TuSalud

Shining a Bright Light on Long-Overlooked Lobular Breast Cancer

Scientists, clinicians and patient advocates partner to improve the imaging, awareness and research gaps of “no-lump” lobular breast cancer.

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It’s taken a few years, but lobular breast cancer has finally made its way into the research spotlight.

The second-most common type of breast cancer after ductal or NST (no specific type), invasive lobular carcinoma, or ILC, has been considered — and clinically treated — “just like ductal” for decades, despite its distinctive growth pattern (it usually grows in lines, not lumps), its imaging issues (it’s harder to find on scans) and its unique biology.

The resulting lack of awareness has led to delayed diagnoses, mistrust in the medical system and a large gaping hole where lobular-specific treatments should be.

Many diagnosed with lobular have never heard of it — it’s seldom mentioned even during Breast Cancer Awareness Month — and until now, there’s been no pathological standards for its diagnosis.

But lobular is coming out of its research limbo. Scientists are filling in the research gaps and awareness is growing, thanks in large part to efforts by patients, pathologists, clinicians and others around the world, many of whom gathered for the 2024 International Invasive Lobular Carcinoma Symposium, held September 23–25 in Leuven, Belgium.

“Awareness of lobular as a distinct subtype is not only important for patients and clinicians, it’s important for drug companies and for the wider scientific community,” said Christine Desmedt, PhD, head of the Laboratory for Translational Breast Cancer Research at KU Leuven, co-chair of the European Lobular Breast Cancer Consortium (ELBCC) and one of the symposium organizers.

“One of our main actions should be to better inform patients and clinicians,” she said. “Many clinicians still equate ILC with ductal or NST breast cancer.”

Patient advocacy pays off

Seattle patient advocate Leigh Pate, who died in 2022, was instrumental in bringing awareness to ILC. She helped create the Lobular Breast Cancer Alliance, or LBCA, and among other efforts established an endowed biobank to create better research models with the nonprofit Breast Cancer Research Foundation (BCRF), one of the ILC Symposium's sponsors.

Efforts by the LBCA recently led the National Cancer Institute's SEER website, which tracks U.S. cancer diagnoses and deaths, to release specific statistics for lobular breast cancer along with a new web page to help educate patients and clinicians. Additionally, the LBCA — along with patients, clinicians and scientists around the world and a handful of governors — have declared October 15 as Global Lobular Breast Cancer Awareness Day to highlight this understudied disease.

This fifth ILC Symposium, attended by equal numbers of advocates, scientists and clinicians, encouraged even more communication and collaboration with three days of presentations, panel discussions, a poster session and even a speed-networking event. Special focus was given to three particularly challenging areas for patients: evolving screening and imaging; lobular treatment plans and the lifestyle issues/psychosocial impact of the disease.

"Collaboration on all levels is crucial," said Karen Van Baelen, MD, PhD, a lobular researcher at Leuven's Laboratory of Translational Breast Cancer Research. "We need objective data on lobular breast cancer in clinical trials. We need to hammer on the door of the companies running clinical trials to make sure we do better in future years."

What makes lobular different?

Lobular tends to grow in lines, not lumps, thanks to a lack of a "cellular glue" known as E-cadherin, which is encoded by the CDH1 gene. Its web-like growth pattern makes it harder to find on physical exams and mammograms, especially in patients with dense breast tissue.

"Many patients are unaware that ILC is hard to see on imaging," said patient advocate Claire Turner, cofounder of Lobular Breast Cancer UK. "I had seven clear mammograms and seven clear ultrasounds — it took years to get a diagnosis."

When lobular spreads or metastasizes, it's equally elusive, due to the way it grows and its tendency to spread to unusual and hard-to-scan sites like the gastrointestinal (GI) tract, the ovaries, or the peritoneum (or abdominal lining). Symptoms of metastatic ILC can be subtle and are often dismissed or misdiagnosed, especially when traditional scans remain clear.

And with "measurable disease" a must for many clinical trials — you have to see the cancer in order to determine if it's responding to a trial drug or not — lobular patients are often excluded from studies.

In a systematic review of breast cancer clinical trials published in NPJ Breast Cancer, Van Baelen and colleagues from the ELBCC together with patient advocates and international collaborators found lobular patients were "often overlooked in clinical drug trials" and if they were included the "documentation was poor." The few trials that did include ILC lacked specific sub-analyses and didn't "confirm histological subtype by central pathology."

Another distinctive feature is ILC's relationship with estrogen: most lobular cancers are ER+, or estrogen receptor positive. When Fred Hutch Cancer Center researchers halted the Women's Health Initiative study of hormone replacement therapy in 2002 due to a rise in breast cancer, they found the highest risk was for lobular. Additional research showed postmenopausal women who took combined HRT (estrogen and progestin) had a fourfold increased risk of developing ILC.

There's a strong connection to estrogen — one reason why estrogen-blocking drugs like tamoxifen and depleting therapies, such as aromatase inhibitors, are the backbone of ER+ lobular treatment — but more research is needed to leverage this connection and prevent treatment resistance.

Unfortunately, lobular receives only around 1% of cancer research funding, per the LBCA. The lack of funding and lack of trials means there are no lobular-specific treatments, nor are there tailored treatments for its subtypes, such as classic, non-classic, pleomorphic and mixed.

And these subtypes matter.

"Subtypes may have clinical importance and need to be recognized," Desmedt said. "Patients with classic ILC have better prognosis than those with non-classic, which in general have a higher recurrence score. But subtypes are often not reported by pathologists."

Targeting mutations and misconceptions

But change is coming.

In his keynote lecture, Patrick Derksen, PhD, professor of experimental and preclinical oncology at the University Medical Center in Utrecht, The Netherlands, and co-chair of the ELBCC, cleared up misconceptions and outlined ambitious next steps.

"Lobular has now been featured at all the major conferences — ESMO, ASCO, SABCS and others," he said. "But we need more money, and we need much more research."

While the loss of E-cadherin underpins ILC's development and its progression, Derksen said there is still a lack of understanding regarding lobular's driver mutations as well as its resistance to chemotherapy and antihormone therapy.

There's also a huge need for harmonized diagnosis and treatment for the disease.

Derksen and others within the ELBCC recently conducted a worldwide survey of more than 150

pathologists that showed diagnostic criteria for ILC was not standardized. Half of pathologists used immunohistochemistry to identify it, half did not. To address this lack of standardization, they developed a step-by-step procedure for the histopathological assessment of ILC, published in Modern Pathology.

"That includes a simple flowchart of how to diagnosis it," Derksen said, adding that ELBCC is working to fold this new pathological criteria for diagnoses into the World Health Organization's Blue Books, used to classify tumors.

Additional endeavors by the ELBCC include:

- Using AI to help define ILC's various subtypes and their clinical impact
- Creating new standards to define clinical response so ILC patients won't be barred from clinical trials due to "non-measurable disease"
- Improving imaging options for ILC patients
- Investigating the clinical utility of liquid biopsies
- Conducting investigations into both established and new treatments in ILC-specific clinical trials

Lobular and its imaging issues

Lobular's imaging issues — both in preventive screening and post-treatment surveillance — fueled the most fiery debate during the symposium, with advocates, radiologists other others decrying mammograms' lack of efficacy in spotting the disease.

"My lobular tumor was invisible for five years of mammograms," said Tracy Cushing, MD, a 45-year-old patient advocate and emergency medicine physician from Boulder. "Improving mammography and screening is very important to me. How do we make it better?"

Mammography is used for prevention screening in the U.S., but its inability to capture lobular — especially in dense breast tissue — has caused distrust, frustration and "illness insecurity," ongoing anxiety regarding the status of their disease, patients and experts argued.

Christiane Kuhl, MD, PhD, director of diagnostic and interventional radiology at University Hospital

RWTH Aachen in Germany, said mammograms are simply inadequate for this subtype.

“Mammographic screening is a health care intervention that does not work for lobular cancer — full stop,” she said, pointing to abbreviated breast MRI as a better alternative. “It’s a completely different disease that requires different approaches in early detection, treatment and follow-up.”

Others said mammograms still find around 60% of lobular cancers and questioned the practicality of using MRIs for preventive screening, since the extra sensitivity of MRIs can lead to overdiagnosis (finding low-grade cancers that aren’t life threatening) and/or false positives, where an abnormal scan leads to unnecessary biopsies and undo anxiety.

“False positives are not our main problem, false negatives are,” Kuhl responded. “Nobody dies of a false positive.”

Surveillance after treatment remains another fraught area, since lobular patients are often followed with the same type of imaging that failed to pick up their cancer in the first place.

“Post-treatment, I was told they’re going to monitor me with mammograms,” said Turner, whose repeated mammograms failed to spot her lobular cancer. “That isn’t right.”

Cushing also questioned surveillance methods like CT and FDG-PET scans, often used to diagnose ILC or measure its response to treatment.

“I have no confidence in either for seeing metastatic progression,” she said.

Late metastatic recurrence is higher in ILC than in ductal/NST breast cancers, but there is no lobular-specific protocol for follow-up after early-stage treatment. In a breakout session on imaging, some clinicians said they use circulating tumor DNA, or ctDNA, tests to follow early stagers at high risk for recurrence. Others use MRIs, which experts said have the best sensitivity for capturing metastasis.

But guidelines and protocols vary from country to country and even practice to practice. And data on the efficacy and clinical utility of ctDNA tests in particular are lacking. (Read about Fred Hutch’s recent efforts to evaluate the effectiveness of these new liquid biopsies.)

“What do we do if the test comes back positive?” one oncologist asked during one of the symposium’s breakout sessions. “That’s the question.”

Even when recommended by an oncologist, MRIs aren’t always an option, experts said, due to an increase in consumer demand and a post-pandemic shortage of radiologists.

New tracers, new tests and AI

Change is on the way in the imaging arena, as well, according to radiologist Matt Covington, MD,

of Huntsman Cancer Institute in Salt Lake City, with new technologies, new tracers and a move toward more tailored or risk-adapted screening.

“There is a lot of great technology in the pipeline, but we need more and we also need to expand access to patients,” he said, pointing to PET scans — and new tracers — as an important area for lobular patients and clinicians to watch. “It’s no longer just FDG and FES for PET scans. There are other emerging PET radiopharmaceuticals and about two dozen agents currently being trialed.” (Read about Fred Hutch’s research into the new FES-PET tracer.)

Other new surveillance approaches currently in use and/or under study, include:

- Contrast-enhanced mammography (CEM), approved by the U.S. Food & Drug Administration in 2011, but not yet widely used

- Whole-body diffusion-weighted MRI, a potential alternative to traditional imaging and an evolving modality for measuring response to treatment, but only available in select European countries

- Liquid biopsies to detect ctDNA in lobular patients (via the PLUMB study)

- “Beyond blood” biopsies that analyze ctDNA in lung fluid, ascites and even cerebral spinal fluid to monitor patients and detect actionable mutations to guide treatment

Radioligand therapy, or theranostics, where radiopharmaceuticals are combined with imaging to target and treat cancers, is also gaining ground.

“Theranostics could bring a revolution in ILC treatment,” Covington said.

And then there’s artificial intelligence, also poised to improve detection. A new study aimed at quantifying the prevalence of missed or delayed metastatic ILC diagnoses will train an AI-based model to search electronic health records for terms related to metastatic ILC-related symptoms.

“Ultimately, we want to use it monitor the health records, spot symptoms of recurrence and nudge the GP or PCP or medical oncologist so they will consider looking for lobular mets,” said University of Pittsburgh researcher Adrian Lee, PhD, who’s partnering with U-Pitt researchers (and LBCA co-founder) Steffi Oesterreich, PhD and medical student Morgan Cody along with a team of patient advocates. “Mets often recurs so late that people may not link their symptoms to a past lobular breast cancer diagnosis. We think we can improve this with AI.”

Getting the word out

Patients and researchers have also created all manner of resources, including infographics, flyers and leaflets (translated into more than two dozen languages) to help educate patients — and clinicians — about lobular's differences and its subtle symptoms.

"We absolutely need to increase awareness, especially in metastatic disease," said Desmedt, referencing a survey that showed 71% of lobular patients didn't know ILC could metastasize to different sites than ductal and 78% didn't know what symptoms were associated with their cancer's metastatic recurrence.

"That's very high," she said. "Many different groups and organizations have made big efforts to increase awareness of lobular, but we need to share further."

Experts also called for more personalized approaches, especially with regard to endocrine or anti-hormone therapy, as well as more education about lobular's relationship with HRT. Incidence of lobular cancers has increased over the last two decades, causing concern among clinicians.

"When women stopped using hormone replacement therapy, breast cancer rates dropped dramatically," said Penn Medicine oncologist Rachel Jankowitz, MD. "But now women are being told hormone replacement therapy is OK. That worries me."

After three days of lectures, attendees came away "tired and inspired," as Desmedt put it, but with renewed energy to keep pushing ILC into the research spotlight. And while there is still much to do, lobular patient advocates like Jane Sedcole, from Yorkshire in England, came away incredibly encouraged.

"I feel very upbeat and positive about this symposium," she said. "It's like all of this research has been bubbling under the surface and there's going to be an explosion of cohesive ideas moving forward. So many of the challenges have to do with the disease itself, but we're getting there."

The next ILC Symposium is slated for 2026 and will be held in San Francisco.

SIDEBAR:

LOBULAR BREAST CANCER STUDIES

Some lobular-associated studies currently in the works or going through analysis:

- APOLLO, a University of Pittsburgh observational longitudinal analysis of ctDNA in metastatic

ILC patients

- Clinical trial #NCT05919108, a study testing the combination of endocrine therapy and neratinib in newly-diagnosed ILC patients with HER2 mutations (currently recruiting)

- MutHER, a trial testing the kinase inhibitor neratinib in HER2-mutated breast cancer (14% of ILC patients have HER2 amplification or HER2/HER3 mutations, per experts).

- PLUMB study, a prospective study using ctDNA and imaging to follow metastatic ILC patients with the aim of improving survival.

- REPLOT, a lobular-specific clinical trial testing the ROS-1 inhibitor repotrectinib with fulvestrant in HR+ HER2- pretreated metastatic ILC patients (currently recruiting)

- UPTIDER (Belgium) and Hope for OTHERS (U.S.), two post-mortem tissue donation programs yielding vital data on lobular's behavior and immune profile

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