Metastatic ILC Survival Varies by Mutational Signature

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> Metastatic invasive lobular carcinoma (ILC) presents a clinical challenge due to its diffuse growth pattern and often delayed diagnosis compared to invasive ductal carcinoma. Understanding the molecular underpinnings that drive its varied clinical course is essential for refining prognostic assessments and guiding therapeutic strategies. Recent analyses indicate that distinct mutational signatures within metastatic ILC correlate with significant differences in patient survival.

KEY TAKEAWAYS

- The Pivot: Survival in metastatic ILC is not uniform; it is influenced by specific mutational signatures.
- The Data: Patients with certain mutational profiles demonstrate significantly altered median overall survival.
- The Action: Molecular profiling of metastatic ILC may offer prognostic insights and inform treatment selection beyond traditional clinical factors.

Invasive lobular carcinoma (ILC) accounts for approximately 10-15% of all breast cancers and is characterised by its unique histological features, including discohesive cells often arranged in single files. Unlike invasive ductal carcinoma (IDC), ILC frequently presents with diffuse infiltration, making detection challenging and often leading to presentation at a more advanced stage. The metastatic patterns of ILC also differ, with a propensity for spread to unusual sites such as the gastrointestinal tract, peritoneum, and retroperitoneum, in addition to common sites like bone and liver. Despite these known clinical distinctions, prognostic stratification within metastatic ILC has largely relied on conventional clinicopathological factors, which may not fully capture the biological heterogeneity of the disease.

Epidemiologically, ILC incidence has shown a slight increase over recent decades, particularly in postmenopausal women, which some studies attribute to hormonal factors, including hormone replacement therapy. The diffuse growth pattern of ILC often leads to larger tumor sizes at diagnosis compared to IDC, and its infiltrative nature can obscure its true extent on imaging, contributing to higher rates of positive surgical margins. At the metastatic stage, the disease presents significant therapeutic challenges, with endocrine therapy being a cornerstone of treatment due to the high prevalence of estrogen receptor (ER) positivity in ILC. However, resistance to endocrine therapy and progression to chemotherapy are common, underscoring the need for more precise prognostic and predictive biomarkers.

Mutational Signatures and Survival Outcomes

Recent investigations into the genomic landscape of metastatic ILC have identified specific mutational signatures that correlate with differential survival outcomes. These signatures reflect distinct DNA damage and repair processes active within the tumour. For example, tumours exhibiting a high burden of specific single nucleotide variant (SNV) signatures, such as those associated with homologous recombination deficiency (HRD) or APOBEC activity, have been linked to varied prognoses. One analysis demonstrated that patients with metastatic ILC whose tumours harboured a specific mutational signature, often linked to defective DNA repair mechanisms, experienced a median overall survival (OS) of 28 months compared to 45 months in patients without this signature (HR 1.85, P=0.003). This difference remained statistically significant after adjusting for established prognostic factors such as hormone receptor status, HER2 status, and number of metastatic sites.

The methodology for identifying these mutational signatures typically involves whole-genome or whole-exome sequencing of tumor tissue, followed by bioinformatic analysis to extract characteristic patterns of somatic mutations. These patterns, or signatures, are then correlated with clinical outcomes in cohorts of patients with metastatic ILC. Patient populations in these studies often consist of individuals diagnosed with metastatic ILC who have undergone comprehensive genomic profiling as part of research protocols or clinical trials. Careful consideration is given to ensure homogeneity in treatment regimens where possible, or to adjust for treatment differences in statistical models, to isolate the prognostic impact of the mutational signatures.

Conversely, other mutational signatures, potentially indicative of less aggressive biological pathways or greater sensitivity to certain therapies, were associated with more favourable survival. For instance, tumours with a predominant signature linked to age-related DNA damage accumulation showed a median OS of 52 months. These findings suggest that the underlying genomic instability and the specific mechanisms of mutagenesis play a substantial role in determining the clinical trajectory of metastatic ILC. The presence or absence of particular mutational signatures could serve as an independent prognostic biomarker, offering a more refined risk assessment than currently available methods.

The clinical utility of these findings lies in their potential to guide treatment decisions. For patients with mutational signatures associated with poorer prognosis, more aggressive or novel therapeutic approaches might be warranted. Conversely, those with more favourable signatures might benefit from less intensive treatments, potentially reducing treatment-related toxicities without compromising efficacy. Further research is required to validate these associations in larger, prospective cohorts and to explore the predictive value of these signatures for response to specific targeted therapies, such as PARP inhibitors in HRD-positive tumours or immune checkpoint inhibitors in tumours with high mutational burden.

Limitations of current research include the retrospective nature of many studies, which introduces potential biases. The heterogeneity of treatment regimens in metastatic settings also complicates the interpretation of survival data. Furthermore, the precise biological mechanisms by which some mutational signatures influence prognosis are not fully elucidated, requiring further functional studies. The generalizability of these findings to diverse patient populations, particularly those from different ethnic backgrounds or with varying access to advanced genomic testing, also requires

careful evaluation. Standardizing the methodology for mutational signature analysis across different laboratories will be crucial for clinical implementation.

CLINICAL IMPLICATIONS

The observation that specific mutational signatures dictate survival in metastatic ILC is not merely an academic point; it is a direct challenge to the current, largely morphology-driven approach to prognosis. Clinicians treating patients with metastatic ILC should consider that a 'lobular' diagnosis alone provides insufficient granularity for precise prognostic assessment. The era of broad brushstrokes for breast cancer subtypes is receding, and this data underscores the necessity of molecular profiling to inform treatment decisions. Relying solely on hormone receptor and HER2 status for metastatic ILC may lead to suboptimal stratification, potentially exposing patients to therapies that are either insufficient or unnecessarily toxic.

From an industry perspective, these findings highlight a clear unmet need for diagnostic tools that can reliably identify these mutational signatures in a clinically actionable timeframe. Companies developing next-generation sequencing panels or targeted assays have an opportunity to integrate these prognostic markers, moving beyond purely predictive markers for specific drug classes. Furthermore, pharmaceutical companies should consider these molecular subgroups when designing clinical trials for novel agents in metastatic ILC, rather than treating ILC as a monolithic entity. A drug that fails in a broad ILC population might show significant efficacy in a molecularly defined subgroup.

For patients, this research offers a glimmer of hope for more personalised and effective care. The prospect of understanding their tumour's unique mutational landscape means moving away from a one-size-fits-all approach. It empowers them and their clinicians to make more informed decisions, potentially avoiding ineffective treatments and accessing therapies more likely to extend survival. While these findings require further validation in prospective studies, they lay the groundwork for a future where genomic profiling is as standard for metastatic ILC as it is becoming for other advanced cancers, ensuring that treatment aligns with the specific biology of the disease rather than just its histological appearance.

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