**Surgical Management of LCIS**

SEER 18, LCIS 1983-2013, n=19,462

- Decline in mastectomy: 58.8% to 10.3% (p<0.001)
- Increase in surgical excision: 41.2% to 85.8% (p<0.001)

**Classic LCIS and ALH Managed without routine surgical excision**

127 pts with lobular neoplasia followed in our high-risk clinic
median follow-up 36 mo
3yr actuarial rate of cancer development: 3.9%

n=2 ipsilateral breast
different quadrant
n=3 contralateral

Observation N=102
Excision N=25
ILC is a pathological diagnosis, made based on the morphological appearance under the microscope.
Correct classification is critical – for clinical management, epidemiological and biology studies.
Diagnosis is challenging, despite guidelines from the WHO.
There is a large variability in practice between pathologists worldwide for the diagnosis of ILC.
Helpful tools – recognizing morphological variants, and using Immunohistochemistry & Artificial Intelligence.

Collectively the morphological variants have worse prognosis to classic ILC.
But not enough data to treat differently.

Other ‘rogue’ variants:
- grade 3
- ER and/or PR -ve
- TN 2-9%
- HER2+ve <5%
- HER2-low 40-65%
[HER2 mutations]
• Helpful tools – recognizing **morphological variants**, and using **Immunohistochemistry & Artificial Intelligence**
• Helpful tools – recognizing **morphological variants**, and using **Immunohistochemistry & Artificial Intelligence**
Spatial profiling of mixed invasive ductal-lobular carcinoma reveals intrinsic molecular subtype and oncogenic signaling heterogeneity.

E-cadherin inactivation shapes tumor microenvironment specificities in ILC.

Mixed Tumors

Genomic Profiling

Spatial Transcriptomics

Single Cell Profiling

Clinical Significance

Distinct Histology ↔ Distinct Biology ↔ Distinct Prognosis (Important to Profile Individual Regions)

Intrinsic Subtype Heterogeneity ↔ Therapy Dilemma (Chemotherapy for Basal & Endocrine therapy for Luminal Regions)

RECAP OF SESSION 2:
E-CADHERIN, GROWTH FACTORS, AND THE ILC TUMOR MICROENVIRONMENT

Patrick WB Derksen, PhD
Professor of Experimental & Preclinical Oncology
Two neighbouring cells adapted from: Faezi et al. Dev Cell (2002)
histological ILC (154 samples) 

Michaut M., Bernards R Cell Rep (2016)

exon capture (~100 genes) 
passing grade seqs. (146 samples)

62 CDH1\textsuperscript{WT} (43%) 
84 CDH1\textsuperscript{MUT} (57%)

308 candidates

no CDH1/AFDN mutations

AFDN loss of function

ILC R-L1047-D 
(\textit{CDH1}\textsuperscript{WT}; AFDN p.Phe629fs)
CLINICAL RAMIFICATIONS:
Define biomarkers for:
- Breast cancer diagnosis
- Inclusion and treatment

Classical ILC
TYPE
- E-cadherin mutation
  CDH1 (nonsense, fs, epigenetic?)

BIOLOGY
- F-actin disruption
- GFR activation
- Cell cycle repression

Non-classical ILC
TYPE
- Adhesome mutation
  CNTTA1, AFDN, CDH1<sup>S180Y</sup>

BIOLOGY
- F-actin disruption / aberrant function
- GFR activation (?)
- Cell cycle repression
Cancer associated fibroblasts (CAFs) are ‘healthy’ cells that can support breast cancer progression but until recently haven’t been investigated in Invasive Lobular Cancer.

We have identified two ILC CAF secreted proteins — PAPP-A and IL-6 — that are more highly expressed in Invasive Lobular (ILC) than Invasive Ductal (IDC) Cancer.

PAPP-A cuts IGF-1 binding proteins so more IGF-1 is available and can activate the tumour promoting IGF-1/PI3K pathway.

IL-6 switches on genes in Lobular Breast Cancer cells that can promote increased migration and metastasis.
High levels of PAPP-A are associated with poorer survival for ER+ Breast Cancer patients.

IL-6 treated Lobular breast cancer cells more readily migrate away from the injection site in this Zebrafish model of metastasis.

- Untreated Lobular Breast Cancer Cells
- IL-6 Treated Lobular Breast Cancer Cells
- Human Lobular Breast Cancer Cells
- Zebrafish blood vessels
- Human and fish nuclei
- Breast cancer cells that have migrated away from the injection site
E-cadherin loss

activation of KART

GFR/AKT Activation

slow growth

survival

Rätze & Koorman et al. Oncogene (2022)
Sijnesael et al. J Pathol (2023)

**Invasive Ductal BC cells**

**AKT** (ipatasertib)

**Invasive lobular BC cells**

**AKT** (ipatasertib)

**CDK4/6** (palbociclib)

**CDK4/6** (palbociclib)

**Trp53Δ**

**mILC**

**mILC**

**Tumor Volume (mm³)**

**Tumor Volume (mm³)**

**Tumor Volume (mm³)**

**Tumor Volume (mm³)**

**Weeks**

**Weeks**

**Weeks**

**Weeks**
THIJS KOORMAN. TARGETING SURVIVAL CUES IN ILC

precursor lesion  primary tumour / metastatic site  disseminating cells

E-cadherin loss
GFR/PI3K/Akt activation

Id2↑
dormancy

CELL CYCLE RE-ENTRY
PALBOCICLIB

SURVIVAL / VIABILITY
AKT inhibition
HER2 amplification

“HER2+” only

HER2 mutations

All clinical subtypes

Endocrine resistance

~5% HER2+/ER+ MBC
~10% lobular ER+ MBC

Croessmann et al., Clin Cancer Res. 2019
Razavi et al., Cancer Cell 2018
Nayyar et al., Nat Genet. 2019
Kalra et al., Cancer Res. 2022

Resistance to anti-HER2 therapies

Hanker et al., Cancer Cell 2021
Cocco et al., Sci Signal. 2018
Smith et al., Nature Commun. 2021
- Patients previously treated with CDK4/6i + endocrine therapy
- ILC ORR: 41%
- CBR: 52%
- Median PFS: 8.3 months
- Median DOR: 14.4 months
- Acquired HER2 mutations (including gatekeeper mutation) identified at progression, suggesting that resistant tumors remain dependent on mutant HER2

Jhaveri et al., *Ann Oncol*. 2023
SUMMIT trial: ER+ breast cancer expansion cohort
NCT05919108: Neoadjuvant Neratinib in Stage I-III HER2-Mutated Lobular Breast Cancers

NCI R01 CA273246
RINATH JESELSOHN.  
EPIGENETIC REGULATION OF ILC THERAPY RESISTANCE

Dana-Farber Cancer Institute

MCF7 T47D SUM44 MDA134

Ductal Lobular

Gain ILC sites (11,777 peaks)

Gain IDC sites (5,444 peaks)

Motifs enriched in ILC gained sites

Motifs enriched in IDC gained sites

Nardone A, Can Res 2022
RINATH JESELSON.

EPIGENETIC REGULATION OF ILC THERAPY RESISTANCE

FOXA1 peak knockout

2ΔΔCT Day 9

FOXA1 ESR1 PgR CCND1 MYC Actin

gCTR gP1 FOXA1

SUM44

normalized cell count

CTR gP1

Days

****
Epigenomic analysis of Invasive lobular breast cancer reveals an altered chromatin state and a FOXA1-ER axis, which drives therapy resistance and tumor progression.
Lobular Carcinoma In Situ

ECM remodelling

Invasive Lobular Carcinoma

Pagetoid spread

single cell files

Metastatic Disease

MM134

SUM44

MDA-MB-134IV
(ILC cell line)

mammary intraductal (MIND) injections

The LOX inhibitor PXS-5505 inhibits tumor progression in preclinical xenograft models.

**CATHRIN BRISKEN. KEYNOTE LECTURE**

**MIND MODELS OF ILC**

**The LOX inhibitor PXS-5505 inhibits tumor progression in preclinical xenograft models**

- **LOXL1**
- **Collagens**
- **Elastin**
- **ADAMTSs**

**ER signaling**
- **Autocrine IGF**
- **FGF**

**LOXL1 Inhibition**
- Disruption of fibrillar collagen
- ER signaling
- MYC targets

**Cell proliferation**
- Invasion
- Metastasis

**Tumour cell growth and invasion**
- Tumour matrix organisation

**?Matrix stiffness**
- ?ER signalling
Understand ILC Models

### Table: ILC Driver Altersations and Other Altered Genes

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Molecular Subtype</th>
<th>CDH1 Alteration</th>
<th>CTNNA1</th>
<th>TP53 Alteration</th>
<th>PIK3CA</th>
<th>ERBB2</th>
<th>PTEN</th>
<th>FOXA1</th>
<th>Molecular Similarity to ILC Patient Tumors</th>
<th>Suitable Model for ER+/Luminal ILC Disease</th>
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<tr>
<td>BCK4</td>
<td>Lum</td>
<td>MUT;LOH</td>
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<td>NS</td>
<td>-0.4</td>
<td>No, basal subtype</td>
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</tbody>
</table>


Also see: Hollestelle *et al.* (2010) Breast Cancer Res Treat
Our Panelists

Patrick Derksen, PhD
Peter Simpson, PhD
Bhuvaneswari Ramaswamy, MD
Matt Covington, MD
Priscilla McAuliffe, MD, PhD
Jason Mouabbi, MD
Bench-Bedside - Can we translate our discoveries to improve lives of patients with invasive lobular cancers?

Bhuvaneswari Ramaswamy MD
Professor
DISCLOSURES

• Seagen- Honoraria- 2022
Distinct Molecular Feature: Loss of E-Cadherin

Normal cell

Low density

E-cadherin

proliferation

Integrin

Contact inhibition - monolayer of normal cells

High density

Cell-cell adhesion

ECM

Loss of E-cadherin / mutation in E-cadherin

Disrupted cell-cell adhesion

Mutation / loss of E-cadherin

Integrin

Loss of contact inhibition - cells grow on top of each other

Clinical Challenges Oncologist Face in Managing ILC.

- Delayed/late diagnosis
- Local Therapy - Distinct molecular features
- Choice of Adjuvant Therapy - Role of Oncotype
- Late recurrence - Role of Disseminated tumor cells/dormancy
- Unusual metastatic sites. Why??

The James
Few clinical studies for patients with ILC alone. **Use of retrospective data and tissue.**

**Common Theme for the Challenges**

**Giovanni Corso, MD, PhD**  
Hereditary lobular breast cancer syndrome associated with germline CDH1 variants

**Ethan Sokol, PhD**  
Identification of Targetable Vulnerabilities in ILC Using Comprehensive Genomics Profiling

**Massimo Cristofanilli, MD**  
Liquid biopsy in ILC: What can we learn about clinical and molecular evolution?

**Peter Simpson, PhD**  
ILC-focused biomarkers of progression and prognosis

**Karen Van Baelen, MD**  
Metastatic Spread in Patients with Mixed ILC/NST: Results from Post-Mortem Tissue Donation Programs

- Treatment Resistance and Metastases—Finding markers of dormancy and resistance and using it as a therapeutic target.
- Tissue donation.
• Considering the ‘so-called’ HLBC, without family history of gastric tumour, E-cadherin genetic test should be proposed in the following cases: (A) bilateral LBC with or without family history of LBC, with age at onset <50 years, and (B) unilateral LBC with family history of LBC, with age at onset <45 years. Whenever possible, BRCA1/2 germline mutations should be excluded in both groups, since they are mutually exclusive with CDH1 germline mutations.

• Given the high prevalence of ILC in CDH1 germline mutation carriers, and the histopathological and imaging features of these tumours, breast screening in CDH1-mutated patients should be performed annually with DM (possibly with DBT), ultrasound and contrast-enhanced MRI. A 6-month interval between the US and the MRI is preferable but not mandatory.
Representative model of lobular breast cancer (LBC) progression in CDH1 mutation carries.

Normal lobule
- Wild-type CDH1
- Tight cell-cell adhesiveness
- Well organized lobular structure

Lobular hyperplasia
- CDH1 mutation
- Reduction of cell-cell adhesion
- Increased proliferation

Lobular intraepithelial neoplasia
- CDH1 loss
- Reduction of cell-cell adhesion
- Alteration of lobule organization

Invasive lobular carcinoma
- CDH1 loss
- Cancer cell invasion through the basement membrane
- Lobular structure is destroyed

Invasive lobular carcinoma.
**Identification of Targetable Vulnerabilities in ILC Using Comprehensive Genomics Profiling - Ethan Sokol**

Loss of function of NF1 is a mechanism of acquired resistance to endocrine therapy in lobular breast cancer
*Sokol, E, Annals of oncology 2011*

**Key Message**
This study identifies an enrichment of *NF1* loss of function alterations and high tumor mutational burden in metastatic, therapy-refractory ILC. Our findings reveal potential targeted interventions in this population, with possible sensitivities to RAS/RAF inhibition or Immune checkpoint inhibitors.

FGFR4 overexpression and hotspot mutations in metastatic ER+ breast cancer are enriched in the lobular subtype.
*Levine K et al, NPJ breast cancer*

Targeting FGFR with Dovitinib (TKI258): Preclinical and Clinical Data in Breast Cancer
IDENTIFICATION OF TARGETABLE VULNERABILITIES IN ILC USING COMPREHENSIVE GENOMICS PROFILING - ETHAN SOKOL

APOBEC Mutational Signatures in Hormone Receptor–Positive Human Epidermal Growth Factor Receptor 2–Negative Breast Cancers Are Associated With Poor Outcomes on CDK4/6 Inhibitors and Endocrine Therapy

_Sammos. S et al JCO Precis Oncology_

**Key Message:**
APOBEC mutational signatures were common and identified in 16.7% of lobular and 10% of metastatic HR+/HER2–tumors. APOBEC+ HR+ HER2– patients had a significantly shorter time-to-treatment discontinuation and numerically shorter overall survival on first-line ET and CDK4/6i relative to APOBEC– patients. The clinical benefit of immune checkpoint inhibition was observed in a series of APOBEC+ patients. APOBEC or apolipoprotein B mRNA-editing enzyme catalytic polypeptides are a family of cytidine deaminases, which protect against viral infection by degrading viral genomes via cytosine deamination.

PARTICIPATION IN CLINICAL TRIALS, EVEN FOR A TISSUE COLLECTION STUDY, IT WILL IMPROVE SCIENTIFIC PROGRESS!
ROLE OF LIQUID BIOPSY AND GENOMIC SEQUENCING IN ILC

• L. Pessoa et al ,Nov 2020
Clinical implications of ctDNA Liquid Biopsy in cancer including ILC

- ctDNA – Diagnosis of cancer  
- ctDNA-- To help to monitor disease and response to treatment.
- Genomics on ctDNA- This is the greatest advantage to identify targetable mutations, such as PI3K, ESR-1, FGFR, Tumor mutational burden.
Dr. Simpson et al had undertaken an integrative analysis of gene expression and DNA copy number to identify novel drivers and prognostic biomarkers, using in-house (n = 25), METABRIC (n = 125) and TCGA (n = 146) samples.

Using in silico integrative analyses, a 194-gene set was derived that is highly prognostic in ILC—we named this metagene ‘LobSig’.

Assessing a 10-year follow-up period, LobSig outperformed the Nottingham Prognostic Index, PAM50 risk-of-recurrence (Prosigna), OncotypeDx, and Genomic Grade Index (MapQuantDx) in a stepwise, multivariate Cox proportional hazards model, particularly in grade 2 ILC cases which are difficult to prognosticate clinically.

Importantly, LobSig status predicted outcome with 94.6% accuracy amongst cases classified as ‘moderate-risk’ according to Nottingham Prognostic Index in the METABRIC cohort. Network analysis identified few candidate pathways, though genesets related to proliferation were identified, and a LobSig-high phenotype was associated with the TCGA proliferative subtype ILC with a poor outcome as predicted by LobSig were enriched with mutations in ERBB2, ERBB3, TP53, AKT1 and ROS1. LobSig has the potential to be a clinically relevant prognostic signature and warrants further development.

npj Breast Cancer (2019) 5:18 ; https://doi.org/10.1038/s41523-019-0113-yd
There was a notable prevalence of ERBB2 (20%), ERBB3 (14.28%), AKT1 (8.57%) and ROS1 (8.57%) mutations in the LobSig high group, raising exciting possibilities for applying targeted therapies in LobSig high tumors, with evidence emerging of the value of anti-HER2 therapies, AKT inhibitors and the recently described ROS1 inhibitors via synthetic lethal interaction with CDH1 mutant ILC.

Multivariate analysis demonstrated the significant value of LobSig above individual clinico-pathology features, but more importantly, the value of this signature resides in its ability to stratify the NPI moderate tumors—effectively moving from the ‘intermediate’, unclear group, into one of two groups with clear prognostic outcomes.

The data presented supports LobSig low-risk patients need not receive adjuvant chemotherapy. Our signature is not predictive for chemotherapy administration per se, but likely identifies a group of ILC patients in whom chemotherapies may be beneficial.

A paucity of highly annotated ILC cohorts with sufficient follow-up, as well as molecular profiling data in a clinical trial setting, precludes us from determining if and whether there are specific therapies that may have efficacy.
In conclusion, the molecular signature, LobSig, which captures the peculiar genomic landscape of ILC tumors, and together with clinico-pathology information, provides a robust mechanism for prognostication in ILC. This signature warrants further analysis and development, and validation on expanded retrospective cohorts of ILC with detailed treatment information.
Background. Research in metastatic breast cancer is hampered by limited sample availability. Post-mortem tissue donation programs can help to overcome this problem but are logistically challenging and have thus far mainly focused on histopathological and genomic research. We here present the UPTIDER program (NCT04531696), aimed at the multilevel characterization of advanced breast cancer and generation of tumour models.

Patients and Methods. Patients with stage IV breast cancer receiving their last line(s) of treatment are eligible for participation. Blood, urine and saliva samples are collected upon inclusion. Upon death, a post-mortem MRI (when possible) followed by a rapid autopsy is performed. Liquid biopsies from all body fluids and tissue samples from all macroscopically identified metastatic sites are collected. Samples are processed as mirrored biopsies in different conditions, such as fresh frozen for omics analyses, formalin fixed paraffin-embedded for histopathology, and slowly frozen in freezing medium or fresh for generation of xenograft and organoid models.
Results. A post-mortem MRI was performed in 6 patients. Peripheral blood, central blood and bone marrow were collected from all patients; urine, ascites, cerebrospinal, pericardial and pleural fluid all in more than 2/3 of patients. On average, 232 (range 90-406) tissue samples of which 164 (45-303) pathological from 42 (15 – 79) metastases were collected for each patient. Most often sampled metastatic sites were lymph nodes, liver, bones, pleura and peritoneum. Samples from the primary tumour could be retrieved from all patients, either during the autopsy (n=6) or from historical archives.

In total, 133 tumour samples were sent to collaborating partners for patient-derived xenograft creation. Already some have been successfully established and stored, including models derived from a patient with invasive lobular carcinoma (ILC) and one with metaplastic squamous cell carcinoma. When correlating microscopic and macroscopic findings, patients could largely be divided into three main categories. Eleven patients presented with overt and extensive disease burden, often characterized by diffuse visceral, pleural, peritoneal, bone and lymph node involvement. Two patients, both with ILC, presented with underestimated yet extensive disease burden. While gross examination and cross sectioning of organs did not reveal clear involvement, microscopical invasion of stomach and liver, amongst others, was found. Lastly, limited disease burden was seen in two patients, both with leptomeningeal involvement. In those patients, massive tumoral infiltration in the subarachnoid space and along the blood-brain barrier was seen microscopically, with no grey matter invasion.
They have launched a new and comprehensive post-mortem tissue donation program for patients with metastatic breast cancer, enrolling ~ 1 patient per month. Post-mortem tumour samples already resulted in successful establishment of some patient-derived xenografts. From a clinical point of view, vast underestimation of the disease extent on imaging during life as well as macroscopically during the autopsy was observed in some patients with metastatic ILC. For patients with leptomeningeal metastasis, they showed that the highly aggressive nature of their disease might be explained by extensive meningeal infiltration disrupting the blood-brain barrier. Further work on multi-omics will reveal tumor heterogeneity.
WHAT CAN WE ALL DO?

ADVOCACY- This becomes very important for any rarer tumor

SCIENTISTS- More Basic research to understand markers of dormancy and identify therapeutic targets and development of patient derived cell lines and murine models.

PATIENTS- Participate in clinical trials including tissue collection studies

Clinical Investigators- Identity ILC as Unique disease and open ILC specific clinical trials

GOVERNMENT/NCI- Recognize ILC as rare cancer

INDUSTRY- Focus on discovering novel therapies in ILC

FUNDING AGENCIES- Allocate funds for ILC research.
CHALLENGES- DISPARIETY IN OUTCOMES

EQUITY
ACCESS
EDUCATION
RESOURCES
Our Panelists

Patrick Derksen, PhD
Peter Simpson, PhD
Bhuvaneswari Ramaswamy, MD
Matt Covington, MD
Priscilla McAuliffe, MD, PhD
Jason Mouabbi, MD
ILC Imaging Science Summary

• Imaging of ILC was a hot topic at the 2023 ILC Symposium
• Formal imaging session:
  • Speakers:
    • Matt Covington, MD: Challenges and Potential Solutions for Imaging of ILC
      • Huntsman Cancer Institute, University of Utah
    • Hannah Linden, MD: Imaging and ILC, Advances and Opportunities
      • Fred Hutch Cancer Center, University of Washington
    • Gary Ulaner, MD: ER-targeted PET: Clinical Applications and Interpretation
      • HOAG Family Cancer Institute, University of Southern California
    • Vincent Vandecavaye, MD, PhD: Whole body diffusion-weighted MRI in Lobular Breast Cancer
      • KU Leuven, Belgium
Challenges in imaging of ILC

• It starts with detection of ILC on screening mammography and clinical breast exam

• It continues throughout the course of diagnosis, treatment, and monitoring for many individuals with ILC
Hypothetical cancer in red circle, also placed in the mammograms above. This is easily seen in the breasts with fatty and scattered density but is obscured on the heterogeneously and extremely dense breasts.
ILC challenges for pre-surgical staging

• Problems:
  • Common understaging due to failure to detect disease on mammography, ultrasound, MRI, FDG PET/CT
  • Lymph nodes may be involved with ILC but not enlarged
  • FDG PET/CT may have reduced sensitivity for ILC compared to IDC
  • High rate of surgical re-excisions due to positive margins

• Solutions:
  • Leverage other imaging technologies to include 18F-Fluoroestradiol PET/CT
  • Increased education to radiologists on challenges of ILC detection
    • Lower thresholds for calling disease potentially positive
ILC challenges for surveillance

• Problems
  • Same as before and
  • ILC metastasizes to areas difficult to detect on imaging
    • GI tract, CSF, peritoneum, blastic bone lesions
  • Disseminated cancer cells may transition to active disease at 5-20 years after diagnosis
    • Long latency likely leads to less aggressive monitoring

• Solutions
  • Improved importance of imaging for local staging compared to IDC
  • Circulating tumor DNA and other blood tests
How to improve ILC detection on imaging

• Leverage every technological advance available!

• Breast imaging:
  • breast MRI (abbreviated and full-protocol)
  • contrast-enhanced mammography
  • molecular breast imaging
  • whole breast ultrasound
  • breast CT

• Systemic imaging:
  • Fluoroestradiol PET/CT (and other emerging PET radiopharmaceuticals)
  • DWI whole-body MRI
A review on the added value of whole-body MRI in metastatic lobular breast cancer

Magnetic Resonance | Published: 06 April 2022 | 32, 6514–6525 (2022)
75-year-old with prior ILC, prior bilateral mastectomies, recurrence biopsy-proven in left chest wall

FDG revealed 2 left chest wall masses and some indeterminate mediastinal lymph nodes

FES revealed additional disease:
• >100 bone metastases
• Metastatic lymph nodes (left axilla, mediastinum, left internal mammary)
FDG
No disease identified

FES
Extensive nodal metastatic disease
Osseous metastatic disease

Restaging of ILC
Summary

• We need to shake things up!
• We must use ILC-specific imaging strategies
• More aggressive use of technologies with higher rates of ILC detection used earlier in presentation of disease
  • If dense breasts: supplement screening to allow earlier detection (3D mammography doesn’t count, breast MRI highest detection rate, other options: CEM, MBI, US)
  • Upon initial detection: breast MRI, CEM, or MBI for local staging
  • Fluoroestradiol PET/CT for staging locally advanced ER+ disease at initial presentation and subsequently for monitoring/recurrence
    • Especially if FDG negative at initial presentation
Our Panelists

Patrick Derksen, PhD
Peter Simpson, PhD
Bhuvaneswari Ramaswamy, MD
Matt Covington, MD
Priscilla McAuliffe, MD, PhD
Jason Mouabbi, MD
Clinical Science

Priscilla McAuliffe MD, PhD, FACS
Clinical take-aways from the ILC Symposium

Session 6: Challenges in Treatment of ILC

<table>
<thead>
<tr>
<th>Time</th>
<th>Title</th>
<th>Speaker</th>
</tr>
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<tbody>
<tr>
<td>4:35pm</td>
<td>Session 6: Challenges in Treatment of ILC</td>
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</tr>
<tr>
<td>4:40pm-5:00pm</td>
<td>Suzanne Fuqua, PhD (Baylor College of Medicine, Houston)</td>
<td>When the Breast Cancer Researcher Becomes the Patient with ILC</td>
</tr>
<tr>
<td>5:00pm-5:20pm</td>
<td>Jason Mouabbi, MD (University of Texas, MD Anderson Cancer Center, Houston)</td>
<td>Differential Genomic and Transcriptomic Analysis of Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma</td>
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<td>Julia Foldi, MD, PhD (University of Pittsburgh, UPMC, Pittsburgh, PA)</td>
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Session 7: Local Treatment of ILC

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<td>Session 7: Local Treatment of ILC</td>
<td></td>
</tr>
<tr>
<td>9:00am-9:20am</td>
<td>Rita Mukhtar, MD (UCSF, San Francisco, CA)</td>
<td>Surgical management of ILC: challenges and opportunities</td>
</tr>
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</tbody>
</table>

2 hours → 15 minutes??
When the Breast Cancer Researcher Becomes the Patient with ILC

INTERNATIONAL INVASIVE LOBULAR BREAST CANCER SYMPOSIUM 2023

Suzanne AW Fuqua, PhD, MS

Research Patient Advocate
“It’s a long road.”

Adjuvant Endocrine Therapy (ET)

- Good ER+ BC - 5-10 yrs AI, Tam, Switch
- Bad ER+/HER2- MBC
- ILC: APOBEC mutagenesis?
- Clonal evolution
- Multiple evolutionary trajectories

ILC mutations:
- CDH1, ERBB2, PI3KCA, RUNX1, TBX3, ESR1m, FOXA1, NF1
- Chromatin reprogramming
- Peritoneal metastases

ILC: ROLO trial
- HER-2 agents

Goal: Bring precision medicine to ALL moments of ILC care.
Differential Genomic and Transcriptomic Analysis of Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma

Jason A. Mouabbi MD
Assistant Professor
Department of Breast Medical Oncology at MD Anderson Cancer Center
SAB Chair of the Lobular Breast Cancer Alliance
Introduction: Features of ILC vs IDC – Clinicopathology

<table>
<thead>
<tr>
<th>Stage at diagnosis¹</th>
<th>IDC</th>
<th>ILC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>55%</td>
<td>46%</td>
</tr>
<tr>
<td>Stage II</td>
<td>35%</td>
<td>33%</td>
</tr>
<tr>
<td>Stage III</td>
<td>8%</td>
<td>17%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>2%</td>
<td>5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade²</th>
<th>IDC</th>
<th>ILC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-2</td>
<td>60%</td>
<td>90%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>40%</td>
<td>10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Proliferation Activity (Ki67)³</th>
<th>IDC</th>
<th>ILC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt;20%)</td>
<td>35%</td>
<td>60%</td>
</tr>
</tbody>
</table>

- 90% of ILC express AR (compared to ~50 of IDC)
- All TN ILC (5%) are lumAR and have high AR expression

¹Oesterreich S et al., JNCI, 2022
²Pestalozzi BC et al., J Clin Oncol, 2006
Surgical management of ILC: challenges and opportunities

Rita Mukhtar, MD
Associate Professor of Clinical Surgery
University of California, San Francisco

INTERNATIONAL INVASIVE LOBULAR BREAST CANCER (ILC)
SYMPOSIUM 2023 PITTSBURGH, PA – SEPTEMBER 28-30, 2023
Background

- Patients with ILC have worse **surgical outcomes** compared to patients with invasive ductal carcinoma (IDC)
  - Measured by positive margin rates, mastectomy rates, and axillary dissection rates
- Many potential causes:
  - Higher stage at presentation
  - Higher discordance between clinical stage and pathologic stage
  - Lower sensitivity of standard imaging tools

Should patients with ILC always choose mastectomy?

• Not necessarily!
  • National Cancer Database Analysis of >160,000 showed **same or better overall survival with breast conserving therapy (lumpectomy + radiation)** compared to mastectomy
  • Swedish study of nearly 50,000 patients showed **improved overall survival with breast conserving therapy (lumpectomy + radiation)** compared to mastectomy

• Lymph node positivity → increased likelihood of needing post mastectomy radiation
  • Implications for reconstruction and long-term sequelae

---

**References**

- Chen K et al. Comparative effectiveness study of breast-conserving surgery and mastectomy in the general population: A NCDB analysis. Oncotarget. 2015
Positive margins have negative consequences

- Significantly higher rates of surgical site infection, seroma, hematoma, and fat necrosis
- Significantly lower breast satisfaction and sexual well being
- Healthcare costs increased 4-fold for patients requiring re-excision
- Increased risk of recurrence if negative margins NOT achieved

Metcalfe L et al. Beyond the margins—Economic costs and complications associated with repeated breast conserving surgeries. JAMA Surgery 2017
If a positive margin occurs, what is the chance of success for re-excision in ILC?

Good success rates!

314 cases of ILC treated with lumpectomy

118 positive margins (37.6%)

62 had re-excisions

74.2% successful

Piper M et al. Success rates of re-excision after positive margins for invasive lobular carcinoma of the breast. NPJ Breast Cancer 2019
Summary

• Breast conservation therapy (lumpectomy + radiation) is safe for ILC, even for ILC >4 cm; positive margins are common
  • Goal is to achieve negative margins
  • Consideration for oncoplastic techniques for re-contouring/cosmesis
    • Level 1: local tissue rearrangement only
    • Level 2: parenchymal flaps and skin resection (reduction mastopexy)

• Importantly, for T3 (>5 cm) ILC, even mastectomy can have high positive margin rates. Has implications related to reconstruction, radiation.

• TAKE AWAY: Underscores the need for better imaging for ILC and better systemic therapy for ILC to shrink tumors pre-operatively
Surgical management of the axilla in lobular cancer

Priscilla McAuliffe, MD, PhD, FACS
Axillary management in ILC: Background

• Why is axillary nodal surgery important?
  • Accurate breast cancer staging
  • Major prognostic predictor for breast cancer outcomes
  • Helps determine the extent of oncologic surgery, reconstructive surgery, radiation therapy and systemic therapy

• Why can axillary nodal surgery be a problem?
  Morbidity
  • Paresthesia (~20-70% of patients)
  • Lymphedema (~3-25% of patients)
  No significant impact on relapse-free or overall survival
  • NSABP B04 study

• Do current data support similar management of the axilla in ILC, as with IDC?
  • Lobular histology independently predicts risk of micrometastatic axillary disease

Axillary management in ILC – take away

• For patients who present with a normal axilla on physical exam and imaging:
  • Sentinel lymph node biopsy (SLNB) adequately stages the axilla
  • Surgical results:
    • If no lymph node involvement: no further axillary surgery needed
    • If low volume lymph node involvement: ~2 or fewer lymph nodes involved, no completion axillary lymph node dissection (ALND)
    • If high volume lymph node involvement: ALND
Axillary management in ILC: Take away

• For patients who present with lymph node involvement on exam/imaging:
  • Generally, ALND is recommended
  • For appropriately selected patients, sometimes after a good response to neoadjuvant systemic therapy, ALND can be avoided

Right-sizing axillary surgical management for lobular cancer is critical and evolving
Systemic therapy
## Summary of four large NSABP RCTs

<table>
<thead>
<tr>
<th>Trial</th>
<th>ILC/NST (IDC) sample size</th>
<th>% ER+</th>
<th>Chemotherapy being tested</th>
<th>Endocrine therapy</th>
<th>Outcome measures</th>
<th>Median follow-up (yrs)</th>
<th>Major clinical conclusion of trial</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-22</td>
<td>143/1975</td>
<td>66%</td>
<td>AC vs AC with intensification of C</td>
<td>TAM x 5 yrs if age ≥ 50 yrs</td>
<td>DFS, OS</td>
<td>15.0</td>
<td>No benefit from C dose intensification.</td>
<td>(1)</td>
</tr>
<tr>
<td>B-25</td>
<td>197/2252</td>
<td>60%</td>
<td>AC vs AC with intensification of C</td>
<td>TAM x 5 yrs if age ≥ 50 yrs</td>
<td>DFS, OS</td>
<td>12.1</td>
<td>No benefit from C dose intensification.</td>
<td>(2)</td>
</tr>
<tr>
<td>B-28</td>
<td>275/2720</td>
<td>66%</td>
<td>AC vs AC→T (T=Paclitaxel)</td>
<td>TAM x 5 yrs if age ≥ 50 yrs or &lt;50 if ER+</td>
<td>DFS, OS</td>
<td>11.2</td>
<td>The addition of T to AC led to significant improvement in DFS but not OS, with acceptable toxicity.</td>
<td>(3)</td>
</tr>
<tr>
<td>B-30</td>
<td>616/4304</td>
<td>75%</td>
<td>AC→T vs AT vs ACT (T=docetaxel)</td>
<td>TAM x 5 yrs if ER+; anastrozole allowed after 10/2002 in postmenopausal patients</td>
<td>DFS, OS</td>
<td>10.2</td>
<td>Sequential AC→T improved DFS compared with AT and concurrent ACT; and improved OS compared with AT.</td>
<td>(4)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ER: estrogen receptor; A: adriamycin; C: cyclophosphamide; T: paclitaxel/docetaxel; TAM: tamoxifen; DFS: disease-free survival; OS: overall survival

Summary and conclusions

In four large RCTs conducted by the NSABP including a total of 12,494 patients (1,233 with ILC) accrued between 1989 and 2004, we found:

- Significant differences in baseline characteristics between patients with ILC and NST/IDC:
  - Older age, higher prevalence of ER+ disease, higher number of involved LN’s and larger tumors

- After propensity matching for age, ER status, tumor size and LN status, we found:
  - Overall, no differences in clinical outcomes of DFS, OS and recurrences
  - When looking at early (0-5 yrs) and late events (5+ yrs) separately, patients with ILC do better early, while they do worse compared to patients with NST/IDC later in follow-up
  - More late recurrences in patients with ILC
  - Similar pattern of outcomes in patients with ER+ and ER- disease

In this analysis of data from the largest cohort of ILC patients from prospectively randomized clinical trials of adjuvant chemotherapy, long-term clinical outcomes were different between patients with ILC versus NST/IDC despite receiving the same modern adjuvant treatment.
Differential Genomic and Transcriptomic Analysis of Invasive Lobular Carcinoma Versus Invasive Ductal Carcinoma

Jason A. Mouabbi MD
Assistant Professor
Department of Breast Medical Oncology at MD Anderson Cancer Center
SAB Chair of the Lobular Breast Cancer Alliance
Identify novel biomarkers, genetic alterations, transcriptomic features, and tumor microenvironment (TME) variations to facilitate the development of personalized treatments for patients with ILC
Methods

• We collected ILC and luminal IDC samples from two datasets (TCGA, METABRIC) and performed differential expression and gene set enrichment analyses, revealing novel genomic, transcriptomic, and TME differences.
  • We analyzed 1,735 samples: 1,442 luminal IDCs and 293 ILC
• In the TCGA and METABRIC samples were labeled “IDC” or “ILC solely on morphological analysis (histology)

• CDH1 alterations and low CDH1 and CTNNB1 (catenin beta-1) expression are well established associations with ILC histology

• We established a **histo-molecular classification** that incorporates histological findings in combination with CDH1 alterations (mutation, deep deletion, or low expression) and CTNNB1 low expression
Tumor Microenvironment Types (TME)
A component of BostonGene Tumor Portrait™ test

- BostonGene identified 4 distinct Tumor Microenvironment Subtypes by analyzing **29 functional gene expression signatures**
- There are **4 portrait types** associated with disease prognosis
- This model is prognostic in **multiple cancer types**
TME Prognostic tool — predicts survival. GOAL: personalize care!
A component of BostonGene Tumor Portrait™ test

- Immune-enriched, non-fibrotic
- Immune-enriched, fibrotic
- Immune desert
- Fibrotic

Tickler: what if lobular pathology could be managed before it was ever invasive? (Session 1)
What can you do RIGHT NOW? Exercise!

Exercise Is Medicine in Medical Oncology

Kathryn H. Schmitz, PhD, MPH, FACSM, FTOS, FNAK
Professor, University of Pittsburgh
Past President, ACSM
Founder, Moving Through Cancer
American Cancer Society Clinical Research Professor

@fitaftercancer
@fitnessaftercancer
#ExerciseOncology

DrKatieSchmitz@gmail.com
Documented Benefits of Exercise during Cancer Tx

• Fatigue
• Sleep
• Quality of life
• Anxiety
• Depression
• Body composition
• Function
• Breast cancer related lymphedema
Outcomes Documented to be Improved by Exercise with Clinical Relevance during Cancer Treatment

- **Inflammation**
  - Contributes to infections, diarrhea, nausea/vomiting, fatigue

- **Comorbidities**
  - Cancer patients with worse comorbidities are more likely to be hospitalized

- **Frailty**
  - Frail patients more likely to be hospitalized or visit the ER
Dr. Schmitz’s Seminal Contribution: The PAL Trial

August 18, 2009

R01-CA106851

December 8, 2010
# Summary of Exercise Guidelines

<table>
<thead>
<tr>
<th>Source</th>
<th>During Treatment</th>
<th>Post Treatment</th>
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</thead>
<tbody>
<tr>
<td>American College of Sports Medicine (ACSM)</td>
<td>30 min 3x/week</td>
<td>150-300 min/week Moderate</td>
</tr>
<tr>
<td>American Cancer Society (ACS)</td>
<td>Recommended but not specific</td>
<td>150-300 min/week Moderate</td>
</tr>
<tr>
<td>American Society of Clinical Oncology (ASCO)</td>
<td>Recommended</td>
<td>Recommended</td>
</tr>
</tbody>
</table>

- **Intensity:**
  - “Gone are the days of ‘don’t push yourself, take it easy.’”
  - ‘Talk test’ to judge intensity: During exercise, if you cannot talk, you’re working too hard. If you can sing, you’re not working hard enough.”
Clinical take-away from the ILC Symposium?

Session 6: Challenges in Treatment of ILC

4:35pm  Session 6: Challenges in Treatment of ILC  
Chair: Vikram Gorantla, MD (UPMC, Pittsburgh)

4:40pm-5:00pm  Suzanne Fuqua, PhD (Baylor College of Medicine, Houston)  
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Exercise is Medicine in the Setting of Oncology

Session 7: Local Treatment of ILC

8:55am  Session 7: Local Treatment of ILC  
Chair: Bhuvaneswari Ramaswamy, MD (The Ohio State, Columbus, OH)

9:00am-9:20am  Rita Mukhtar, MD (UCSF, San Francisco, CA)  
Surgical management of ILC: challenges and opportunities

9:20am-9:40am  Priscilla McAuliffe, MD, PhD (UPMC Magee-Womens Hospital and UPMC Hillman Cancer Center, Pittsburgh, PA)  
Surgical management of the axilla in lobular cancer.

Precision treatment for ILC is evolving in all clinical areas!
Thank you!
Q & A
Our Panelists

- Jason Mouabbi, MD
- Patrick Derksen, PhD
- Bhuvaneswari Ramaswamy, MD
- Peter Simpson, PhD
- Matt Covington, MD
- Priscilla McAuliffe, MD, PhD
- Jason Mouabbi, MD
Thank You!

We are grateful for the support from GE Healthcare that helped make the production of this webinar possible.