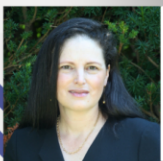


LBCA's 2023 Free, Live Streamed Webinar What's New in Screening and Treatment for Lobular Breast Cancer



Rinath Jeselsohn, MD
LBCA Scientific Advisory
Board Member, Dana-Farber
Cancer Institute



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Memorial Sloan Kettering
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Today's Agenda

Welcome and Introductions- Laurie Hutcheson

ILC Imaging/Detection- Tali Amir, MD

ILC and Surgery- Anita Mamtani, MD, FACS

ILC and Treatment- Rinath Jeselsohn, MD

Q&A - Laurie Hutcheson

Our Panelists



Tali Amir, MD



Anita Mamtani, MD, FACS



Rinath Jeselsohn, MD

Invasive Lobular Breast Carcinoma

- Detection and Surveillance

- September 12, 2023

Tali Amir, MD

Assistant Attending Radiologist

Director of Breast Imaging MSK-Bergen



Memorial Sloan Kettering
Cancer Center

Invasive Lobular Carcinoma: Detection and Surveillance

- Invasive Lobular Carcinoma (ILC) – Brief Overview
- Best Screening Practices
- Challenges in Detection and Diagnosis
- Surveillance
- Looking into the future

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Invasive Lobular Carcinoma: An overview

- Second most common type of breast cancer
- Accounts for 10-15% of all breast cancers
- Often diagnosed at a larger tumor size
- More commonly presents as multifocal disease (multiple tumors)
- Tends to recur later (>10 years after initial diagnosis)

Invasive Lobular Carcinoma: Detection and Surveillance

- Invasive Lobular Carcinoma – Brief Overview
- **Best Screening Practices**
- Challenges in Detection and Diagnosis
- Surveillance
- Looking into the future

Screening & Detection: How do we screen?

Standard of breast cancer screening = Mammography



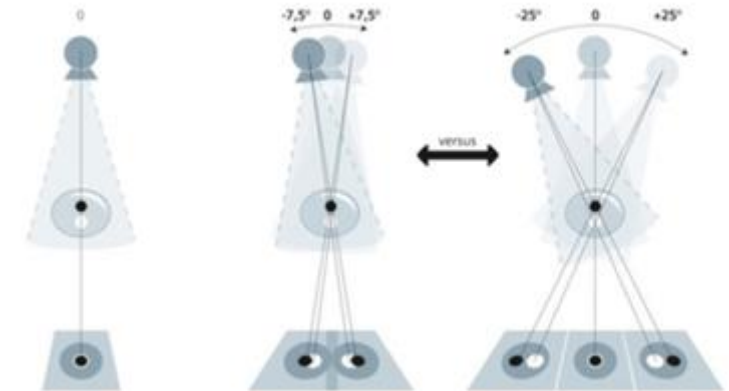
**1980's
Film screen
mammography**



**2000's
Digital
mammography**



**Present
Digital breast
tomosynthesis**

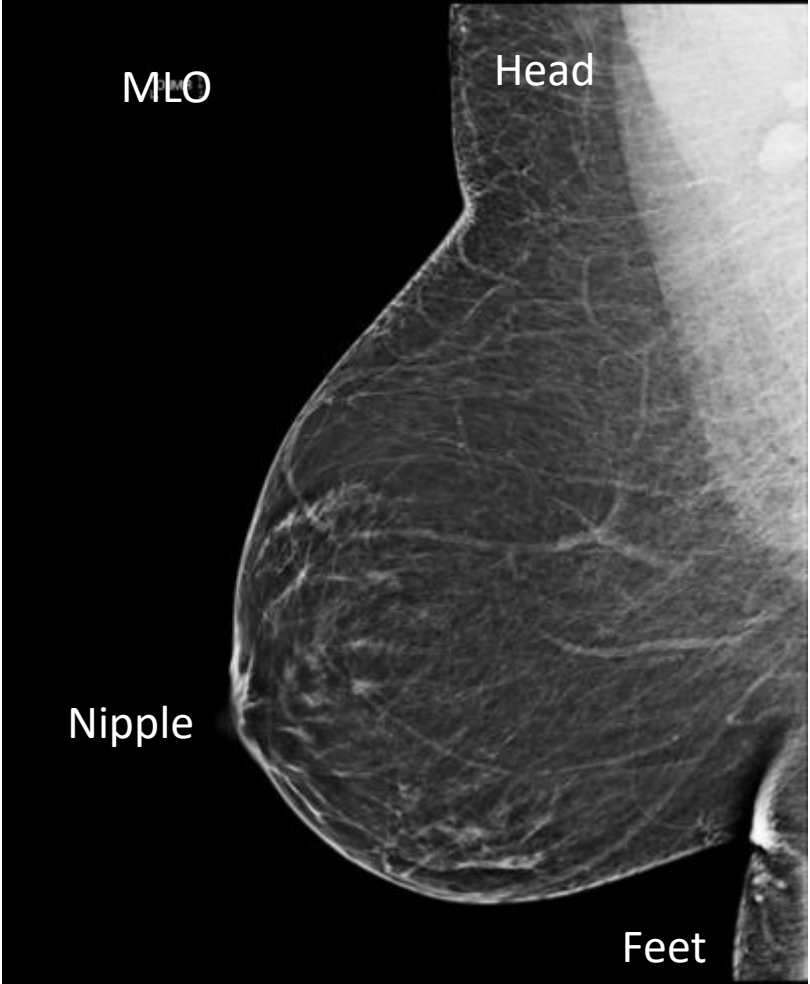
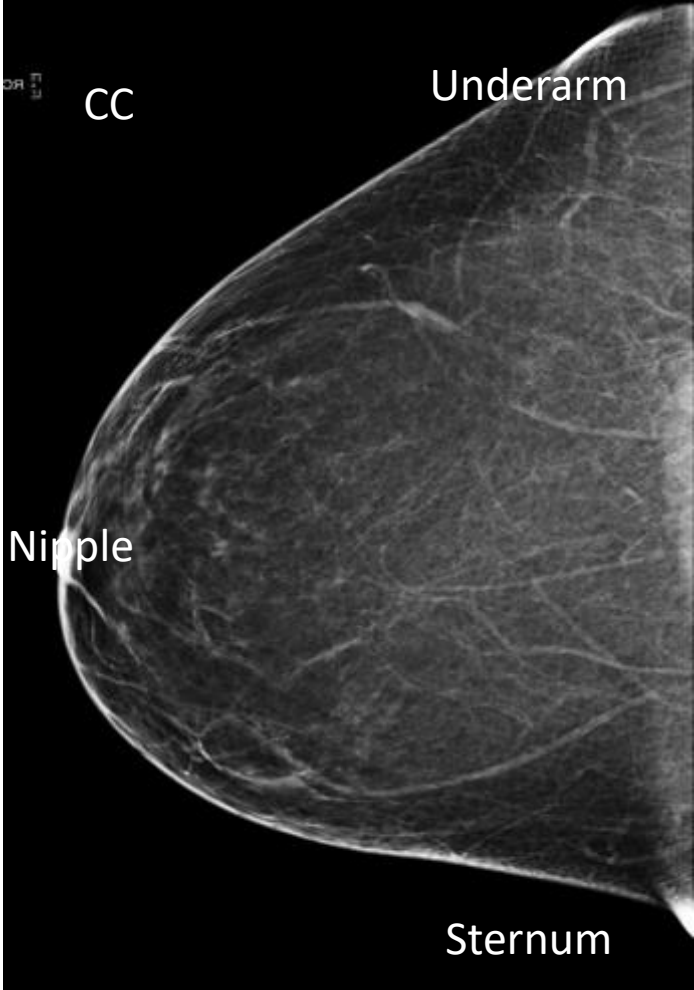


<https://www.mammoguide.com/tomosynthesis.html>

Screening & Detection: How do we screen?



<http://www.cancer.gov/types/breast/patient/breast-screening-pdq>



Screening & Detection: How do we screen?

Screening average risk women (<15% lifetime risk of breast cancer)

- Mammogram starting at age 40
 - 2D (full field digital mammogram)
 - 3D (digital breast tomosynthesis, DBT)
 - Dense breasts
- Ultrasound
 - Supplemental screening in dense breasts

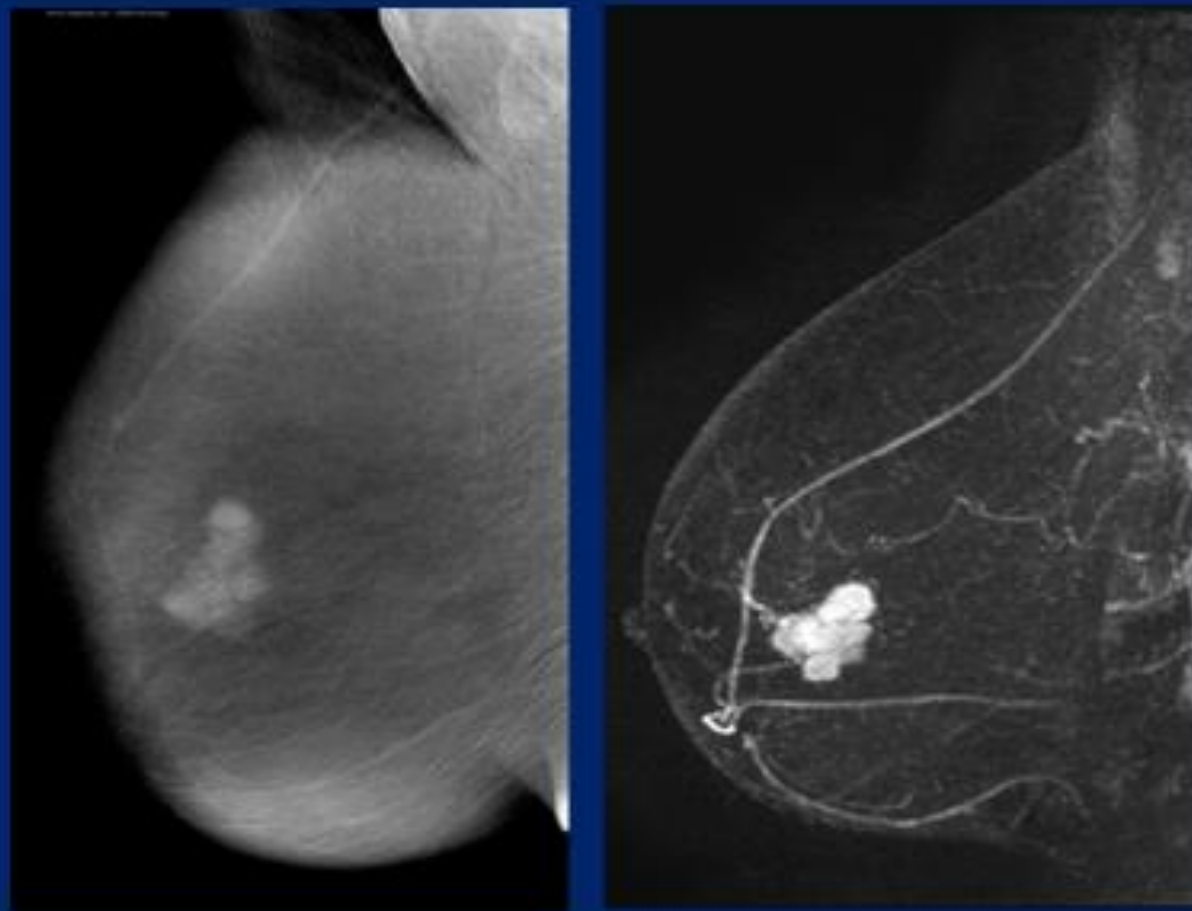
Screening & Detection: How do we screen?

Screening above average risk women

- Intermediate risk: 15-20% lifetime risk
- High risk: >20% lifetime risk

Consider:

- Contrast Enhanced Mammography (CEM)
- Contrast Enhanced Magnetic Resonance Imaging (MRI)



Images courtesy of Dr. Maxine Jochelson

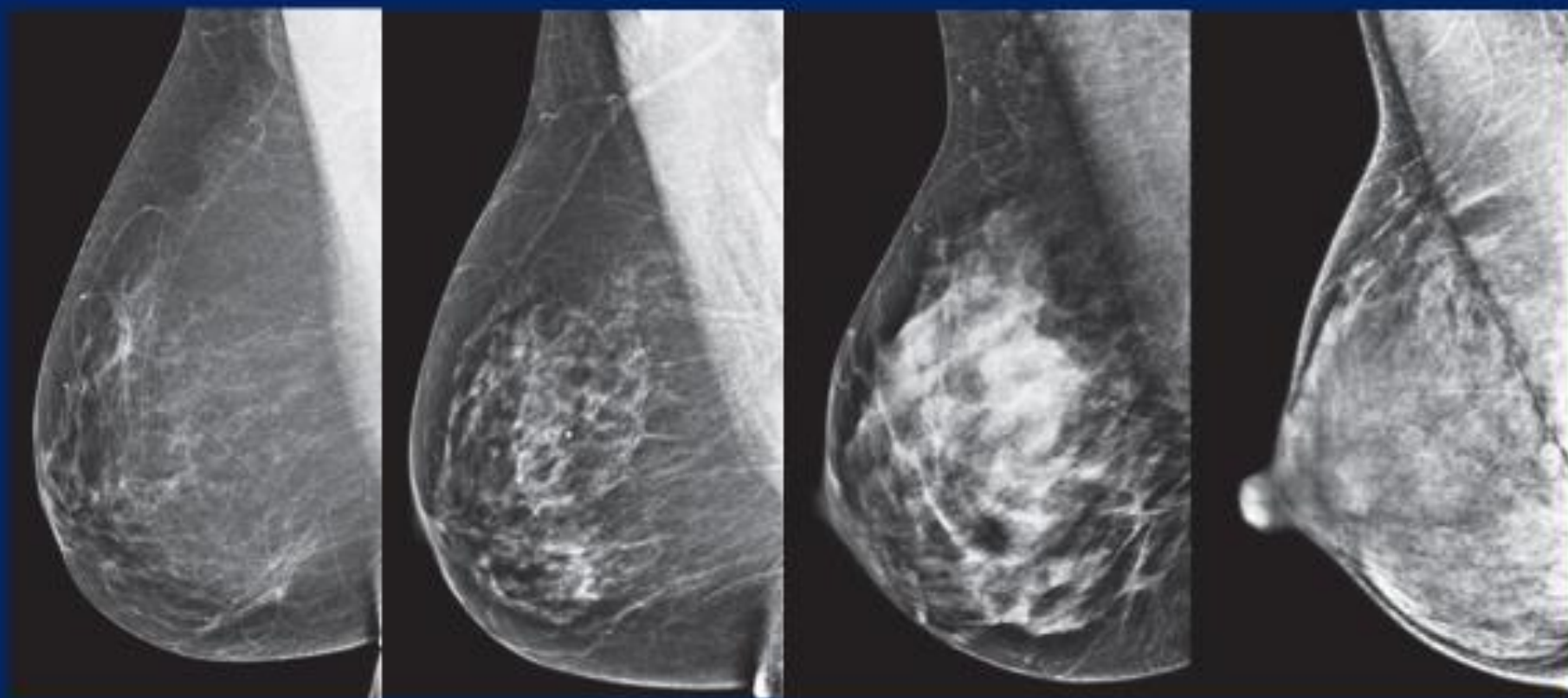
Screening & Detection: Breast Symptoms

- Breast Symptoms
 - Palpable lump
 - Nipple symptoms (discharge, inversion)
 - Skin changes (redness, thickening)
- Imaging Evaluation
 - Mammogram (starting at 30 years old)
 - Ultrasound
 - CEM
 - MRI (problem solving, persistent symptom)

Invasive Lobular Carcinoma: Detection and Surveillance

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Invasive Lobular Carcinoma: Challenges in Detection and Diagnosis



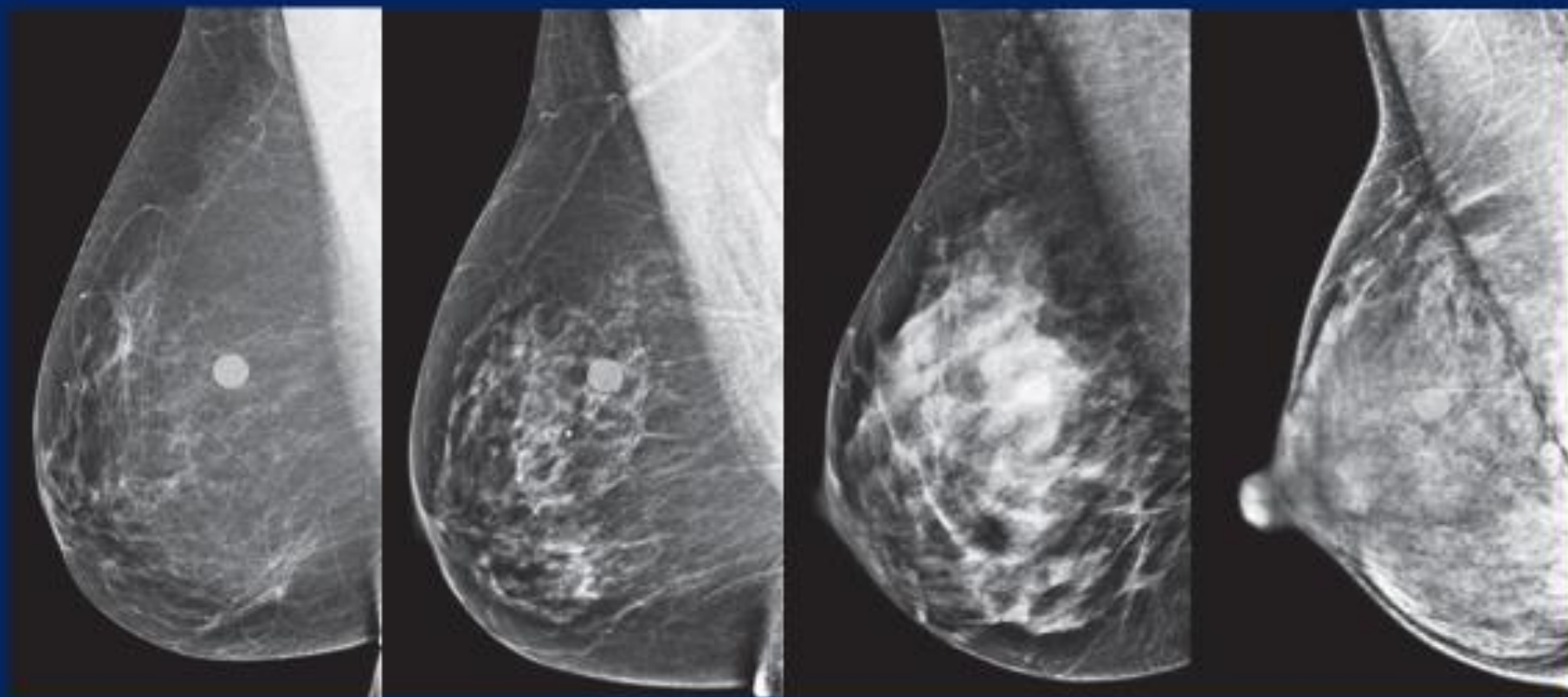
Almost
entirely fatty

Scattered

Heterogeneously
dense

Extremely
dense

Invasive Lobular Carcinoma: Challenges in Detection and Diagnosis



Almost
entirely fatty

Scattered

Heterogeneously
dense

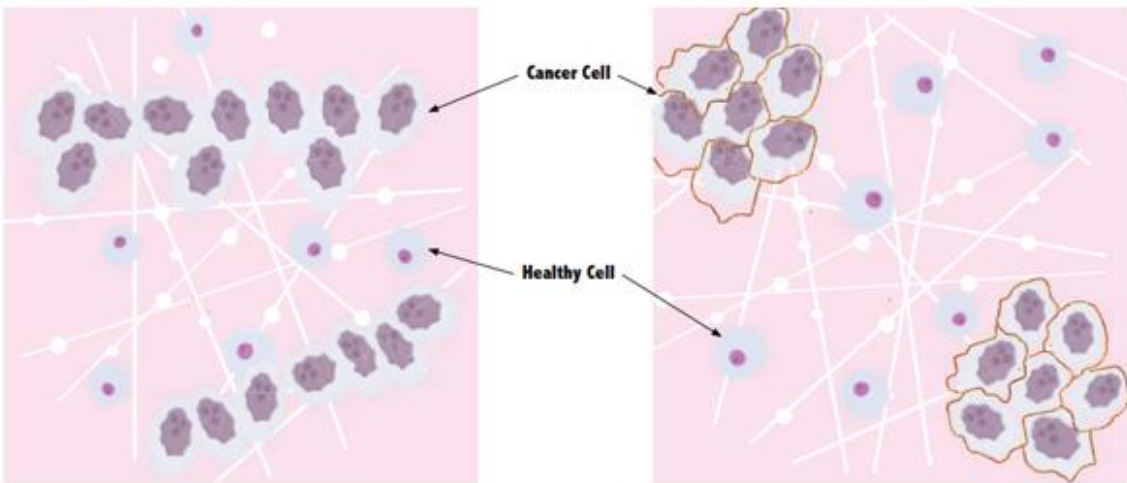
Extremely
dense

Invasive Lobular Carcinoma: Challenges in Detection and Diagnosis

Invasive Lobular Carcinoma (ILC) Tumor Cells VS. **Invasive Ductal Carcinoma (IDC) Tumor Cells**

- >95% lack the protein E-Cadherin that enables clumping
- Cells grow in single file formation

- The protein E-Cadherin acts like "cellular glue"
- Tumors clump together in masses or "lumps"



Healthy VS. Cancer Cells

- Round or elliptical cell shape
- Single nucleus, spheroid shape
- Single nucleolus
- Greater cytoplasmic volume
- Controlled growth
- Does not spread to other sites

- Irregular cell shape and size
- Darker nucleus
- Multiple nucleoli
- Less cytoplasmic volume
- Uncontrolled growth
- Can spread to different locations in the body (metastasis)

Nucleus: the control center of the cell containing DNA and RNA

Nucleolus: composed of RNA and proteins, which form around specific chromosomal regions

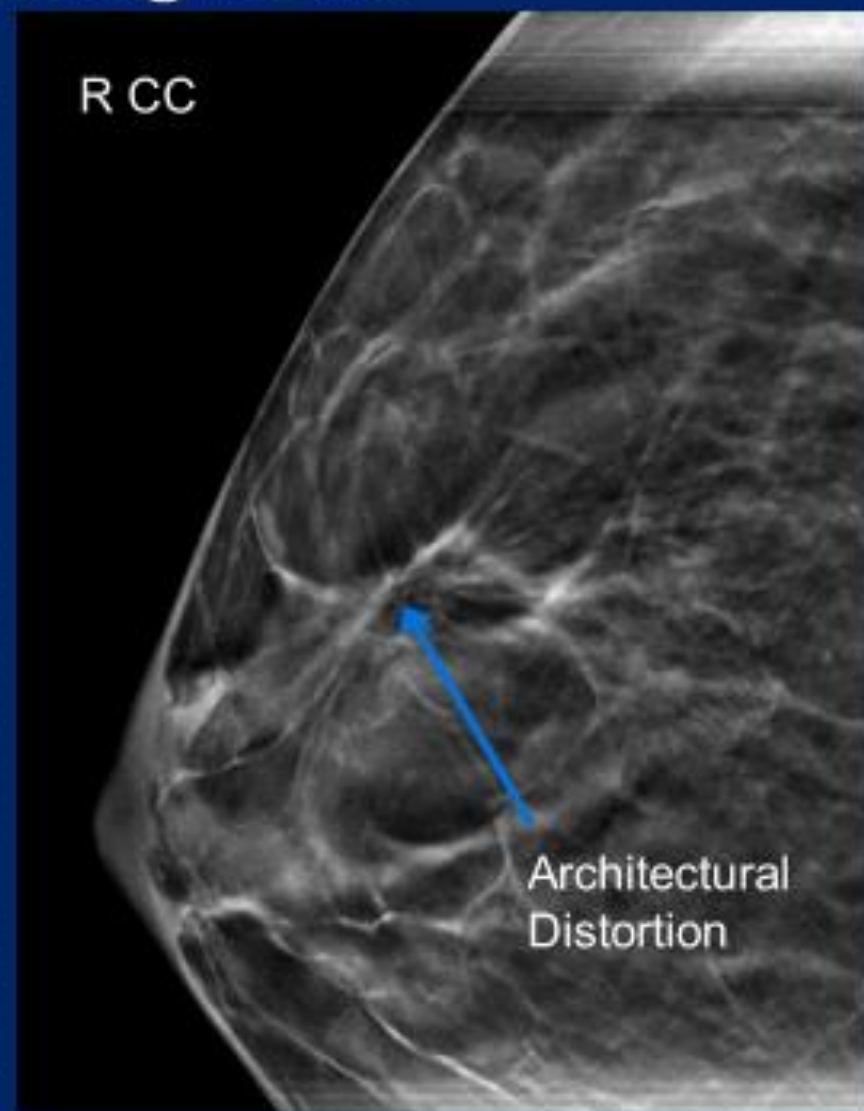
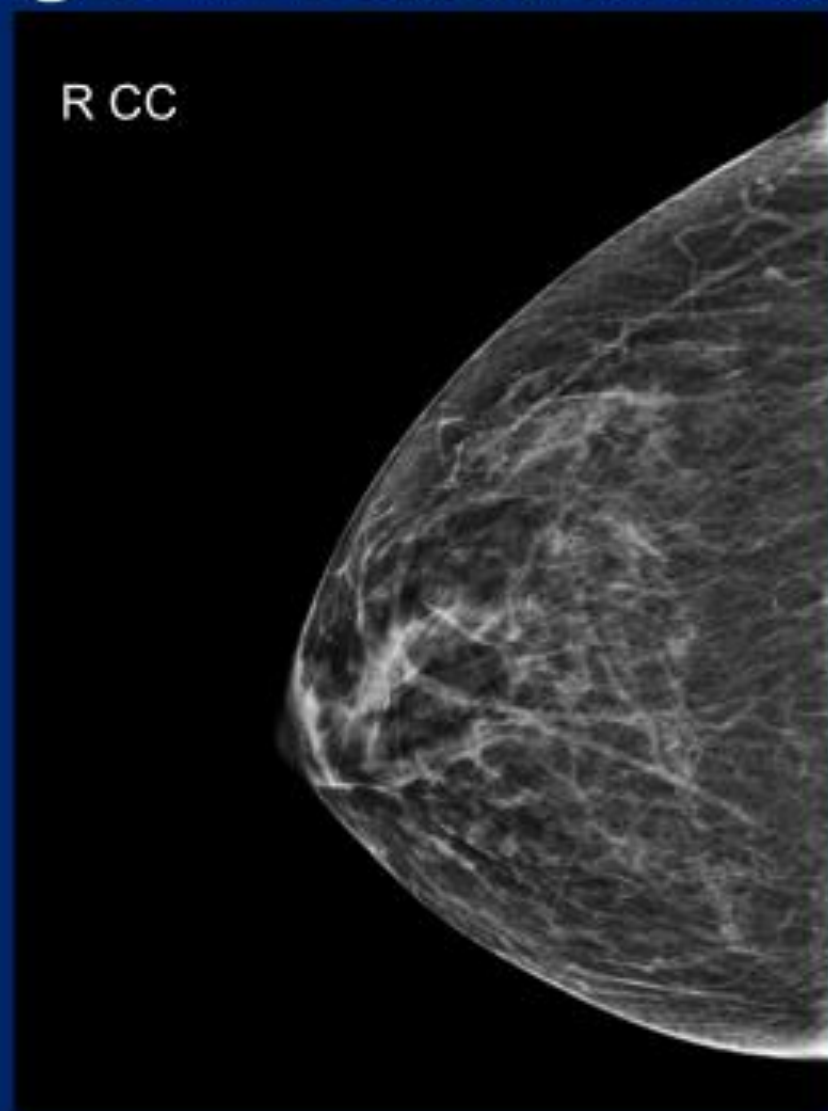
Cytoplasm: gelatinous liquid that fills the inside of a cell

LBCA Lobular Breast Cancer Alliance

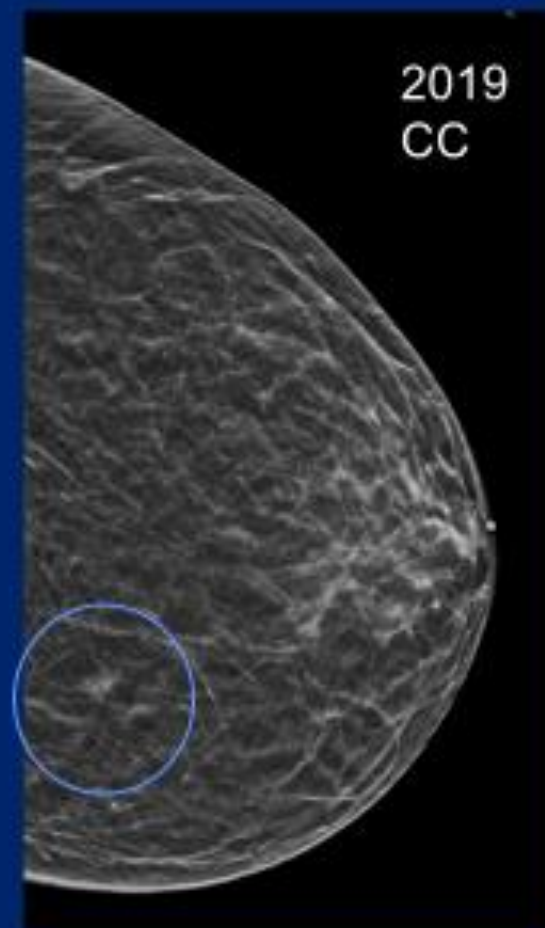
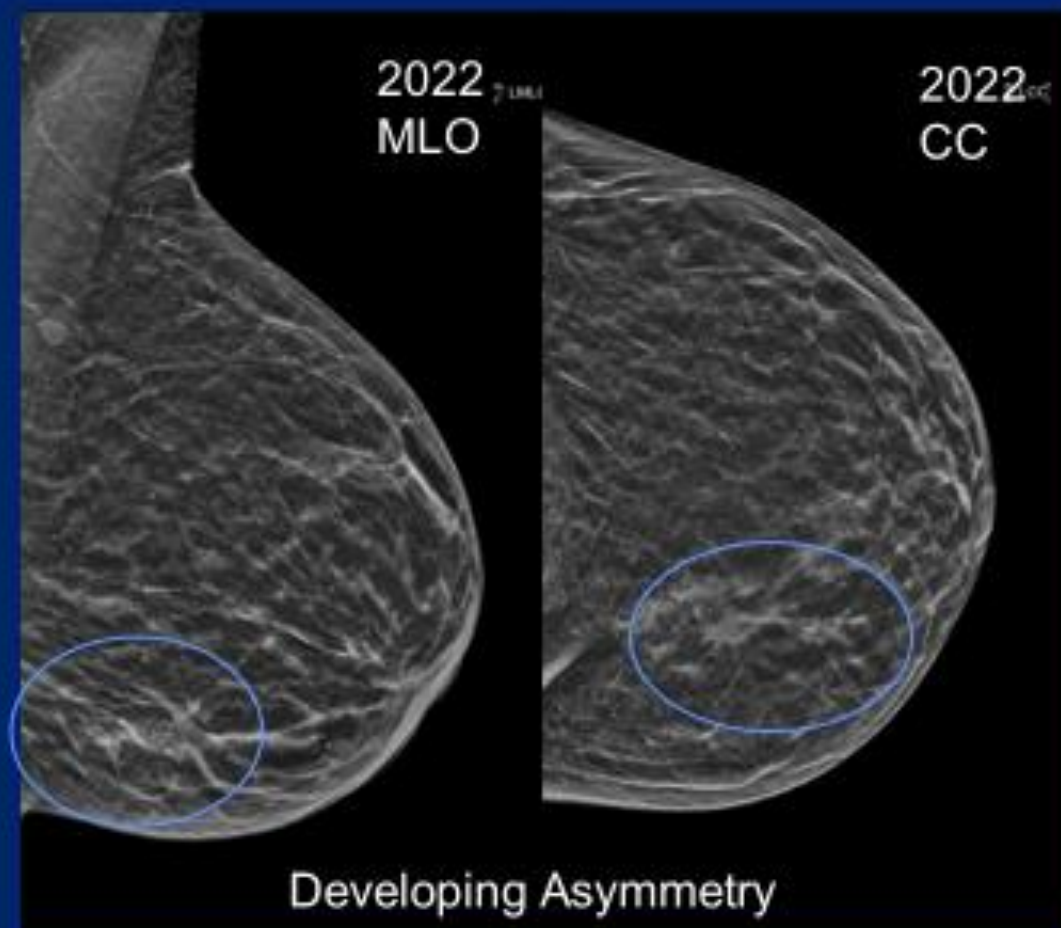
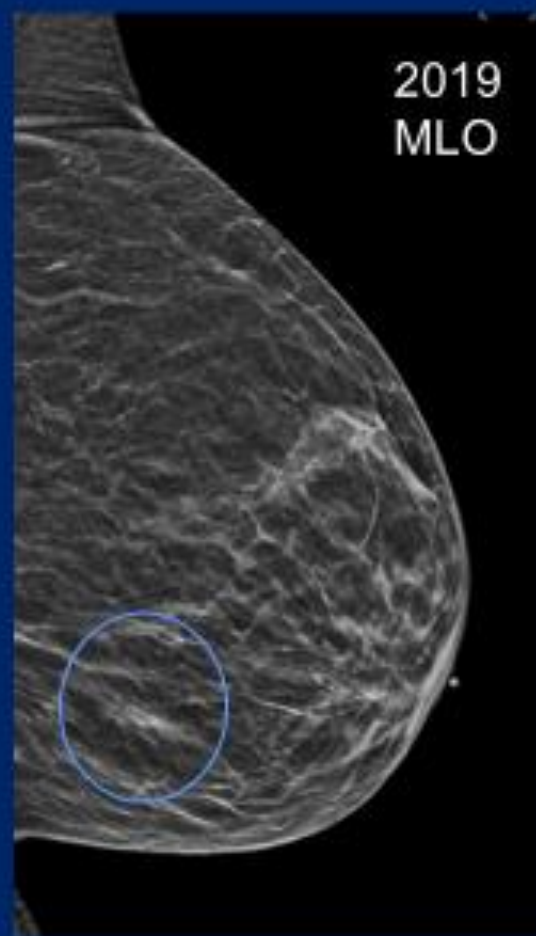
When reprinting or publishing please link to the LBCA website and refrain from making edits that alter the original context

- Can be inconspicuous
 - Cells grow "single file"
- Variable appearance
 - Mass
 - Distortion (pulling appearance)
 - Asymmetry (tissue without discrete mass)

Invasive Lobular Carcinoma: Challenges in Detection and Diagnosis



Invasive Lobular Carcinoma: Challenges in Detection and Diagnosis



Invasive Lobular Carcinoma: Defining extent of disease after biopsy

After mammogram and ultrasound, consider:

- CEM
- MRI

- Studies have demonstrated comparable performance of MRI and CEM for evaluating disease extent

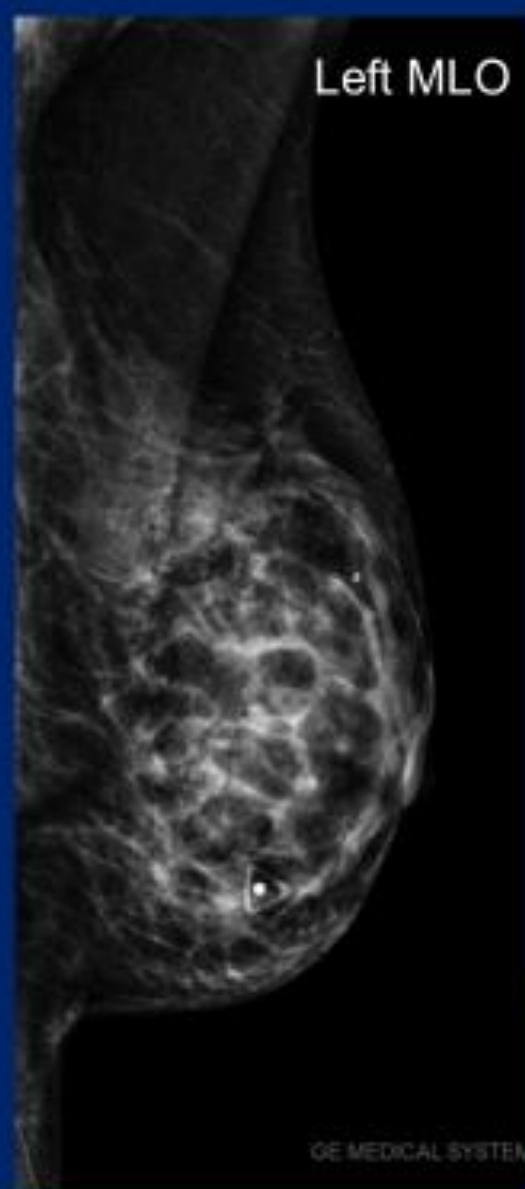
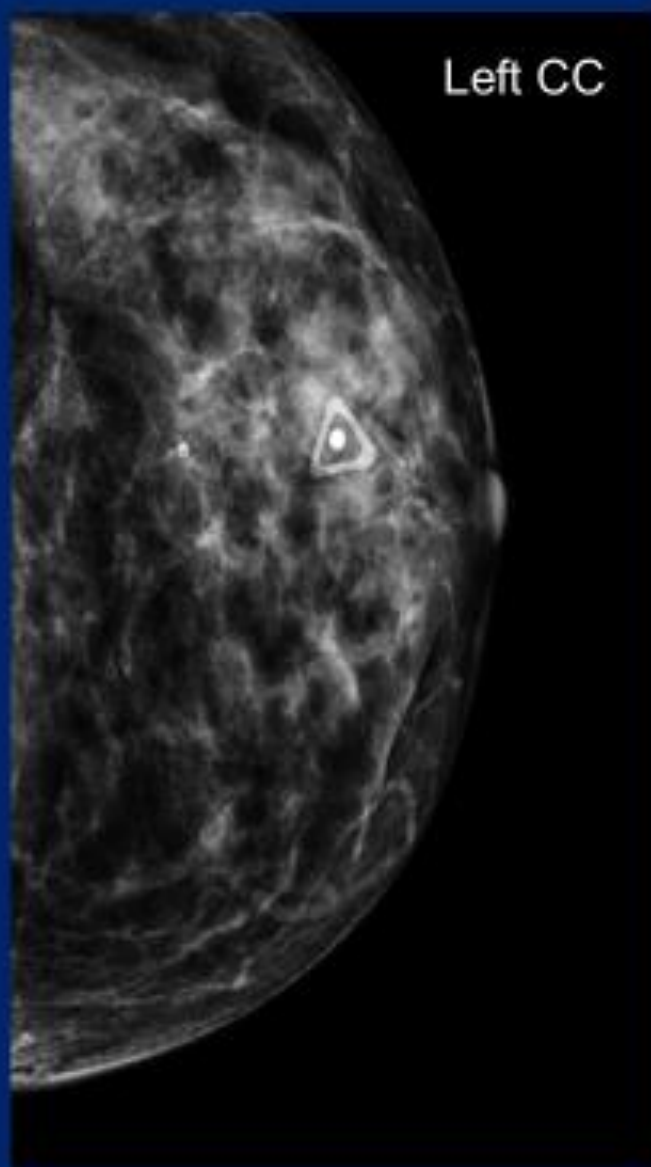
- MRI & ILC
 - Preoperative MRI helps identify additional disease in up to 25% of patients
 - Preoperative MRI imaging can impact clinical management

Balancing potential benefits with potential risk

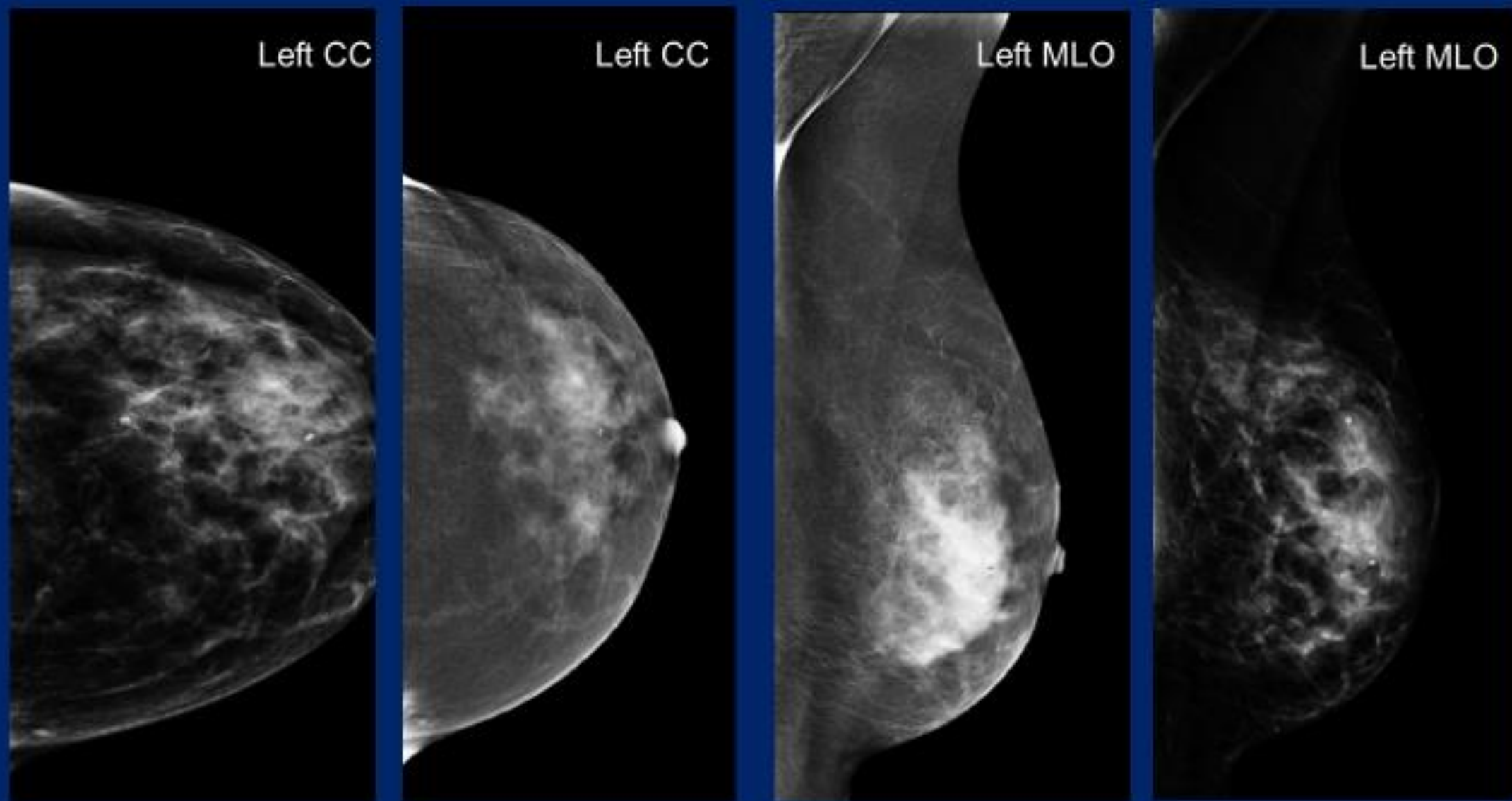
Lee-Felker SA, Tekchandani L, Thomas M, Gupta E, Andrews-Tang D, Roth A, Sayre J, Rahbar G. Newly Diagnosed Breast Cancer: Comparison of Contrast-enhanced Spectral Mammography and Breast MR Imaging in the Evaluation of Extent of Disease. *Radiology*. 2017 Nov;285(2):389-400. doi: 10.1148/radiol.2017161592. Epub 2017 Jun 26. PMID: 28654337. Fallenberg EM, Dromain C, Diekmann F, et al. Contrast-enhanced spectral mammography versus MRI: Initial results in the detection of breast cancer and assessment of tumour size. *Eur Radiol* 2014;24(1):256-264.

Cocco D, ElSherif A, Wright MD, Dempster MS, Kruse ML, Li H, Valente SA. Invasive Lobular Breast Cancer: Data to Support Surgical Decision Making. *Ann Surg Oncol*. 2021 Oct;28(10):5723-5729. doi: 10.1245/s10434-021-10455-7. Epub 2021 Jul 29. PMID: 34324111.

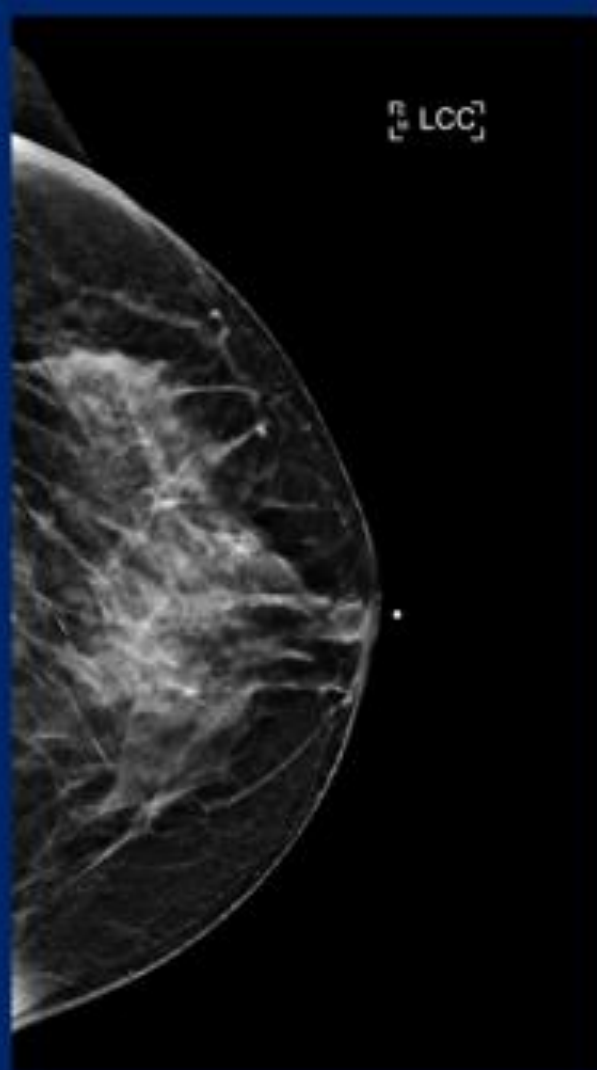
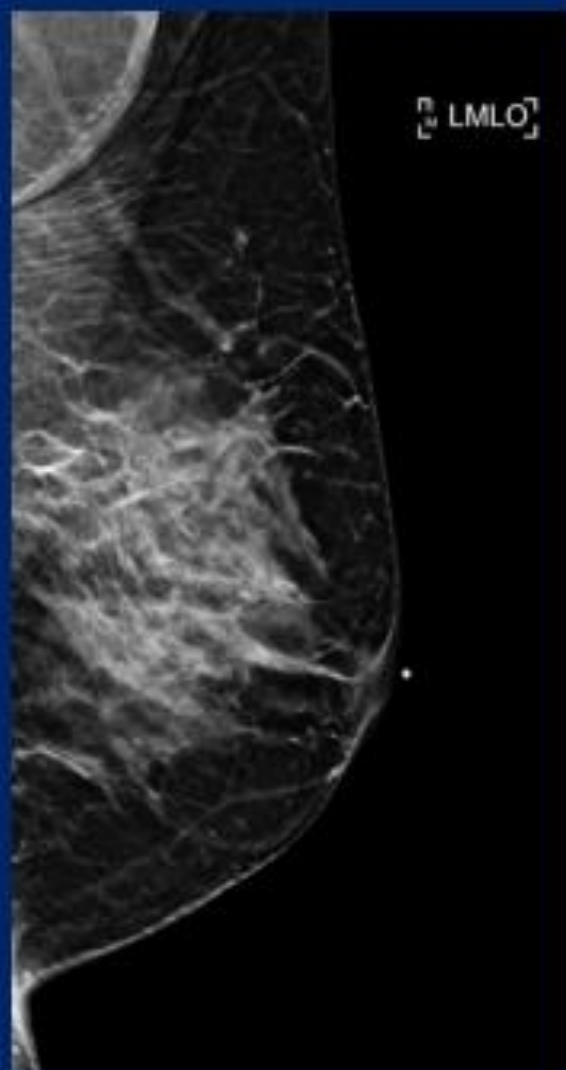
ILC: Defining extent of disease after biopsy



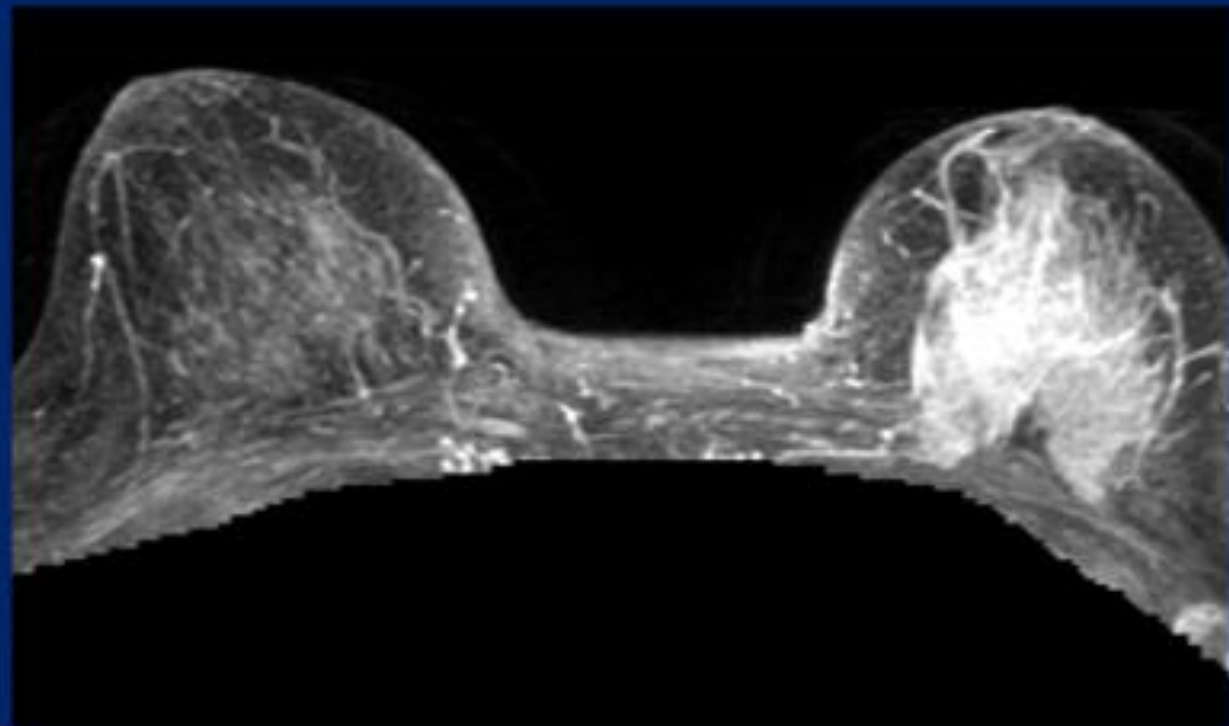
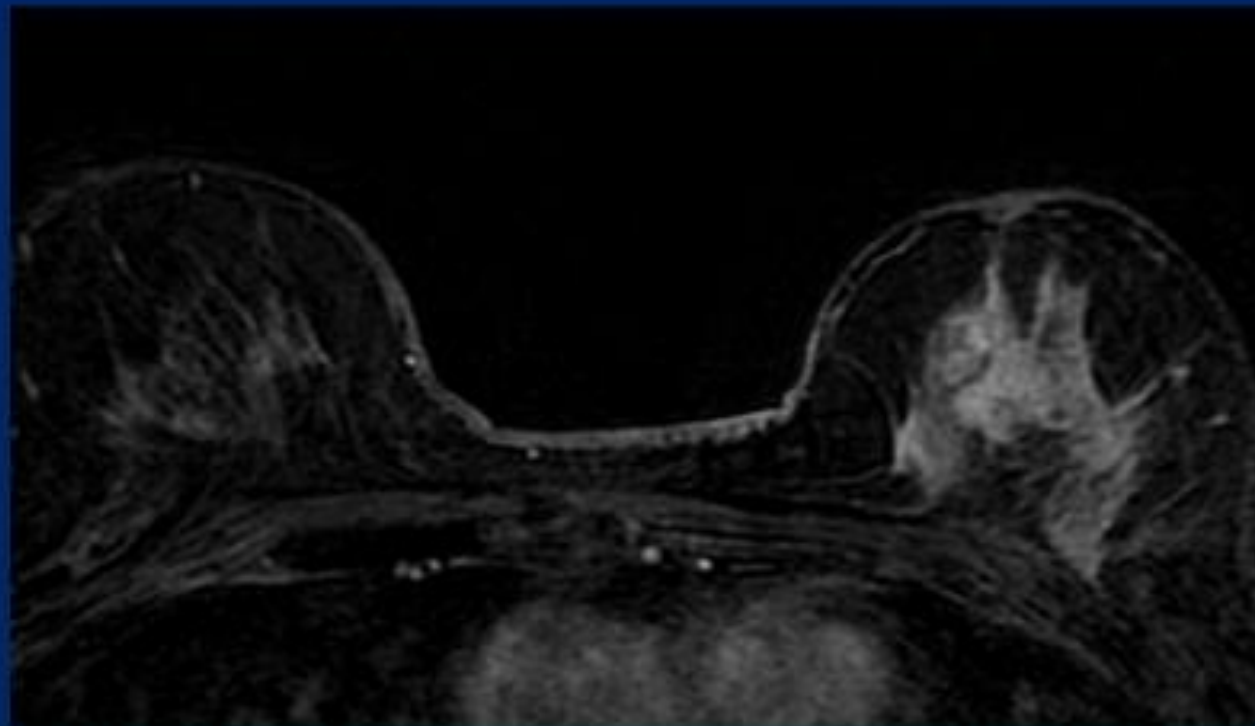
ILC: Defining extent of disease with CEM



ILC: Defining extent of disease after biopsy



ILC: Defining extent of disease with MRI



Invasive Lobular Carcinoma: Detection and Surveillance

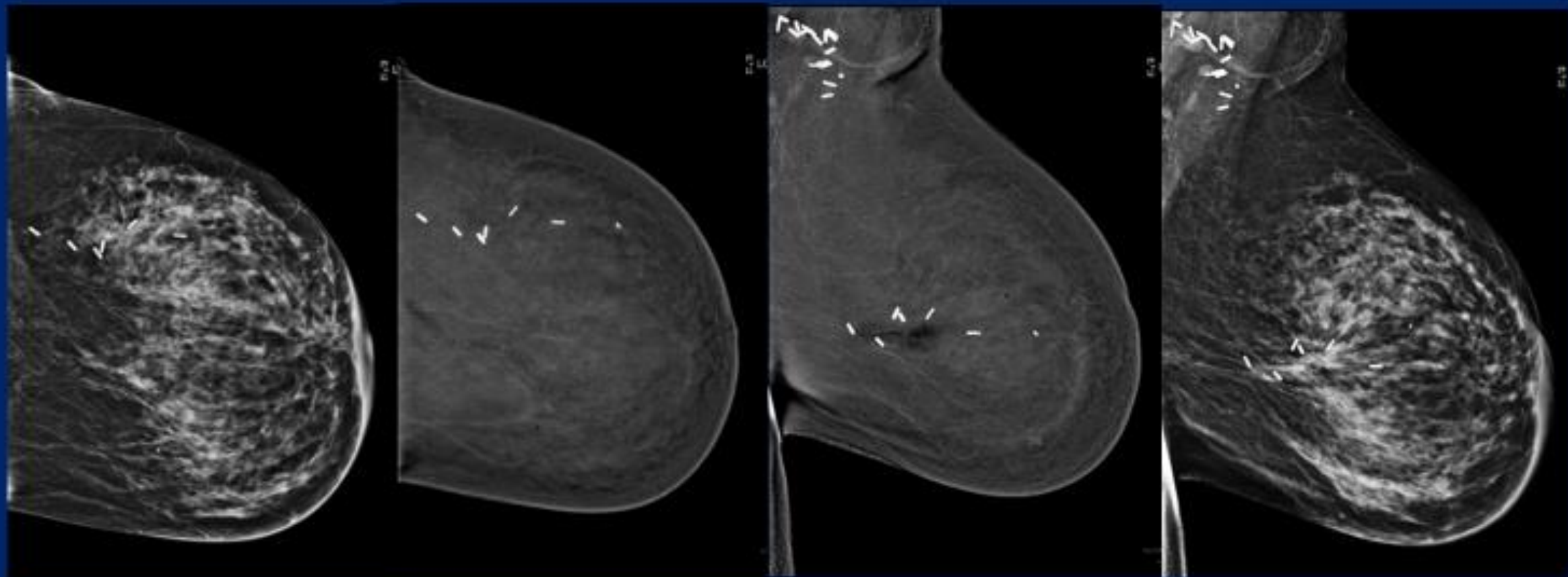
- Invasive Lobular Carcinoma – Brief Overview
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- **Surveillance**
- Looking into the future

ILC Surveillance

- Surveillance in women with a history of ILC
- Consider:
 - 3D Mammogram (DBT)
 - US
 - CEM
 - MRI with and without contrast

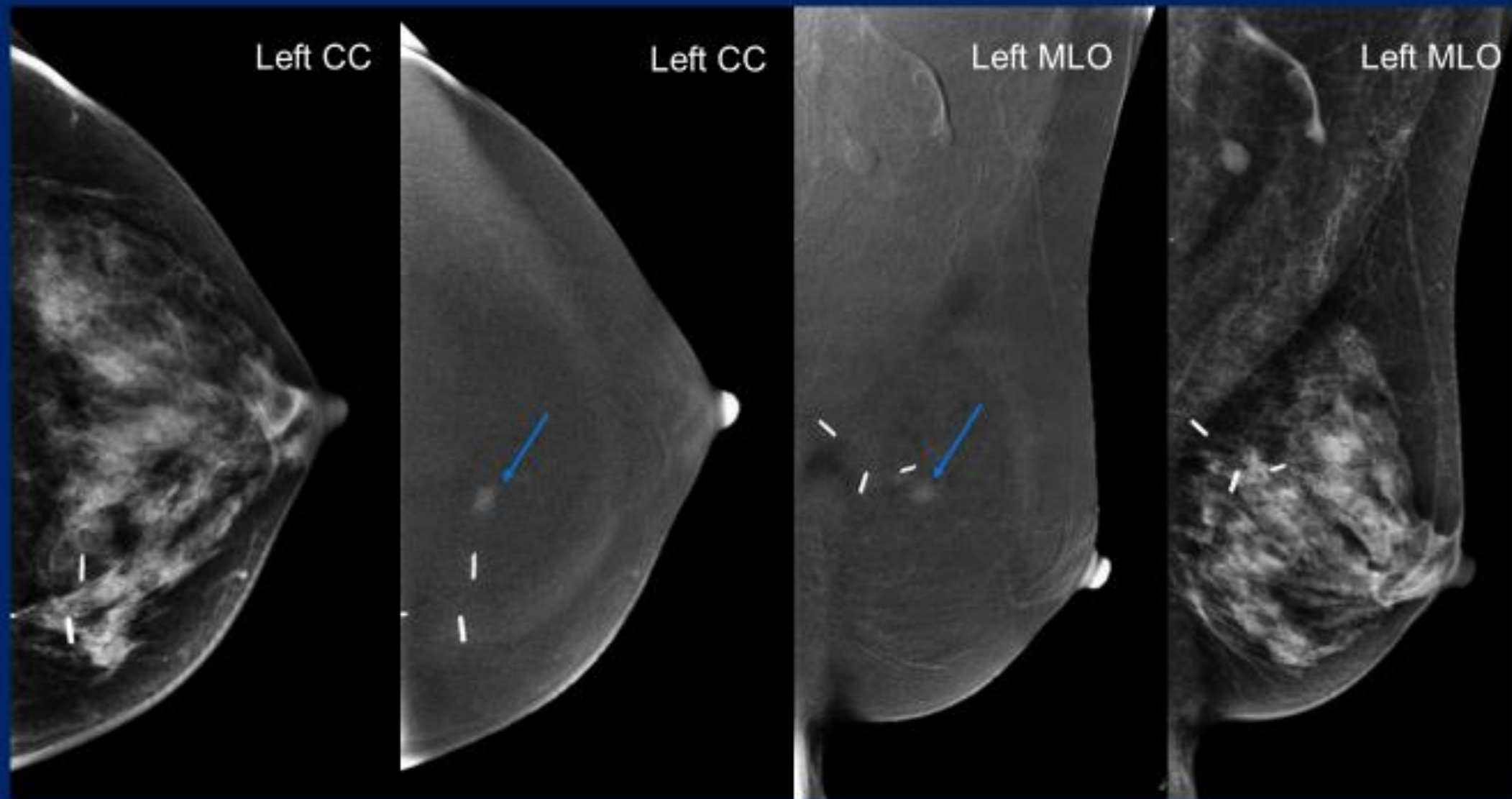
Surveillance:

Contrast Enhanced Mammography

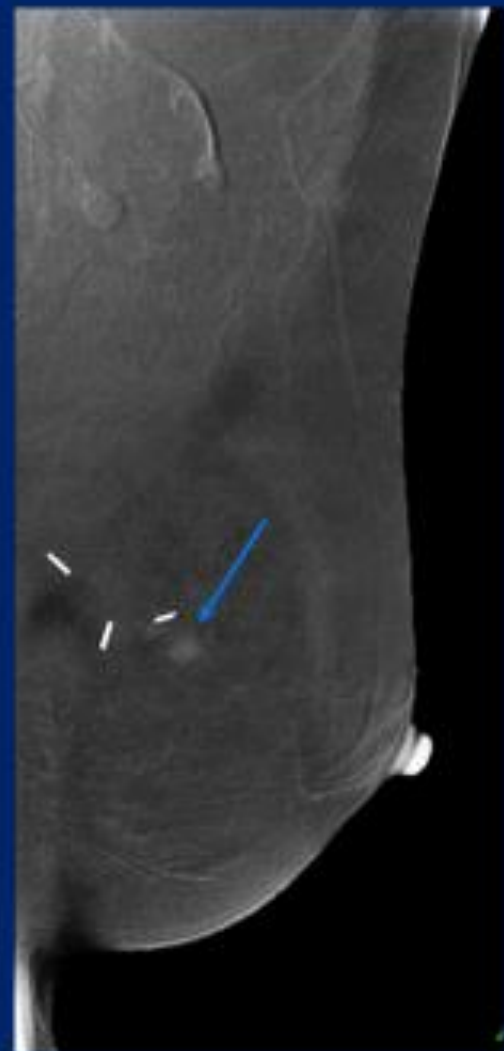
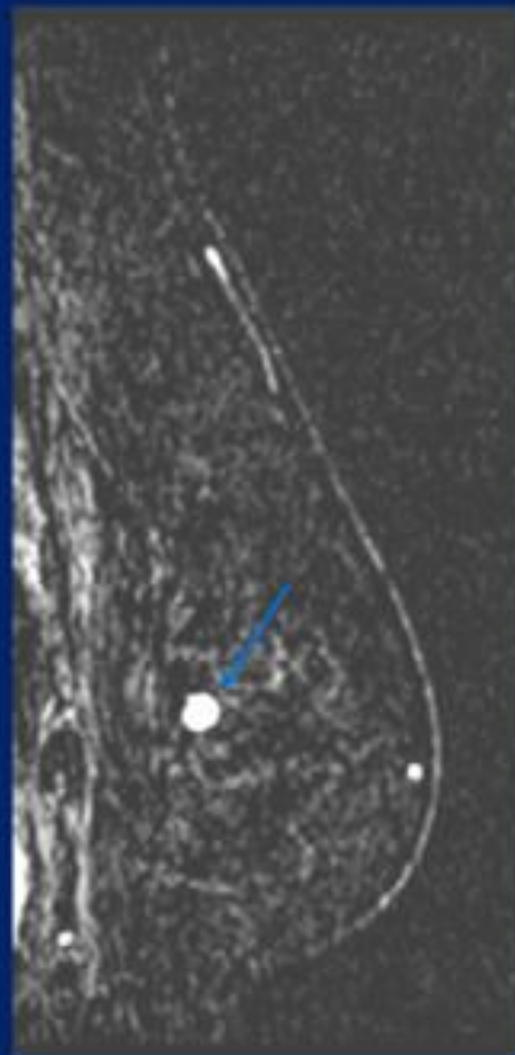
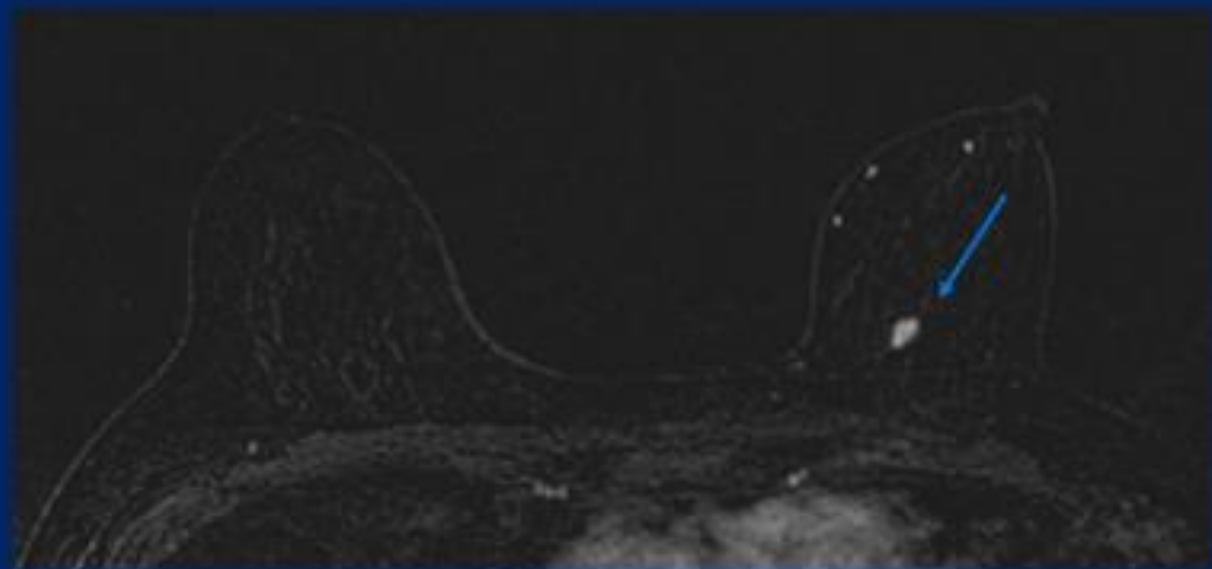


- CEM has a higher cancer detection rate than 2D mammograms

Screening CEM after lumpectomy



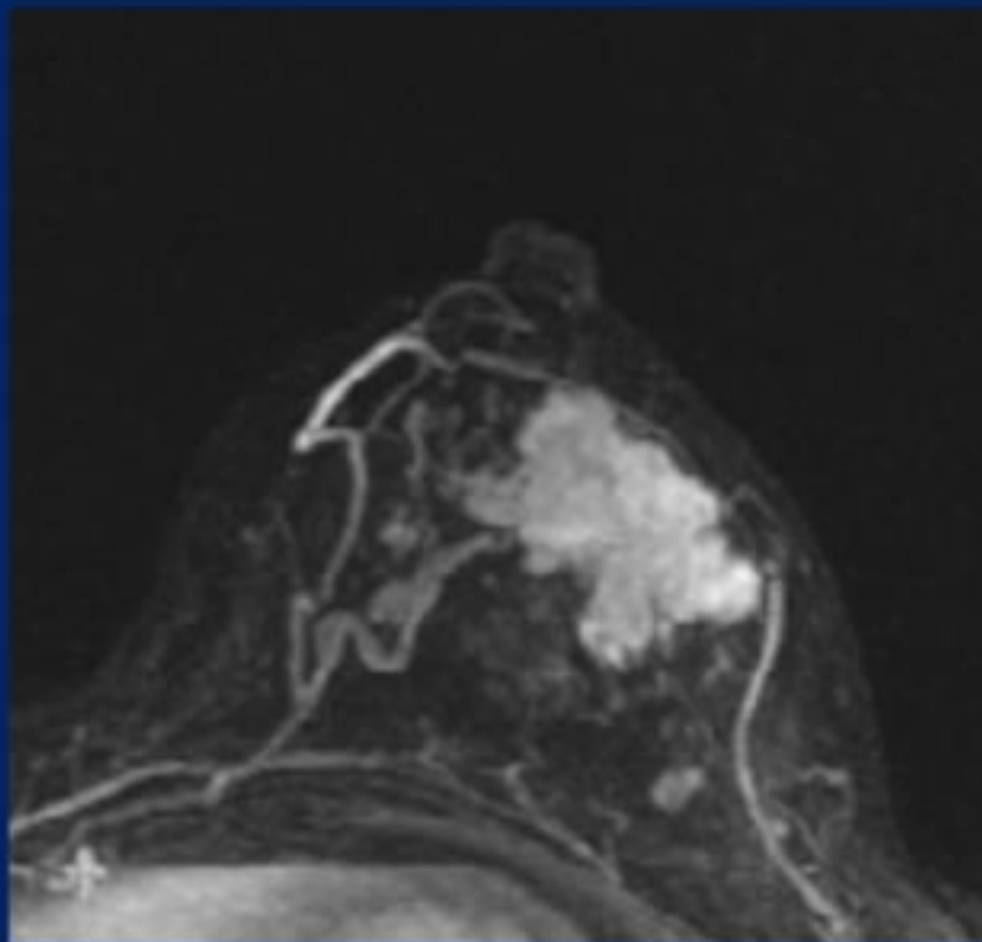
Screening CEM after lumpectomy



Surveillance:

Breast MRI with and without contrast

- Improves the detection of early-stage but biologically aggressive tumors in patients diagnosed at 50 years or younger



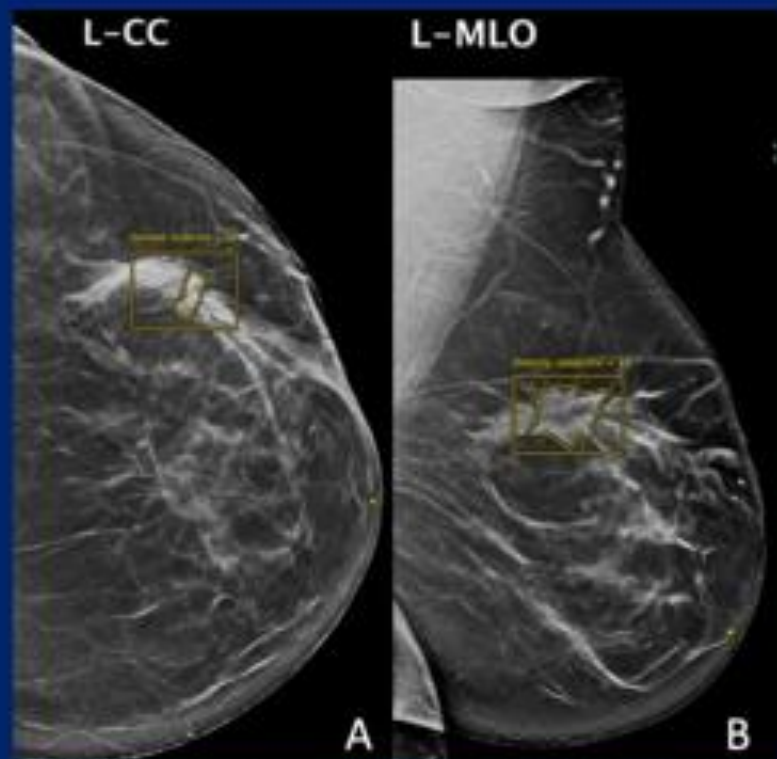
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Detection, Diagnosis & Surveillance

Looking into the future

A Role for Artificial Intelligence



Amir T, Coffey K, Sevilimedu V, Fardanesh R, Mango VL. A role for breast ultrasound Artificial intelligence decision support in the evaluation of small invasive lobular carcinomas. Clin Imaging. 2023

Arce S, et al. Evaluation of an Artificial Intelligence System for Detection of Invasive Lobular Carcinoma on Digital Mammography. Cureus. 2023 May

Invasive Lobular Carcinoma: Detection and Surveillance

- Take home points
 - ILC is not a rare cancer
 - ILC can be inconspicuous and present with variable appearance
 - 3D Mammography, US, CEM, and MRI are tools we can consider, depending upon a person's personal risk profile

Thank you

- Thank you, Laurie Hutcheson, and LBCA
- Acknowledgements:
- Dr. Maxine Jochelson and Dr. Victoria Mango

Surgery for Lobular Breast Cancer in 2023

Lobular Breast Cancer Alliance Webinar
September 12th, 2023

Anita Mamtani, MD, FACS
Breast Service, Department of Surgery
Memorial Sloan Kettering Cancer Center



Disclosures

None

Treatment Approach

- Initial evaluation
 - History
 - Physical exam
 - Imaging
 - Pathology: lobular history, receptor subtype
- Not all patients and not all breast cancers are the same
- **Precision medicine**: integrating information about the cancer, the patient, to create an individualized plan

Treatment Approach

- Timeline
 - **“Upfront” surgery** (surgery first)
 - Early-stage cancers
 - **“Neoadjuvant” approach** (medicine first, surgery later)
 - More advanced cancers (larger tumors, known to have positive lymph nodes, etc.)
 - Certain subtypes of cancer (HER2+, TN: relatively uncommon in ILC)

Surgery in ILC

- Similar fundamentals as other breast cancer
 - Breast
 - Axilla

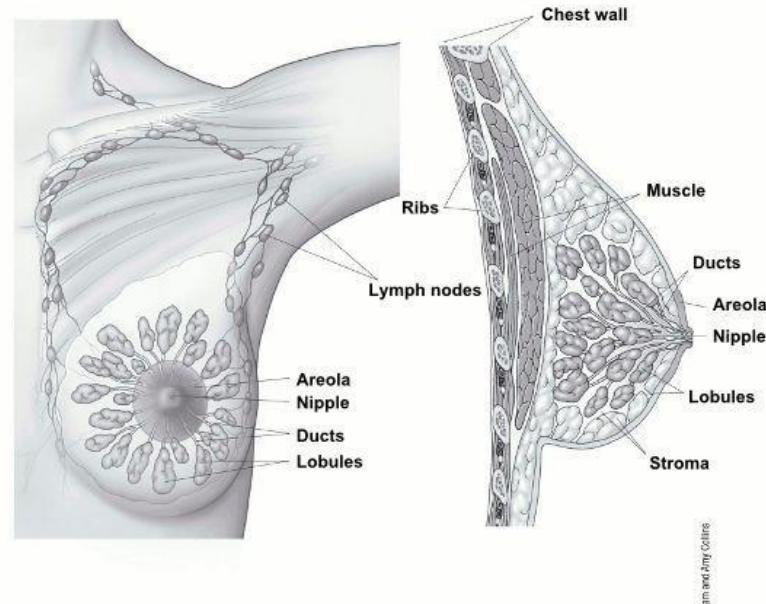
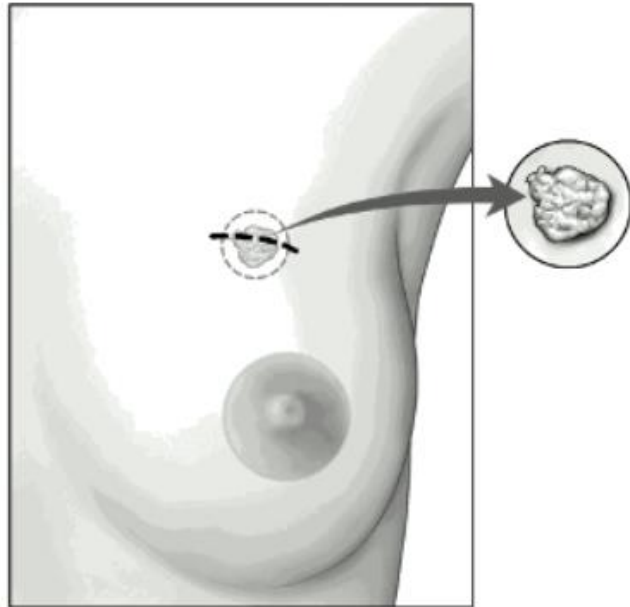


Illustration courtesy of American Cancer Society

Surgery in ILC: Breast

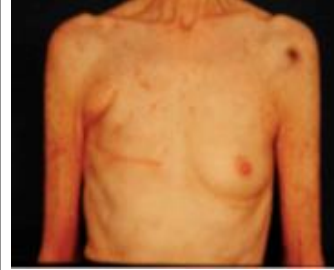
- 2 options:
 - Breast-conserving surgery (“lumpectomy”)
 - Mastectomy

Lumpectomy

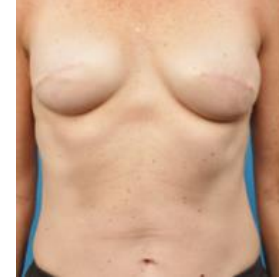


The tumor is removed with a rim of normal breast tissue.

Total mastectomy - no reconstruction



Skin Sparing Mastectomy + reconstruction

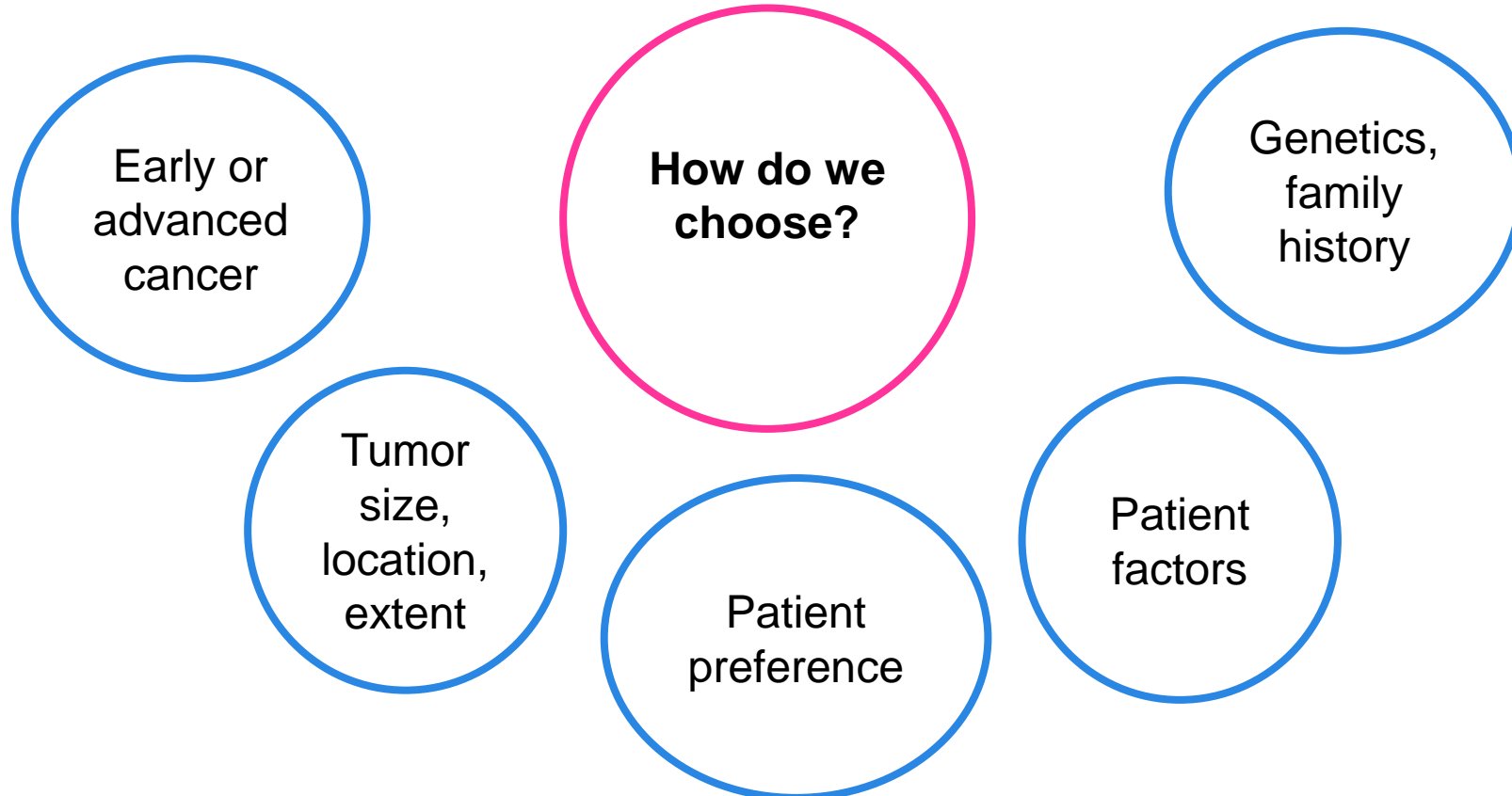


Nipple Sparing Mastectomy + reconstruction



Surgery in ILC: Breast

- 2 options:
 - Breast-conserving surgery (“lumpectomy”)
 - Mastectomy



Surgery in ILC: Breast

- 2 options:
 - Breast-conserving surgery (“lumpectomy”)
 - Mastectomy
- **Survival** after BCT (lumpectomy + radiation) is equivalent to survival after mastectomy for **early-stage** breast cancers.
- Multiple randomized trials with **>25 years** of follow-up
- 10-year local recurrence rates of **<10%** with adjuvant therapy

Surgery in ILC: Breast

- **Do lumpectomy and mastectomy result in equivalent survival for patients with ILC as well?**
- **Yes:** if negative margins are achieved.
 - Small studies including early ILC-only population
N = 235 (treated from 1983-1987)
Lumpectomy + RT vs. mastectomy
15-year follow-up
No difference in breast cancer specific survival
- Subsequently validated

Surgery in ILC: Breast

- **Are positive margins more frequent in ILC patients who undergo lumpectomy? Is mastectomy required more frequently in ILC?**
- **Mixed findings**
 - Some studies: no difference (Morrow *Cancer*, 2006)
 - Others: association with positive margins and likelihood of reoperation (Moore *Ann Surg*, 2000; Biglia *Eur J Surg Oncol*, 2013; Arps *ASO*, 2014)
- Heavily rely on pre-operative workup (particularly imaging) to determine optimal surgical plan

Surgery in ILC: Breast

- **Are ILC patients at a higher risk of local recurrence compared to other types of breast cancer?**
- **No:** similar risk as other types of breast cancer.
 - After lumpectomy with negative margins: **3.1–5.7%**
- Factors predictive of recurrence are similar to other types:
 - Larger tumor size, heavy nodal disease burden, high grade, more aggressive receptor subtypes, omission of adjuvant therapies

Molland J *Breast*, 2004
2015

Sagara Y *Ann Surg Oncol*, 2015

Braunstein L *Breast Cancer Res Treat*,

Rothschild H, *Ann Surg Oncol*, 2023

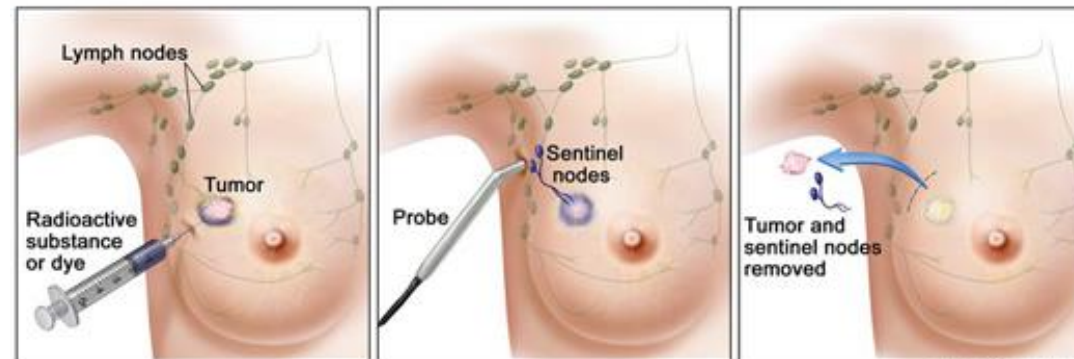
Surgery in ILC: Breast

- **Can ILC patients have breast reconstruction?**
- **Yes:** no differences in reconstructive options
 - Implant-based
 - Autologous

Surgery in ILC: Axilla

- 2 options:
 - Sentinel lymph node biopsy (SLNB)
 - Axillary lymph node dissection (ALND)
 - None* (select patients: age >70 with stage I HR+/HER2- tumor, significant comorbidities)

SLNB



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Surgery in ILC: Axilla

- Do ILC patients more often have lymph node involvement?
- **Mixed findings**
 - Some studies: no difference (Wasif *ASO*, 2010)
 - Others: increased likelihood of positive lymph nodes (Vandorpe *Breast Cancer Res Treat*, 2011)

Surgery in ILC: Axilla

- Do ILC patients more often need ALND?
- **No**
 - SLNB is equally feasible in ILC as compared to other breast cancer types
 - SLNB provides equivalent axillary control in ILC patients with negative sentinel nodes
 - Even if positive nodes: lobular histology **does not** predict need for ALND

Surgery in ILC: Summary

- The fundamentals of surgical management of ILC remain very similar to other breast cancer types
- Breast cancer detection and treatment continues to evolve
- Tailoring our medical treatments is the next frontier: tumor biology is **key**
- Ultimate goals:

Individually tailor treatment
Decrease the morbidity of surgery
Achieve excellent cancer outcomes
Improve quality of life

Thank you



Invasive Lobular Breast Cancer: Current treatment and future directions

Rinath Jeselsohn MD
Director for ER+ Translational
and Discovery Research

Breast Oncology Center
Dana Farber Cancer Institute

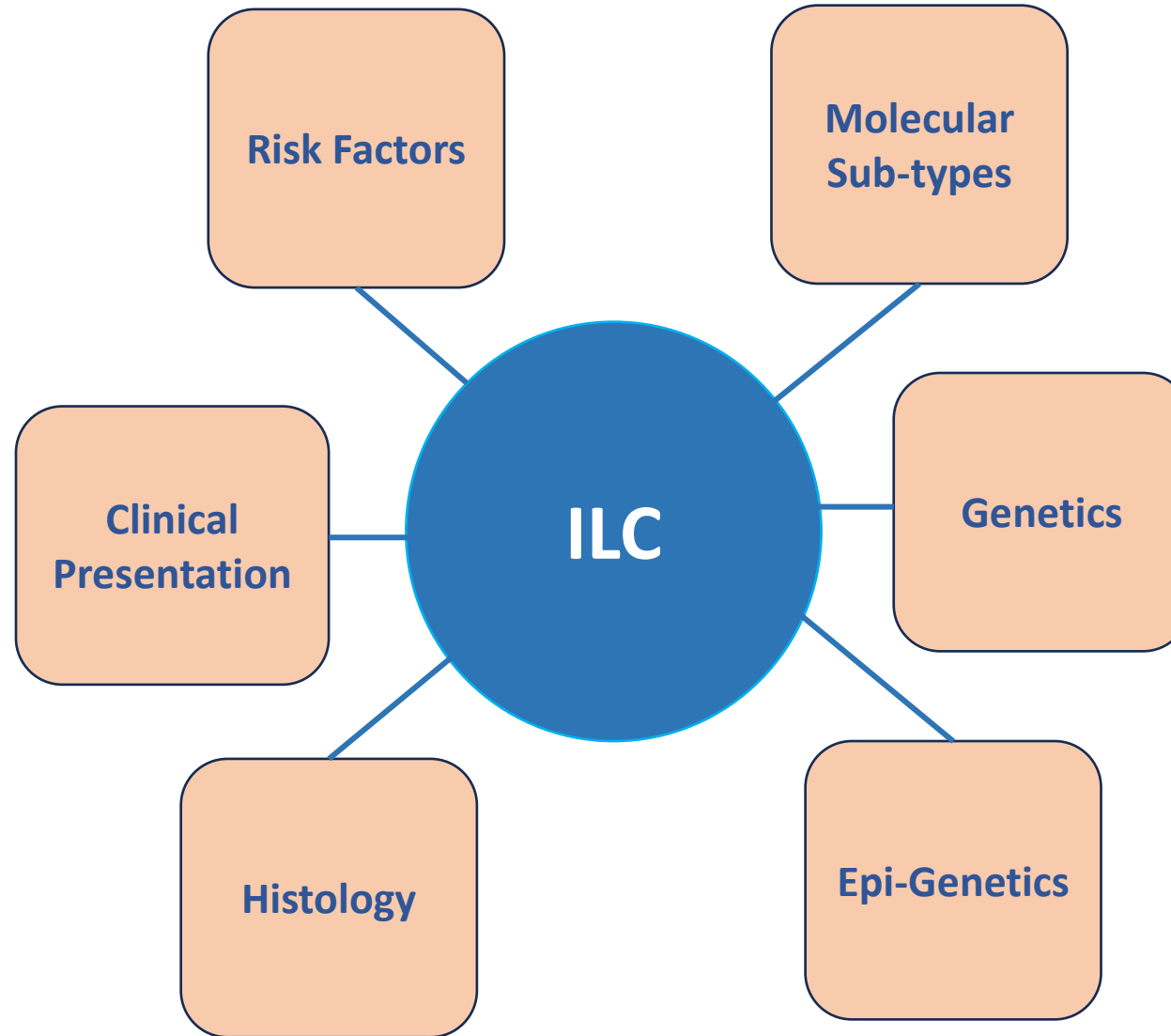


Incidence of Invasive Lobular Breast Cancer (ILC)

- ILC is the second most common histological type of breast cancer after invasive cancer of no special type (NST)[#].
- Approximately 15% of all breast cancers.
- The incidence of ILC has increased over the past 2 decades.

#Invasive ductal cancer

ILC is a unique Breast Cancer



Risk factors that are more strongly associated with ILC compared to NST (Nurses Health Study)

- Age at 1st menstrual period
- Age at first birth
- Post-menopausal hormone use

(No differences in associations with age, parity, age of menopause, family history of breast cancer or alcohol intake)

Clinical Presentation: ILC vs NST

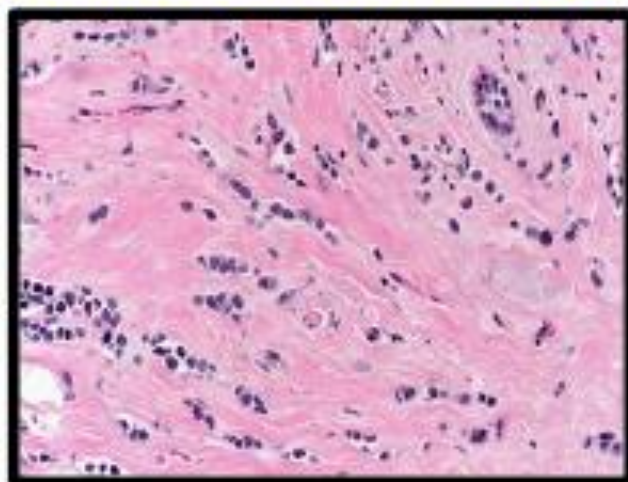
- Average age at diagnosis of ILC is mildly higher compared to NST (61 vs 57 yrs).
- Presents more often with larger tumors² and lymph node³ involvement (more frequently classified as Stage III and IV; 20.7% vs 10.4%⁴).
- More often presents as multi-focal.
- Difficult to detect by MMG.

²Pestalozzi BC, JCO 2008, ⁴Oestrerreich S, JNCI 2022

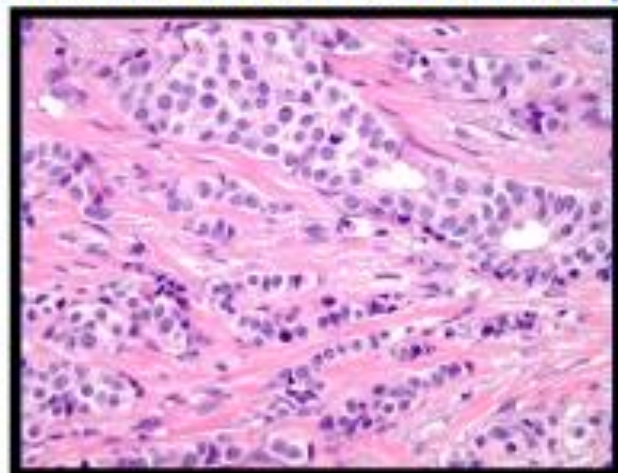
ILC Unique Histology

- Unique histology of non-cohesive cells with a single file pattern.

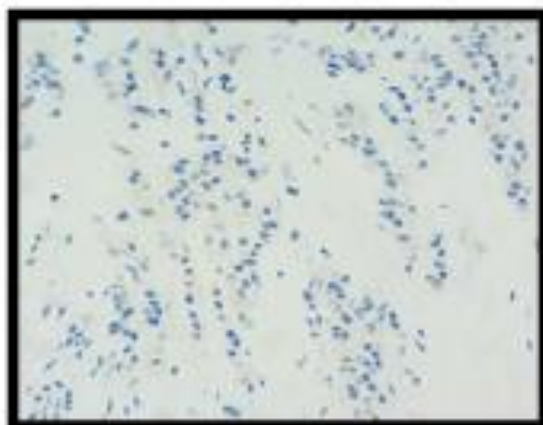
Invasive lobular breast cancer



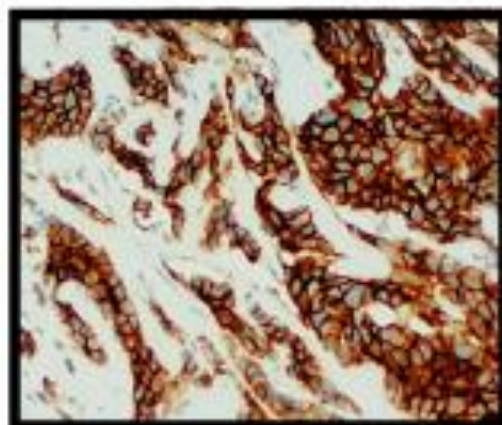
Invasive ductal breast cancer (NST)



- Loss of the the cell adhesion protein E-cadherin is a hallmark of ILC (E-cadherin is absent in ~90% of all ILCs).



Invasive lobular breast cancer-negative for E-cadherin

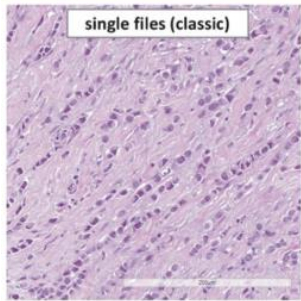


Invasive lobular breast cancer-positive for E-cadherin

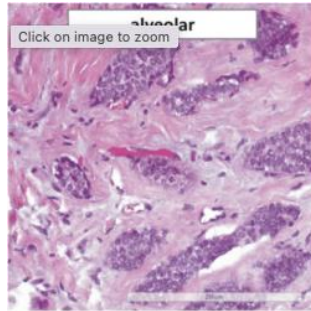
ILC has several histological variants

High grade/ high proliferation
Worse prognosis

Classic
(56%)

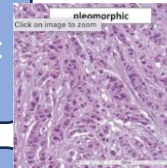


Alveolar
(15%)

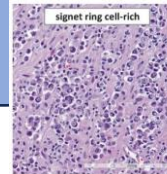


Mixed,
Non-classical
(15%)

pleomorphic

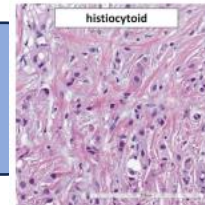


Signet ring
cells

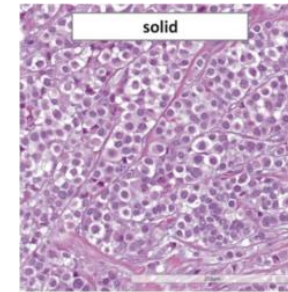


Apocrine

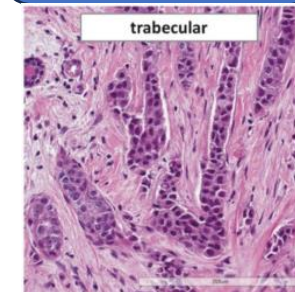
Histiocytoid



Solid
(10%)



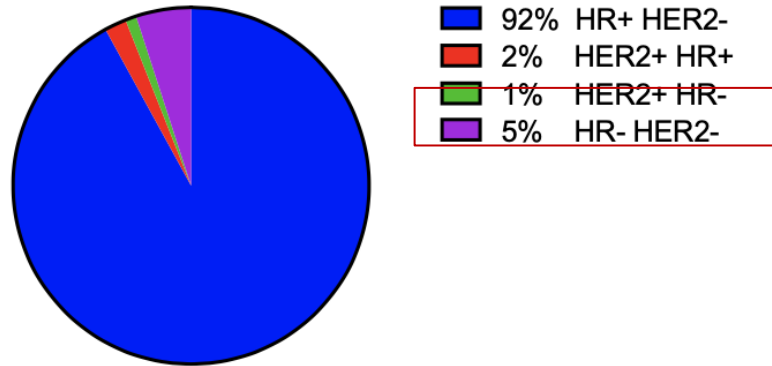
Trabecular
(4%)



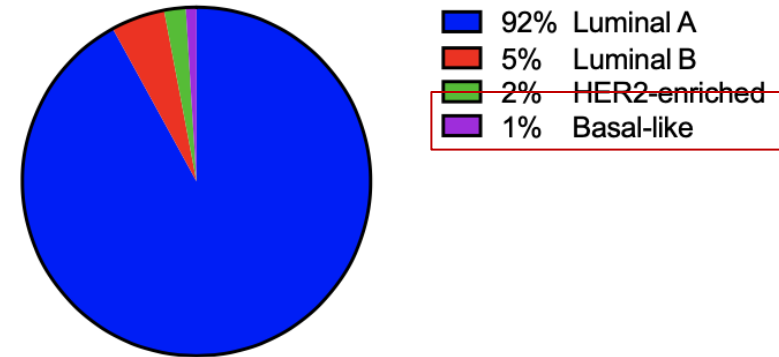
Most studies do not differentiate between the variants, even though they have very different outcomes

Molecular Subtypes in ILC

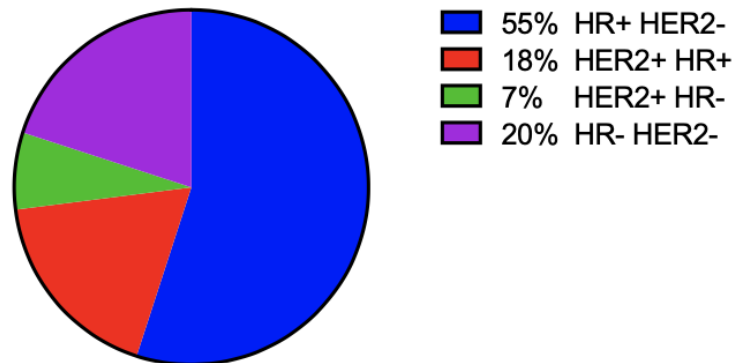
ILC subtypes by IHC



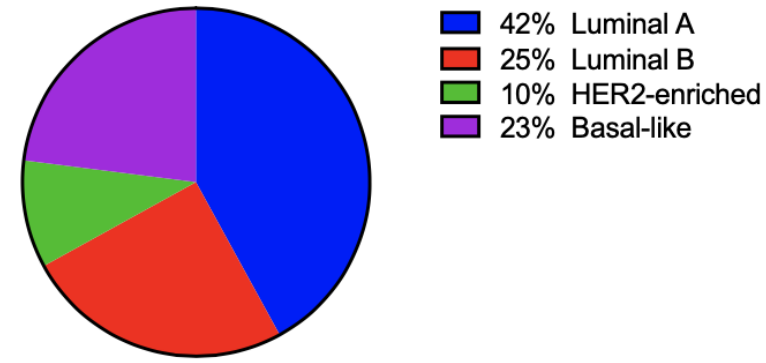
ILC intrinsic subtype by PAM50



IDC subtypes by IHC

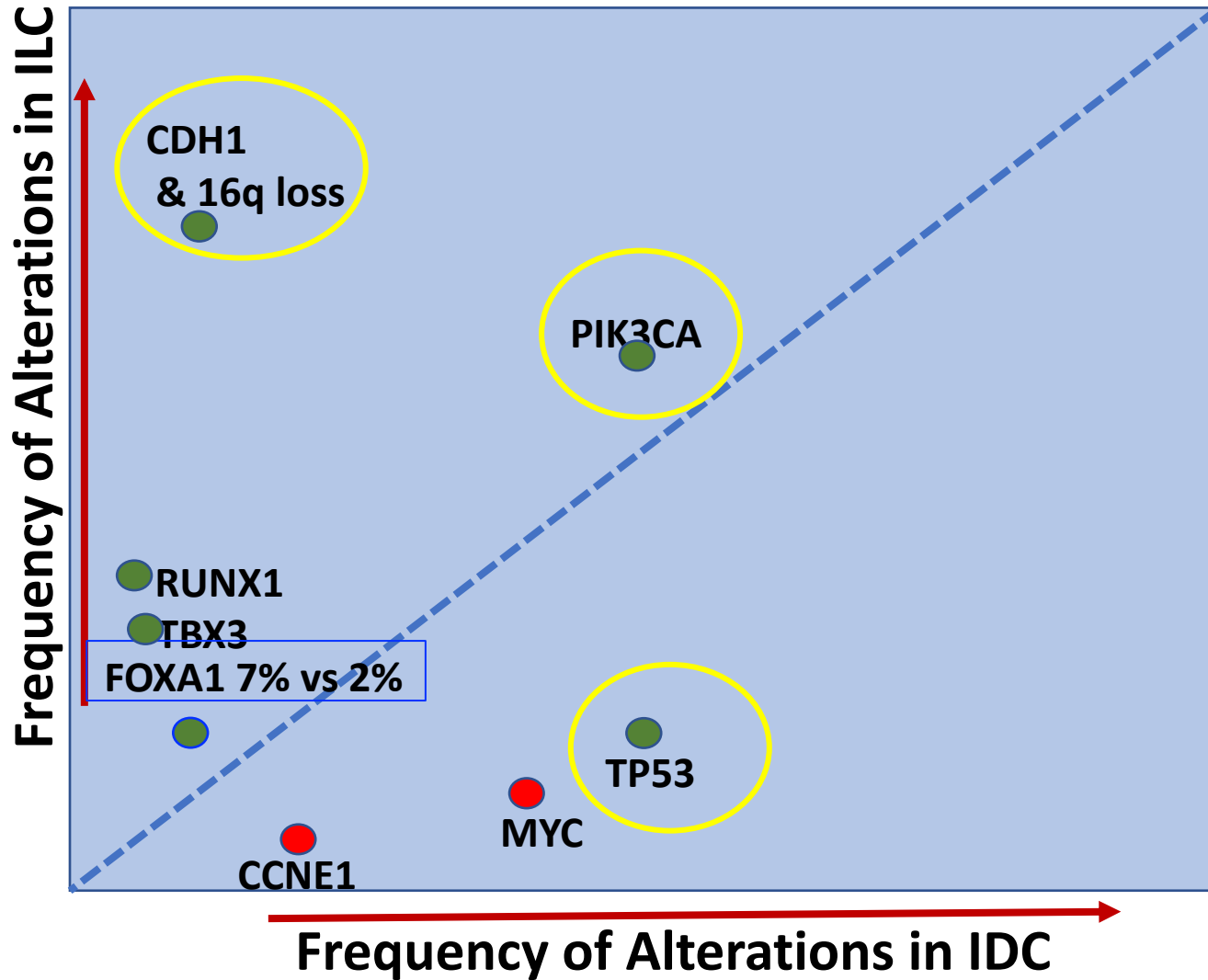


IDC intrinsic subtype by PAM50



Mouabbi J, Breast Cancer Research and Treat, 2022, Williams LA, CCC 2019

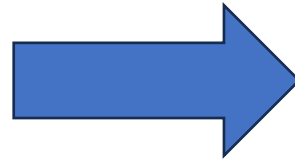
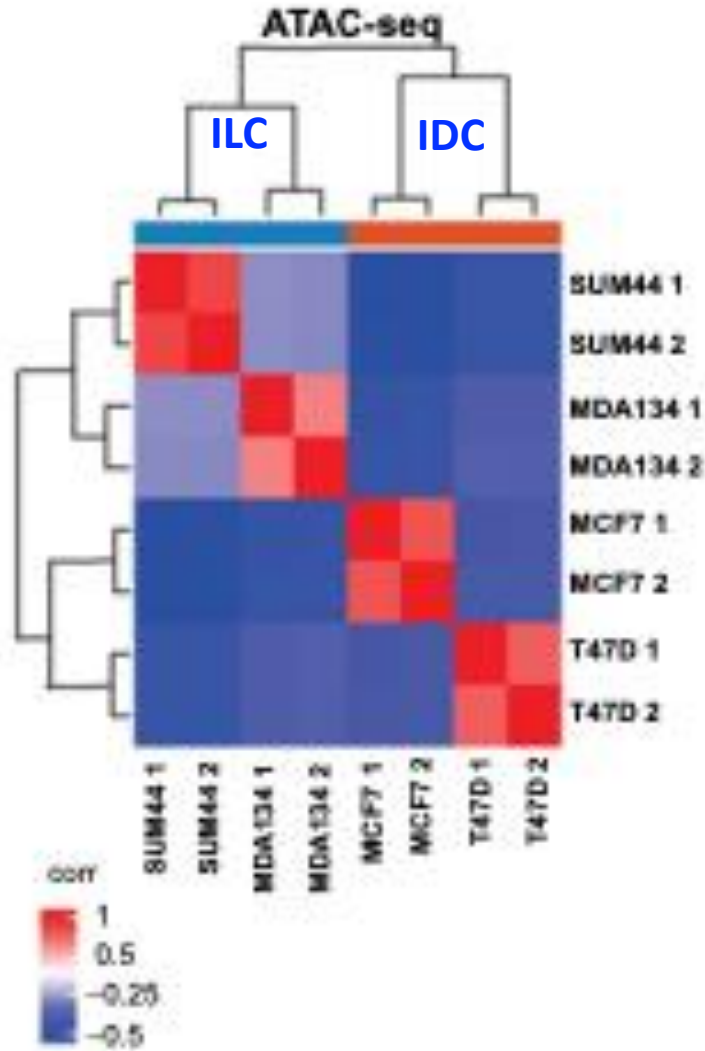
Unique Genetic Landscape of ILC



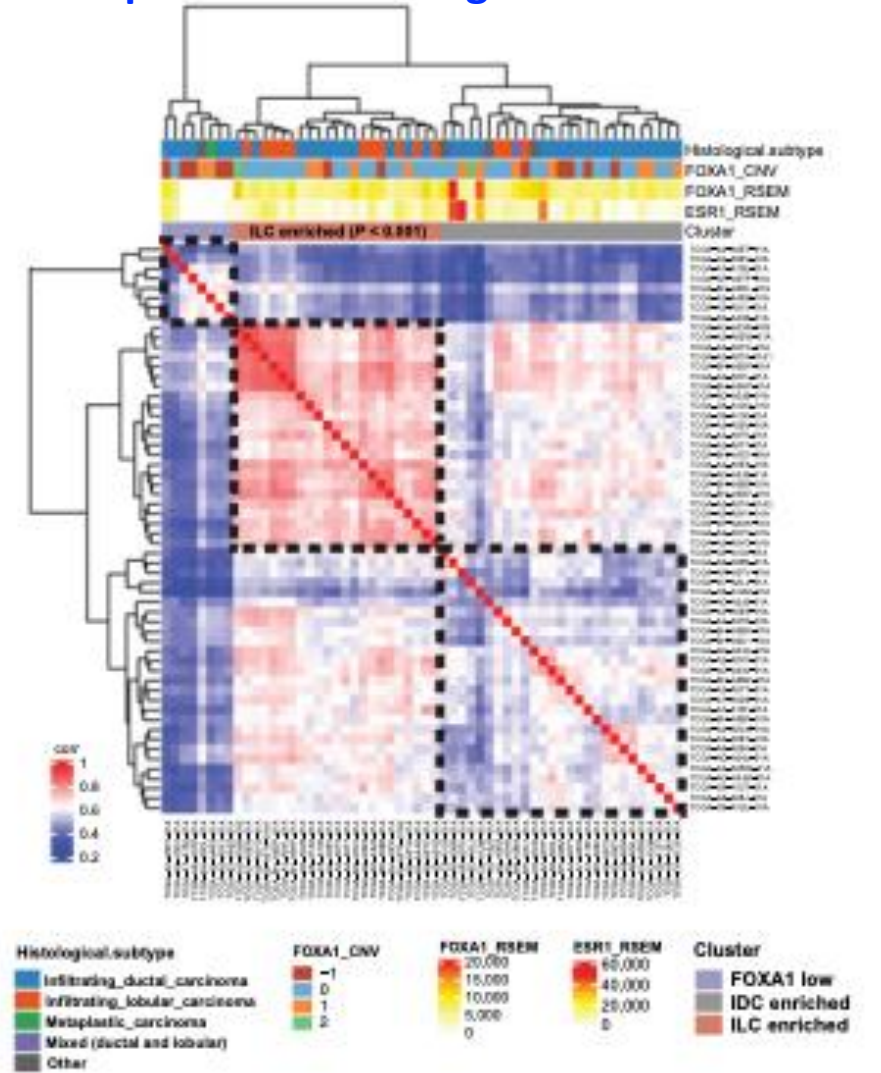
Ciriello G, Cell 2015,
Desmedt C, JCO 2016
Michaut M, Scientific Reports 2016

ILC has a Unique Chromatin state driven by FOXA1

Cell line studies



Primary Breast Cancers (TCGA cohort)
Unique FOXA1 binding sites enrich for ILC



Treatment in Early Stage ILC

- Currently there are no specific guidelines for the systemic treatment of ILC
- Treatment includes +/- neo/ adjuvant chemotherapy and endocrine therapies.
- Decisions regarding chemotherapy in early-stage ER+ BC are made based on molecular risk (grade, molecular stratification tools) and tumor burden (size/number of positive lymph nodes, menopausal status).

Do patients with early-stage ILC benefit from chemotherapy?

Neoadjuvant Chemotherapy is less effective in Early Stage ILC compared to IDC

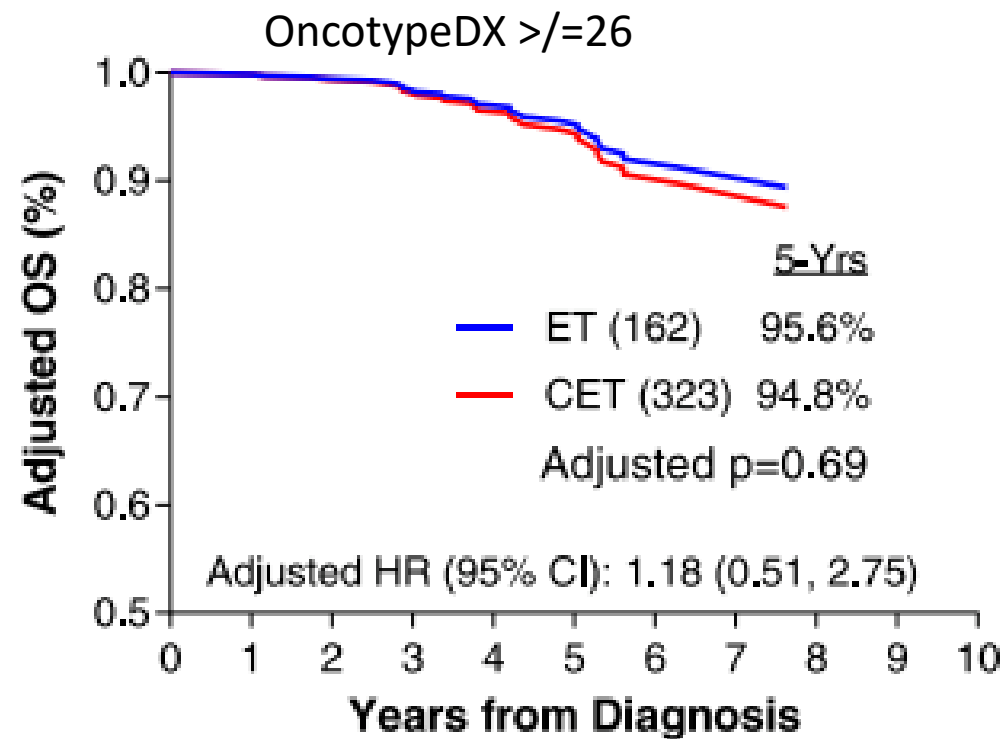
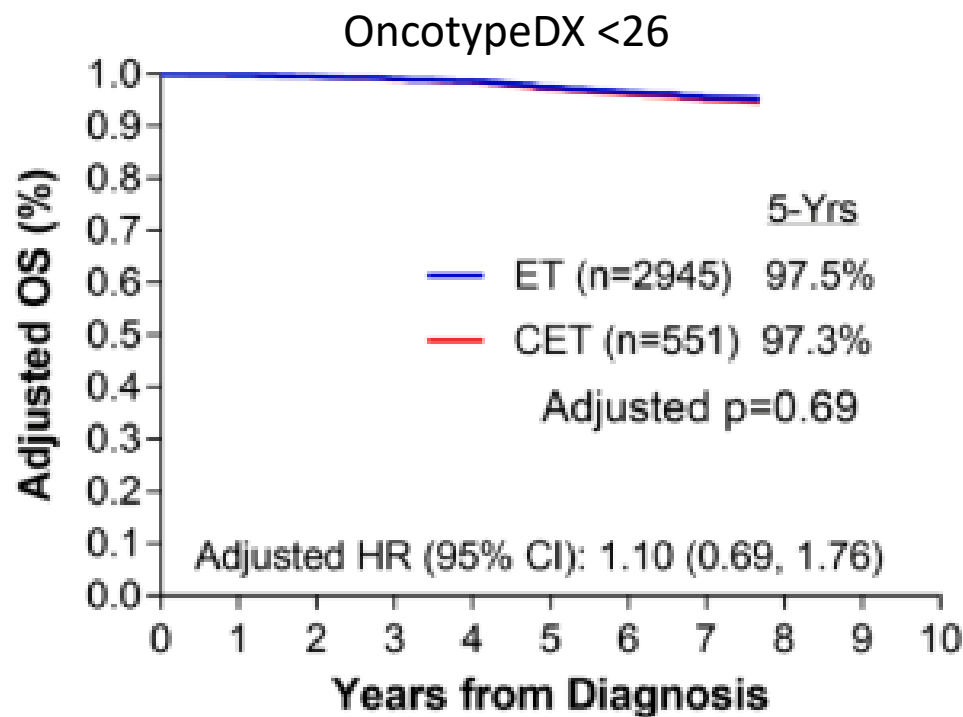
STUDY / Number of Patients	Treatment	Outcomes		
		outcome	IDC(%)	ILC (%)
Cocquyt, 2003 (prospective) IDC N=102 ILC N=26	CMF or CAF	BCS	50%	38%
		pCR	15%	0%
		PFS (5yrs)	67%	81%
		OS (5yrs)	79%	85%
Cristofanilli, 2005 (retrospective) IDC N=908 ILC N=122	All had A ,or A+T	pCR	15%	3%
		RFS (5yrs)	66%	87%
		OS (5yrs)	70%	93%
Tubiana-Hulin, 2006 (retrospective) IDC N=742 ILC N=118	A or A+T	BCS	48%	30%
		pCR	9%	1%
		RFS (5 yrs)	60.8%	76.1
		OS (5yrs)	79.3%	91.7%
Delpech, 2013 (retrospective) IDC N=1718 ILC N=177	A+T, A alone, or T alone	BCS	34%	19%
		pCR	14%	3%

*Limitations:
 -Mostly Retrospective
 -Lacking molecular classification data
 -Late Recurrence data lacking

The role of adjuvant chemotherapy in early stage ILC

Study/ Number of patients	Treatment		10 YR OS				
		IDC	ILC	IDC		ILC	
Truin W, 2012 IDC N=19,603 ILC N=3,685	Chemo -> ET	8,171	1,515	74%	Multi-variate HR=0.7 (95% CI 0.64-0.76) p <0.0001	66%	Multi-variate HR= 1.00 (95% CI 0.7-1.34) p=0.83
	ET	11,438	2,170	69%		68%	
Marmor S, 2017 IDC N=32,149 ILC N= 4,095	Chemo -> ET	11,281	1,347	93%	Multi-variate HR=0.82 (95% CI 0.73-0.92) p=0.0004	92%	Multi-variate HR= 1.18 (95% CI 0.9-1.54) p=0.21
	ET	21,323	2,748	95%		93%	

No benefit to the addition of adjuvant chemotherapy in ILC tumors with an OncotypeDX RS of ≥ 26 (National Cancer Database 2010-2016)



Yaghi M, Ca Treat and Res Com, 2023

Evidence for Benefit from Adjuvant Chemotherapy in patients with high risk ILC

N= 2318 patient with ILC, ET alone =1485, ET+chemo=823
15 academic French cancer centers between 1990-2014

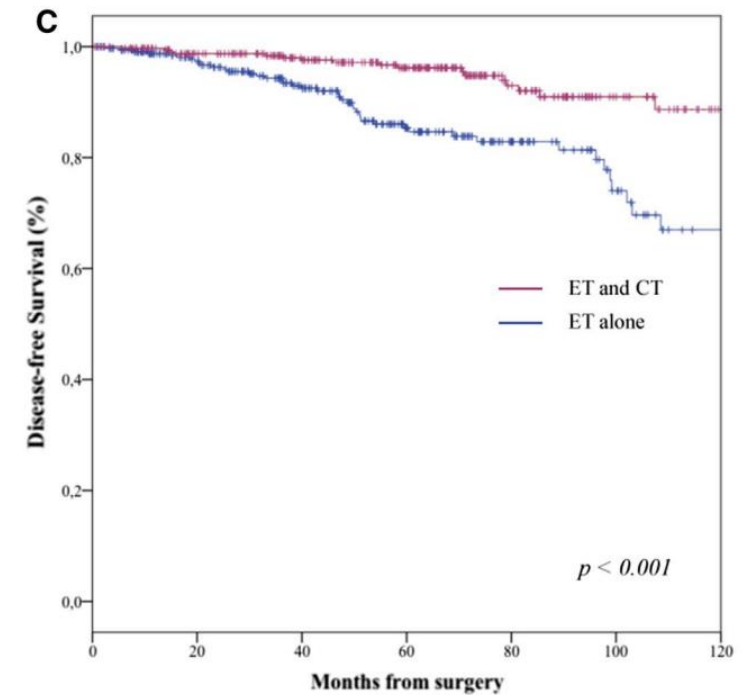
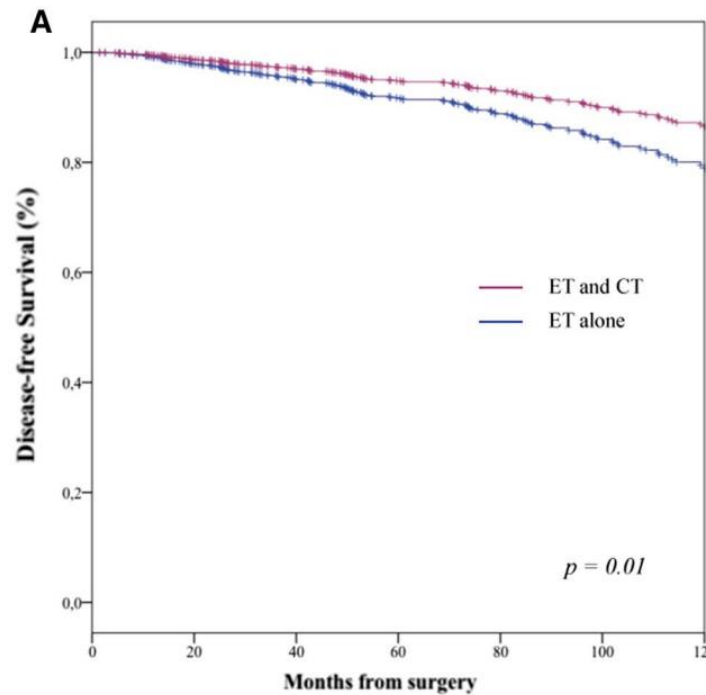
Factors associated with decreased DFS and OS:

- Age
- Tumor size
- Nodal status
- LVI
- grade

	DFS			p values	OS			p values
	OR	[95% CI]			OR	[95% CI]		
		Min	Max			Min	Max	
Age	1.46	1.21	1.76	<0.001	1.63	1.27	2.09	<0.001
Tumor size	1.88	1.36	2.59	<0.001	2.24	1.44	3.49	<0.001
Nodal status	1.40	1.22	1.59	<0.001	1.66	1.38	2.00	<0.001
LVI	1.69	1.21	2.35	<0.001	1.51	0.98	2.31	0.06
Grade	1.21	0.92	1.58	0.18	1.24	0.86	1.79	0.26
Surgery	1.29	0.93	1.79	0.13	1.23	0.82	1.90	0.29
Radiotherapy	1.06	0.57	1.98	0.85	0.97	0.43	2.19	0.95
Period	0.85	0.72	1.00	0.05	0.80	0.65	0.97	0.03
Chemotherapy	0.61	0.41	0.90	0.01	0.52	0.31	0.87	0.01

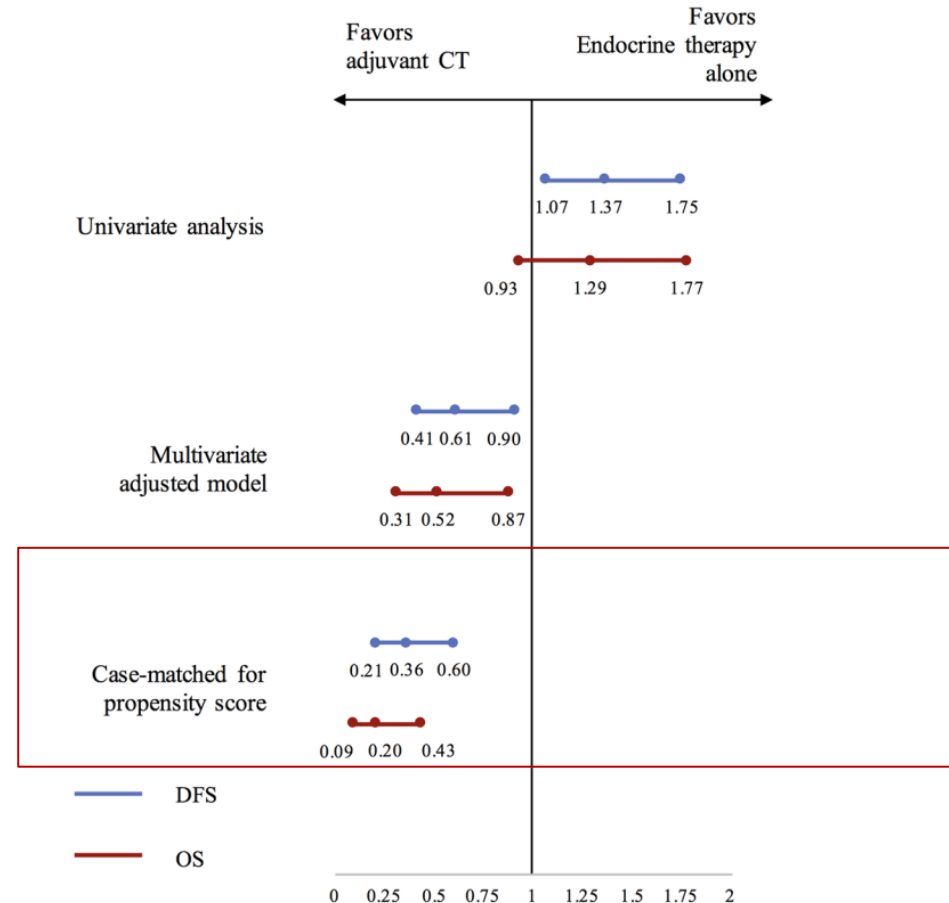
DFS disease-free survival, OS overall survival, OR odds ratio, CI confidence interval, LVI lymphovascular invasion

Multi-variate analysis



de Nonneville, Breast Ca Res and Treat 2019

Clinical factors point score identifies a subgroup of ILC patients that benefit from chemotherapy



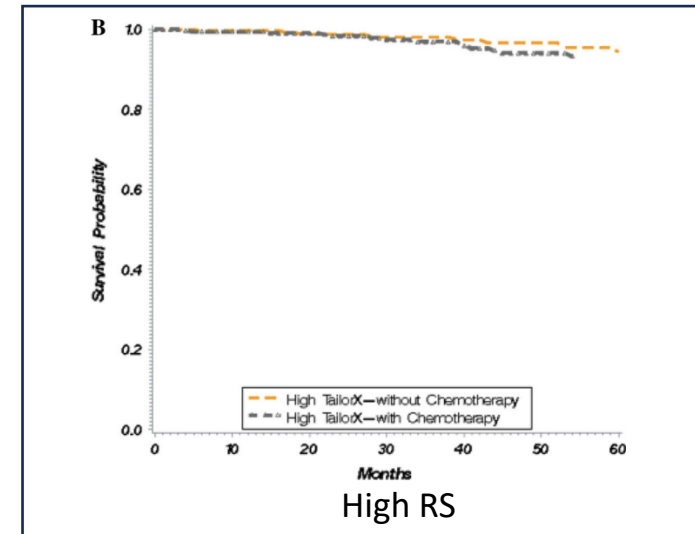
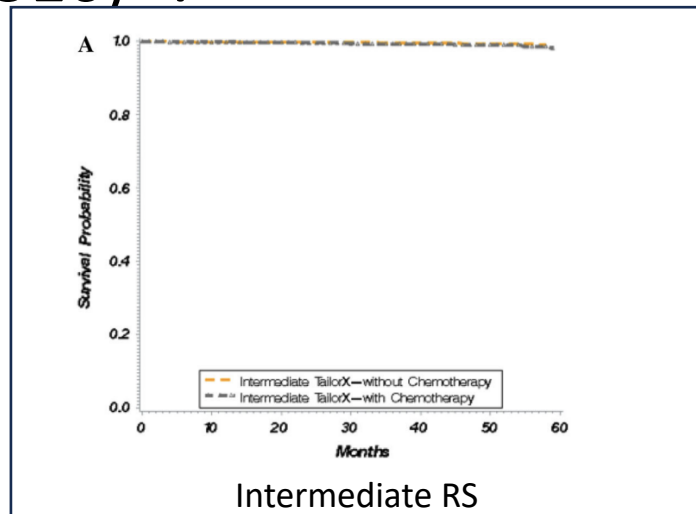
pN1 (macroscopic) 6 pts
 tumor size (>2cm) 3 pts
 LVI 2 pts

Low risk <5
 High risk 5-11

de Nonneville, Breast Ca Res and Treat 2019

Oncotype DX RS is mostly low or intermediate in ILC and may high RS may not be prognostic or predictive of response to chemotherapy

- High RS seen ~10% of patients and mostly seen in the pleomorphic variant¹.
- No significant difference with the addition of chemotherapy to ET in ILC patients with high or intermediate RS in the SEER database (N=7316)².



- Lobsig is a gene set of 194 genes prognostic of survival in ILC³.

1. Christgen M, Cancer 2020 2. Kizy S, Breast Can Res Treat 2017 3. McArt Reed AE, NPJ Breast 2019

Endocrine therapy in ILC

- Most ILCs are ER+/ luminal A and adjuvant ET is standard of care.
- Aromatase inhibitors are superior to tamoxifen in ILC and IDC.
- Retrospective study of BIG-1-98 suggested that the magnitude of the difference between AI and tamoxifen was higher in ILC vs IDC¹. This was not confirmed in a meta-analysis from TEAM, ATAC and Big-1-98².

Is the ER axis different in ILC vs IDC?

Implications for the optimization of endocrine therapy in ILC

1. Metzger O, JCO 2015 2. Hills HK SABCS 2022

Palbociclib and Endocrine Therapy for Lobular Breast Cancer

Pre-operative study (PELOPS): Phase II neoadjuvant study

PI: Otto Metzger

[NCT02764541](https://clinicaltrials.gov/ct2/show/study/NCT02764541)

N = 180

Eligibility:

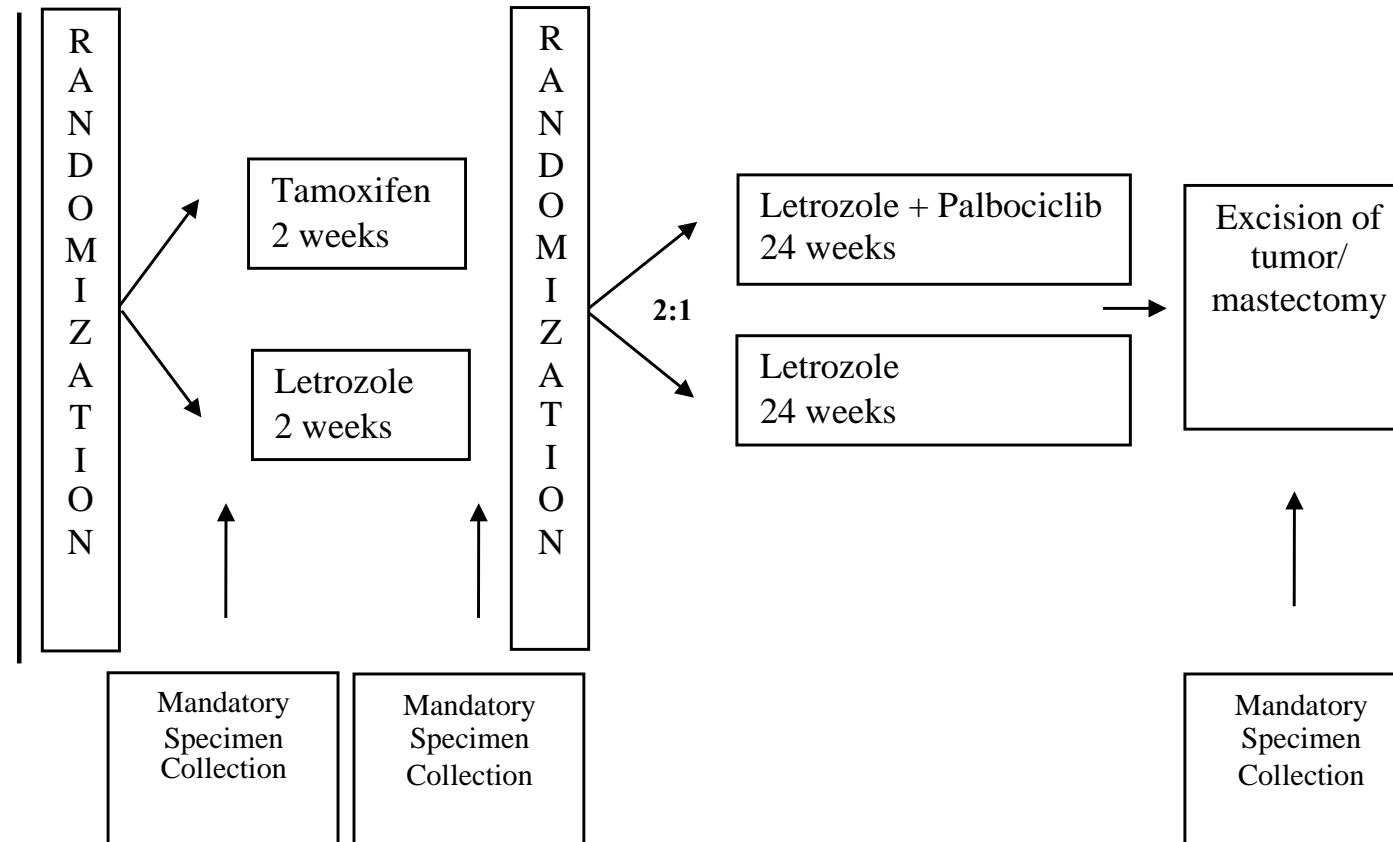
Invasive breast cancer that is:

T1 (>1.5cm only), stage II or stage III

1. ER and/or PR-positive and HER2-negative
2. Invasive ductal carcinoma or invasive lobular carcinoma

Stratification:

1. Initial lymph node status: Positive vs. Negative
2. Pre-treatment tumor size: T1-2 vs. T3



TBCRC037: NCT02206984

- Neoadjuvant study for post-menopausal women with ILC.
- Randomization to tamoxifen, anastrozole and fulvestrant x 21-24 days
- Primary endpoint: change in Ki67

E-Cadherin/ROS1 Inhibitor Synthetic Lethality in Breast Cancer

Ilirjana Bajrami^{1,2}, Rebecca Marlow³, Marieke van de Ven⁴, Rachel Brough^{1,2}, Helen N. Pemberton^{1,2}, Jessica Frankum^{1,2}, Feifei Song^{1,2}, Rumana Rafiq^{1,2}, Asha Konde^{1,2}, Dragomir B. Krastev^{1,2}, Malini Menon^{1,2}, James Campbell^{1,2}, Aditi Gulati^{1,2}, Rahul Kumar^{1,2}, Stephen J. Pettitt^{1,2}, Mark D. Gurden¹, Marta Llorca Cardenosa^{1,5}, Irene Chong¹, Patrycja Gazinska³, Fredrik Wallberg⁶, Elinor J. Sawyer⁷, Lesley-Ann Martin¹, Mitch Dowsett¹, Spiros Linardopoulos^{1,8}, Rachael Natrajan¹, Colm J. Ryan⁹, Patrick W.B. Derksen¹⁰, Jos Jonkers¹¹, Andrew N.J. Tutt^{1,3}, Alan Ashworth¹², and Christopher J. Lord^{1,2}

Cancer Discovery 2018

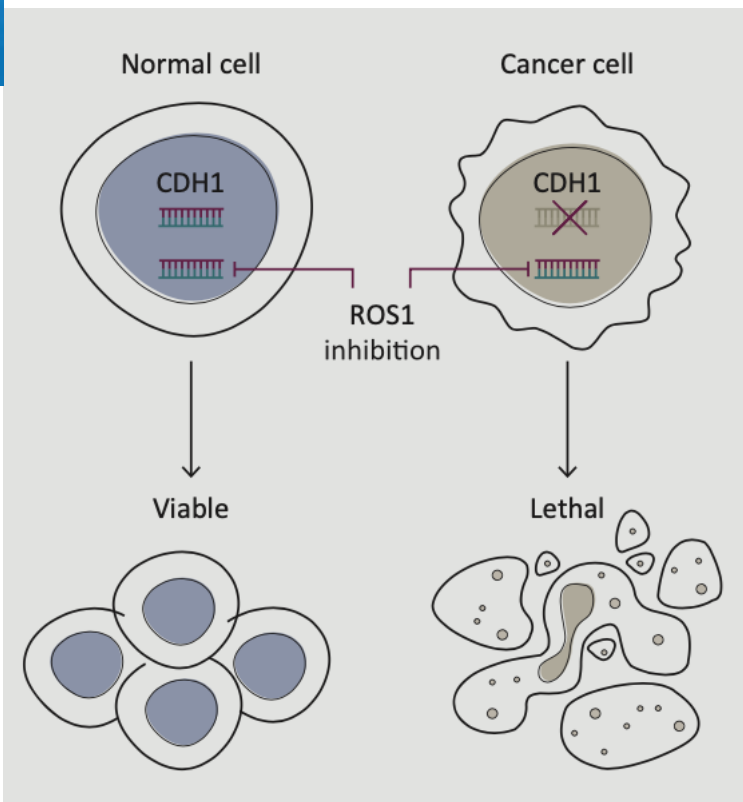


Figure from Van Baelen K, Annals of Oncology 2022

ROSALINE neoadjuvant trial of the ROS1 inhibitor Entrectinib+letrozole in ILC

NCT04551495

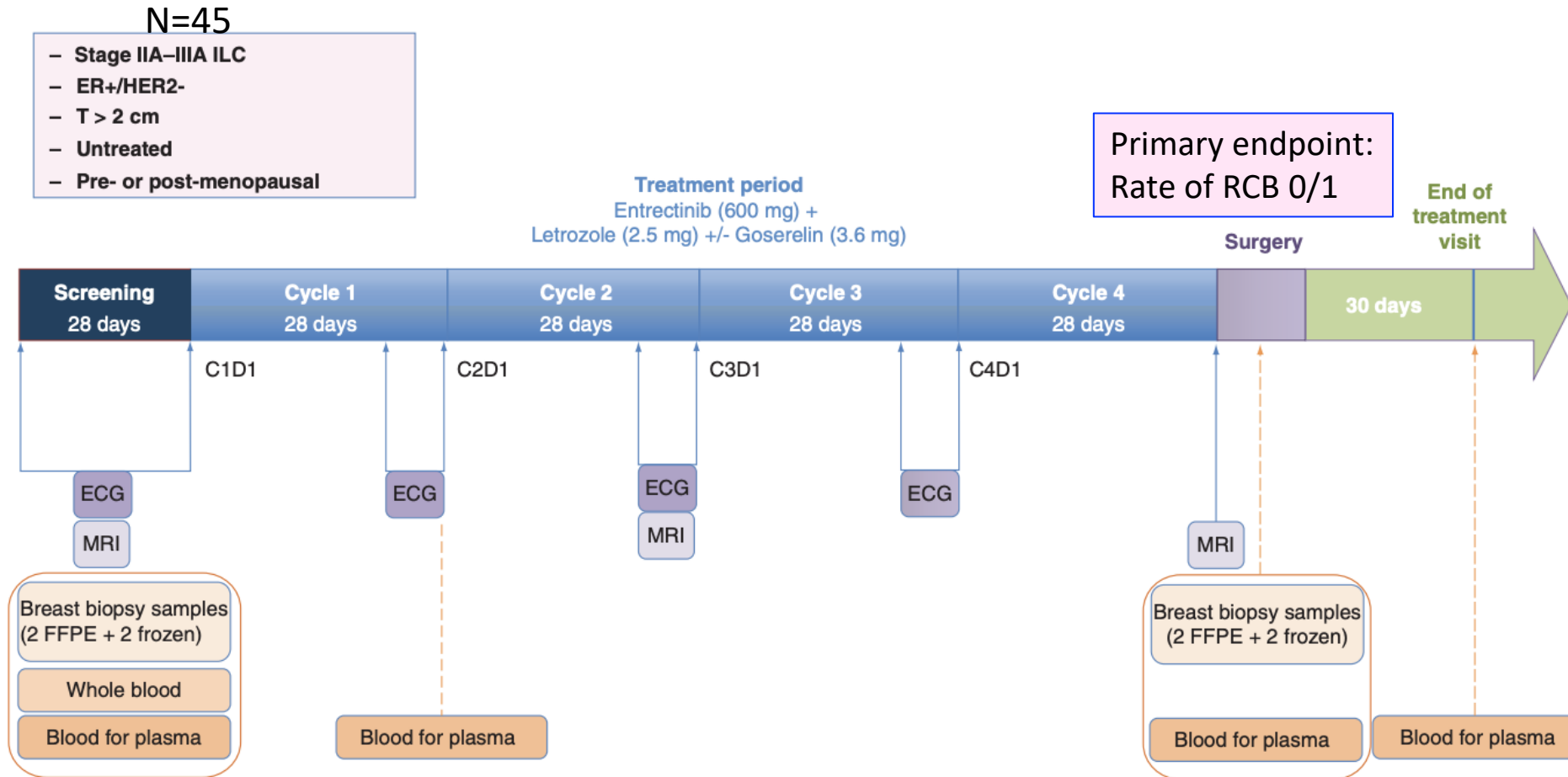


Figure 1. ROSALINE study design.

ER+: Estrogen receptor-positive; FFPE: Formalin-fixed paraffin-embedded; ILC: Invasive lobular breast cancer.

Agostinetti E, Future Oncology

Metastatic ILC

- ILC metastasizes to distinct sites:

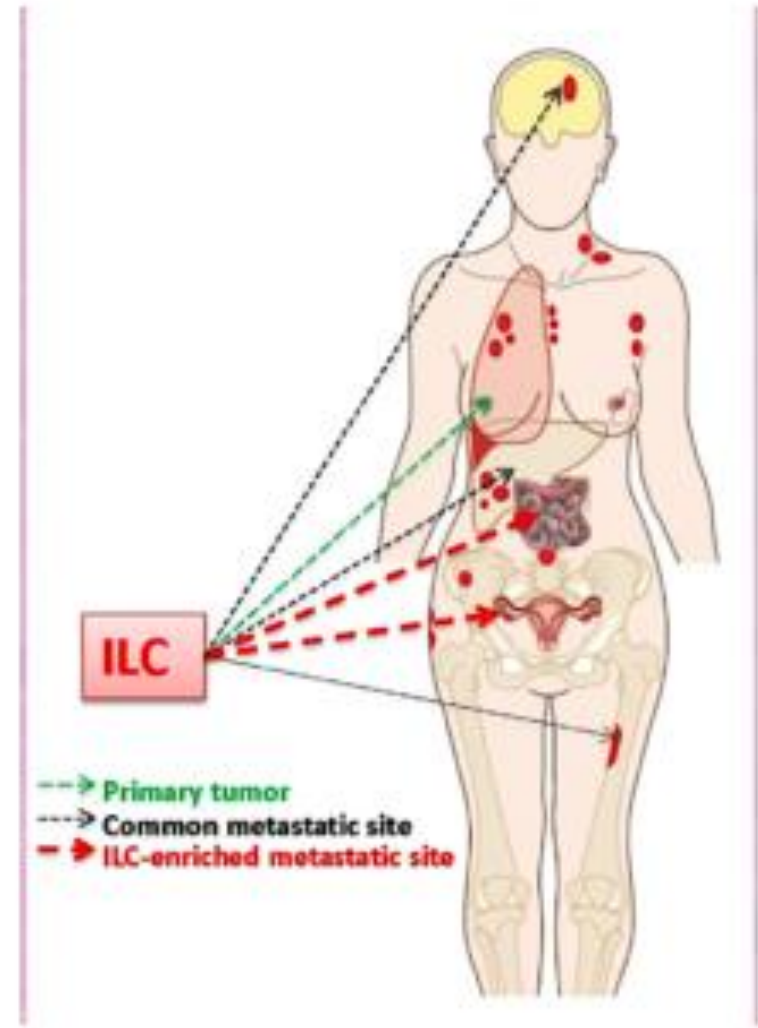
Leptomeningeal dis.

Orbits

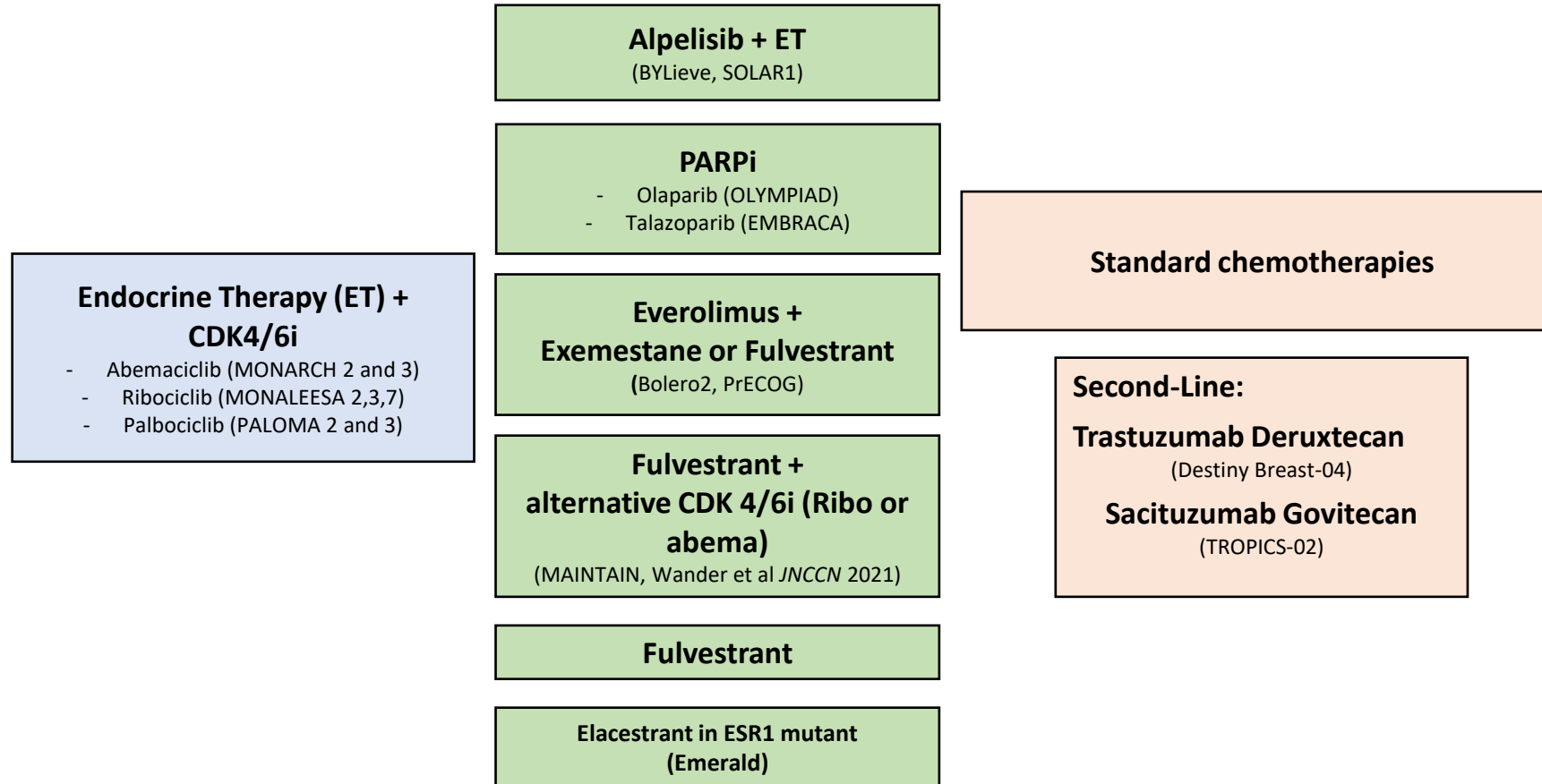
GI tract

Peritoneum/
ascites

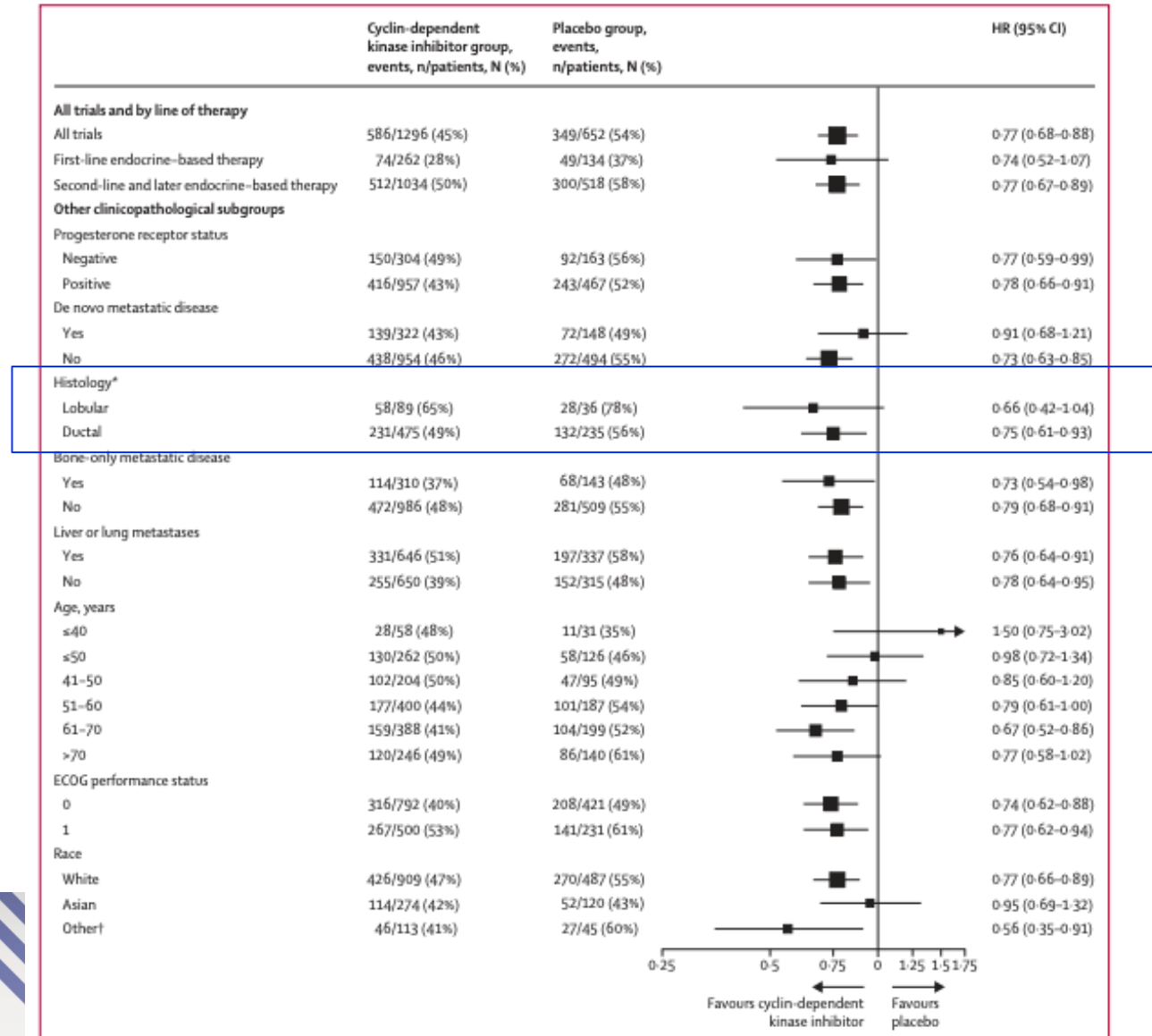
ovaries



Treatment in Metastatic ER+ Breast Cancer Similar ILC and IDC (NST)



Meta-Analyses shows that pts with met. ILC benefit from CDK4/6i comparable to patients with NST



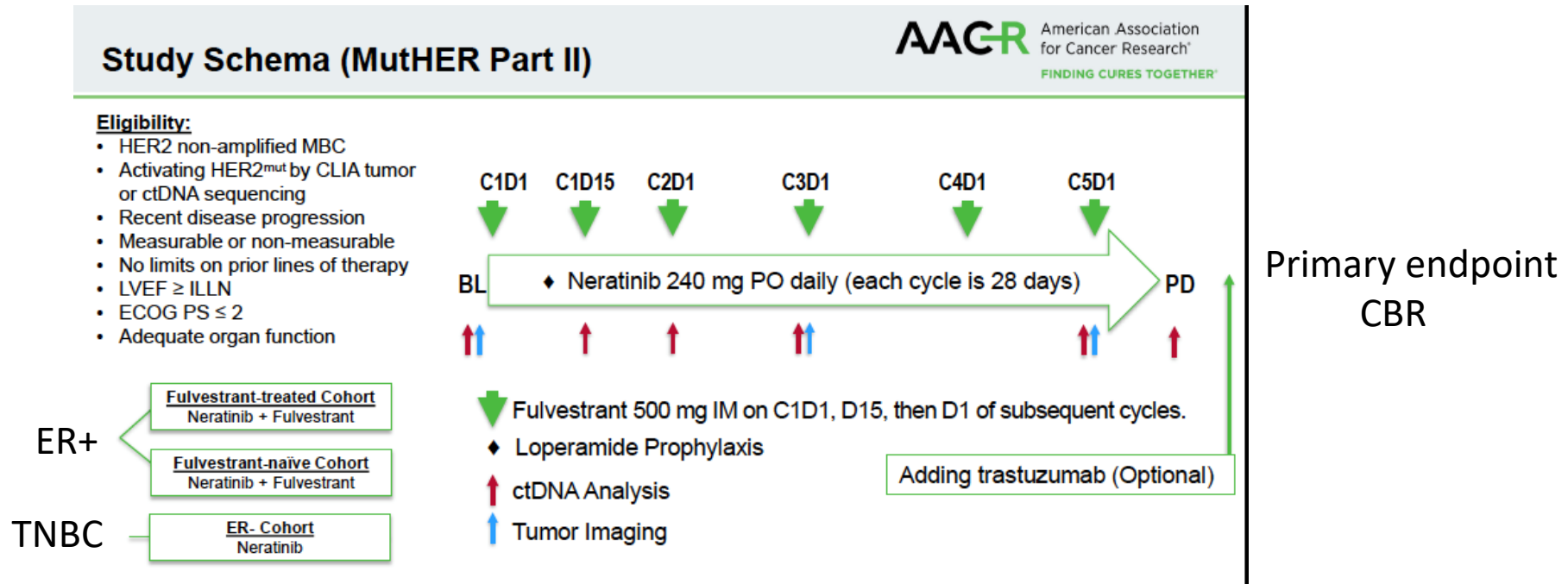
Gao jj, Lancet Onco 2021

Multiple Genetic Alterations in met ILC are Alterations are Potentially targetable

Somatic alteration	Primary ILC [12, 42, 58] (%)	Metastatic ILC [12, 42, 58] (%)
<i>CDH1</i>	53–82	62–76
* <i>PIK3CA</i>	44–57	44–52
* <i>ESR1</i>	2.0–12.5	15
* <i>ERBB2</i> (HER2)	2	12.0–15.6
* <i>PTEN</i>	9	9
* <i>FGFR1</i>	6–7	6–11
<i>RUNX1</i>	3–9	5–6
<i>TBX3</i>	10–21	16.0–18.7
<i>TP53</i>	9–18	9–20
<i>FOXA1</i>	8–15	11–15
<i>ARID1A</i>	8–12	11–12
<i>GATA3</i>	3–15	7–15
* <i>AKT1</i>	6	9.4
* <i>NF1</i>	2–3	6–8

* Have approved drugs that either target the gene or pathway

MutHER part II: Phase II trial of Neratinib in combination with fulvestrant in met. BC with mutated non-amplified HER2



Results: 24 fulvestrant treated 11 fulvestrant naïve ER- = 5

CBR = 38% in fulvestrant treated, 30% in fulvestrant naïve

CBR was positively associated ILC and negatively associated with the HER2 L755 mutation.

ILC and Immunotherapy

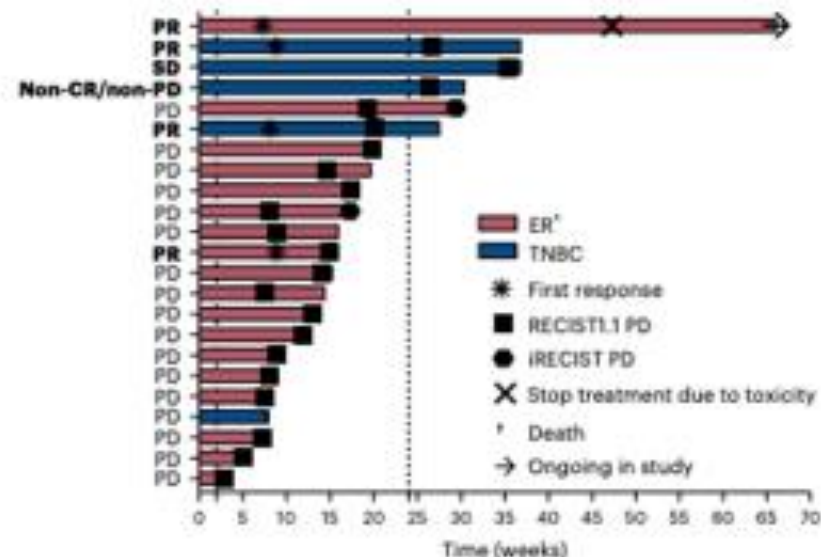
- -A higher proportion of ILC metastases will have a high tumor mutational burden (TMB, >10 mutations per megabase) than NST metastases¹
- -A subset of ILC tumors will have >10% TILs (tumor infiltrating) lymphocytes²
- -These findings along with evidence of immunotherapy working synergistically with platinum-based chemotherapy in mouse models of lobular breast cancer gave rationale for the GELATO trial

1. Sammons S. J Clin Oncol. 2021; 39.

2. Desmedt C. 2018. JNCI 110.

Completed Trial in Metastatic ILC: Phase II GELATO Trial Trial

n=23 evaluable patients		No. (%)
Age at inclusion, years	Median (range)	60 (45–69)
WHO performance status	WHO 0	12 (52)
	WHO 1	11 (48)
Histological subtype (assessed on metastatic lesion) ^a	ER ⁺ HER2 ⁻	18 (78)
	TNBC	5 (22)
	HER2 ⁺	0 (0)
ILC subtype (assessed on metastatic lesion)	Classic	17 (74)
	Pleiomorphic ^b	4 (17)
	Alveolar	2 (9)



- More CBR in ILC that was TNBC vs. ER+ & responses were not durable
- higher benefit in PDL1+ (not s.s.) and trend toward high TMB
- However -one patient with ER+ ILC had response >1 year and had TME with high sTILs and CD8+ Tcells

First trial dedicated to met. ILC

Future trials should select patients with a higher likelihood to benefit from ICI

n=23 evaluable patients	
Best overall response (RECIST1.1), no. (%)	
CR	0 (0)
PR	4 (17) ^a
SD or non-CR/non-PD > 24 weeks ^a	2 (9)
PD	17 (74)
ORR (CR + PR) ^b	17% (95% CI of 5–39%)
Clinical benefit rate (CR + PR + SD > 24 weeks)	26% (95% CI of 10–48%)
Median duration of response	14.9 weeks (95% CI of 6.1 weeks; not reached)
Median progression-free survival according to RECIST1.1 (22 events)	13 weeks (95% CI of 8.1–19.7 weeks)
Median progression-free survival according to iRECIST (22 events)	14 weeks (95% CI of 9.0–20.14 weeks)

The ROLO study (NCT03620643) : non-randomized, phase II study evaluating the use of the ROS1 inhibitor crizotinib in combination with the selective estrogen receptor degrader fulvestrant

-Eligible patients: diagnosis of metastatic or inoperable E-cadherin-negative tumors: either diffuse gastric cancer or ER-positive HER2-negative ILC.

-Patients with ILC receive crizotinib in combination with fulvestrant, with the primary endpoints being response rate & safety/tolerability

Summary

- ILC is a distinct breast cancer (clinical features and biology)
- Significant progress in understanding the unique biology of ILC
- Ongoing first trials dedicated to ILC
- Pathology consensus on the diagnosis of ILC
- Studies will need to investigate the specific variants of ILC
- We need collaborative efforts between multiple centers for further investigation.





Lobular Breast Cancer Alliance

Q&A





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



Thank you for Joining!