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Clinical Guidelines from the 2025 International Symposium on Breast Diseases of Inland São Paulo: GLP-1 Inhibitors, Risk-Reducing Surgery in BRCA Carriers, Liquid Biopsy, and DCIS Treatment De-escalation

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ABSTRACT

Introduction: The 2025 International Symposium on Breast Diseases of Inland São Paulo convened to establish consensus on emerging topics in oncology. This study aims to disseminate the clinical guidelines voted on regarding four aspects of breast cancer management: the impact of glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) on risk reduction; risk-reducing surgery in breast cancer gene (*BRCA*) mutation carriers; use of liquid biopsy (circulating tumor DNA [ctDNA]) in metastatic cases; and management of low-grade ductal carcinoma in situ (DCIS). **Methods:** Four priority topics were presented in evidence-based lectures, followed by technical discussions and anonymous electronic voting by 100 panelists. Consensus was defined as an agreement of ≥75%. **Results:** No consensus was reached on GLP-1RAs for breast cancer risk reduction (50% in favor, 43% citing inconclusive evidence, 7% against). Risk-reducing surgery in *BRCA* mutation carriers achieved consensus (92% in favor) as beneficial for survival. Liquid biopsy was recommended for monitoring metastatic cases (74% in favor, just below the consensus threshold). Standard treatment for low-grade DCIS was preferred (84% in favor) over active surveillance (16%). **Conclusions:** The guidelines highlight the absence of conclusive evidence for GLP-1RAs in breast cancer prevention, the survival benefit of risk-reducing surgery in *BRCA* carriers, the utility of liquid biopsy in metastatic cases, and the preference for standard treatment in low-grade DCIS to prevent progression. Further studies are needed to address unresolved issues.

KEYWORDS: breast neoplasms; glucagon-like peptide 1; prophylactic surgical procedures; liquid biopsy; carcinoma, intraductal, noninfiltrating.

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INTRODUCTION

Breast cancer is a heterogeneous disease that requires personalized preventive and therapeutic approaches based on risk factors, molecular characteristics, and clinical stage. Obesity and type 2 diabetes (T2D) are modifiable risk factors, and glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been investigated for their potential oncologic impact, though results remain conflicting[1-7]. Young patients with breast cancer gene (BRCA) 1 and 2 mutations face a high risk of breast cancer, and risk-reducing surgeries, such as prophylactic mastectomy and salpingo-oophorectomy, are proven preventive strategies[8-15]. Liquid biopsy, through circulating tumor DNA (ctDNA) analysis, enables dynamic monitoring in metastatic cases, guiding targeted therapies and anticipating progression[16-22]. Low-grade ductal carcinoma in situ (DCIS), though often indolent, carries a risk of progression to invasive disease, prompting debates on standard treatment versus active surveillance[23-33]. The 2025 International Symposium on Breast Diseases of Inland São Paulo convened experts to deliberate evidence-based clinical guidelines for these four critical thematic axes.

METHODS

The plenary sessions were organized around four critical thematic axes: (1) impact of GLP-1RAs on breast cancer risk reduction; (2) impact of risk-reducing surgery on survival in young BRCA mutation carriers; (3) use of liquid biopsy (ctDNA) in metastatic breast cancer patients; and (4) management of low-grade DCIS.

Each topic was presented in a 10-minute didactic session with a literature review, followed by 50 minutes of technical debate among panelists, discussants, and speakers, concluding with anonymous electronic voting. Results were tabulated, with consensus defined as ≥75% agreement among the 100 specialists. The analysis was descriptive, and the results were drafted as clinical guidelines.

RESULTS AND DISCUSSION

Impact of GLP-1 receptor agonists on breast cancer risk reduction

Introduction to the topic

Obesity and type 2 diabetes (T2D) are established risk factors for breast cancer, particularly among postmenopausal women[1-3]. GLP-1RAs, widely used for obesity and T2D management, promote weight loss and metabolic control[4]. The hypothesis that these agents may reduce breast cancer risk, beyond their metabolic benefits, has been investigated, but results are conflicting[5-7].

Rationale and evidence

- **Clinical trials and observational studies:** Data from 26 trials involving over 9,000 participants with a minimum 24-week follow-up showed that liraglutide, semaglutide, and other GLP-1RAs did not increase the risk of breast cancer or benign/pre-malignant breast lesions in T2D and obese individuals[5-7].
- **Real-world data:** Retrospective analyses, such as those using the TriNetX database, suggest that oncologic risk profiles may vary among specific agents, with no clear class effect on breast cancer risk reduction[5].
- **Study conclusions:** While some data suggest metabolic benefits that could indirectly reduce cancer risk, recent studies (e.g., JAMA 2023) indicate no significant impact on breast cancer risk in T2D patients treated with GLP-1RAs compared to other treatments[5].

Voting results

- Yes: 50%
- No: 7%
- Inconclusive evidence: 43%

This voting distribution reflects the uncertainty and conflicting data, with half of the experts recognizing potential benefits while a significant proportion evidenced the absence of conclusive evidence.

Practical recommendations

- **Use of GLP-1RAs:** GLP-1RAs should continue to be prescribed primarily for their proven benefits in glycemic control and weight loss in individuals with T2D and obesity.
- **Oncologic impact:** Current evidence does not conclusively support GLP-1RAs for breast cancer risk reduction. Their use should not be based on oncologic prevention but on metabolic effects. Potential risk reduction may be agent-specific (e.g., semaglutide), but this requires confirmation through prospective, randomized trials with oncologic endpoints.
- **Future research:** Prospective, randomized studies focusing on oncologic outcomes are recommended to clarify any direct impact of GLP-1RAs on breast cancer prevention.
- **Clinical decision-making:** GLP-1RA prescriptions should prioritize metabolic benefits, and any perceived breast cancer risk reduction should be considered a hypothesis under investigation, not a basis for oncologic prevention.

Conclusion

Given the available data and partial consensus (50% in favor, 43% citing inconclusive evidence), there is insufficient evidence to confirm that GLP-1RAs reduce breast cancer risk. Their use should focus on metabolic benefits, with further research needed to define any preventive oncologic effect. This guideline integrates current evidence and expert consensus, noting that the impact

of GLP-1RAs on breast cancer risk remains an open question requiring prospective studies.

Impact of risk-reducing surgery on survival in young BRCA mutation carriers

Introduction to the topic

Young patients with pathogenic BRCA1/2 variants face a significantly increased risk of breast cancer[8-15]. Risk-reducing surgeries, including bilateral prophylactic mastectomy and salpingo-oophorectomy, are recommended to reduce cancer incidence and improve oncologic outcomes. This guideline aims to inform clinical practice based on available evidence regarding the survival impact of these interventions.

Rationale and evidence

- **Scientific evidence:** Comprehensive studies, including meta-analyses and reconstructed cohorts, demonstrate that risk-reducing surgery in young BRCA mutation carriers positively impacts survival. Studies by Guindalini et al. (2022), Heemskerk-Gerritsen et al. (2019), and Finch et al. (2014) show that prophylactic interventions reduce breast cancer risk, translating into significant improvements in overall and cancer-specific survival[8,13,14].
- **Data details:** Large cohort studies (n=5,783 and n=5,290) confirmed the efficacy of risk-reducing surgeries, demonstrating a notable reduction in cancer incidence and improved survival. Comparative analyses of groups undergoing bilateral salpingo-oophorectomy versus non-intervention groups support the protective role of surgery, with long-term benefits. These studies indicate that reducing cancer incidence in high-risk patients improves prognosis and quality of life[8-15].

Voting results

- Yes: 92%
- No: 8%

The overwhelming majority (92%) of experts agree that risk-reducing surgery positively impacts survival in young BRCA mutation carriers, solidifying its role in clinical practice.

Practical recommendations

- **Indication for risk-reducing surgery:** Bilateral prophylactic mastectomy and, where appropriate, salpingo-oophorectomy are recommended for young BRCA mutation carriers, given their high breast cancer risk and demonstrated survival benefits.
- **Shared decision-making:** Decisions should involve multidisciplinary evaluation with oncologists, breast surgeons, geneticists, and psychologists, ensuring patients understand risks, benefits, and alternatives.
- **Follow-up and support:** Continuous post-intervention monitoring is essential to manage complications and provide emotional and psychological support, given the complexity and impact of these procedures on quality of life.

Conclusion

Based on robust evidence and strong expert consensus (92% in favor), risk-reducing surgery significantly improves survival in young BRCA mutation carriers. This intervention should be considered a cornerstone of preventive management in high-risk populations, ensuring personalized, evidence-based care. This guideline integrates key research findings and expert consensus, providing clear guidance for clinical practice in preventive management of young BRCA mutation carriers.

Use of liquid biopsy in metastatic breast cancer patients

Introduction to the topic

Liquid biopsy, through analysis of ctDNA and circulating tumor cells (CTCs), is increasingly important for dynamic monitoring in metastatic breast cancer[16-22]. This non-invasive technology enables assessment of genetic alterations and tumor burden over time, guiding targeted therapies and anticipating disease progression.

Rationale and evidence

- **Clinical applications:** ctDNA analysis identifies relevant molecular alterations to guide therapeutic choices (e.g., alpelisib, neratinib, or elacestrant) and enables early interventions before clinical progression. Recent trials, such as plasmaMATCH, PADA-1, and SERENA-6, support the practical use of ctDNA for monitoring and therapeutic decision-making in metastatic disease[17-20].
- **Advantages:** Non-invasive, repeatable technique; reflects active tumor heterogeneity; enables real-time detection of genetic alterations for dynamic therapeutic adjustments[22].
- **Limitations:** Reduced sensitivity in low tumor burden cases (non-shedders); potential for false negatives; requires qualified laboratories and technological investment[22].

Voting results

- Yes: 74%
- No: 26%

Most experts agree that liquid biopsy should be used in metastatic patients, reflecting consensus on its practical utility for monitoring and therapeutic decision-making.

Practical recommendations

- **Integration into clinical practice:** Liquid biopsy (ctDNA) analysis is recommended for monitoring metastatic breast

cancer as part of dynamic disease assessment. It can guide targeted therapy selection, adjust treatment before clinical progression, and identify relevant genetic alterations.

- **Contextual analysis:** Interpretation of results should account for the technique's limitations, such as reduced sensitivity in some cases. Therapeutic decisions based on liquid biopsy findings should involve a multidisciplinary team, integrating clinical, radiological, and pathological data.
- **Infrastructure and access:** Institutions must have qualified laboratories to ensure result accuracy and reproducibility. Where access is limited, strategies should be evaluated within available resources without compromising clinical management.

Conclusion

Based on expert consensus (74% in favor) and current evidence, liquid biopsy is a valuable tool for monitoring and guiding therapy in metastatic breast cancer. Despite limitations, it offers significant advantages for personalized, dynamic treatment. Its use is recommended, integrated with multidisciplinary evaluation and performed in settings with adequate infrastructure. This guideline integrates evidence and expert consensus, guiding clinical practice for the use of liquid biopsy in metastatic breast cancer monitoring.

Management of low-grade ductal carcinoma *in situ*

Introduction to the topic

Low-grade DCIS is a highly prevalent condition, often indolent, but observational studies show a risk of progression to invasive cancer, increasing to approximately 9–10% over ten years. While locoregional therapy does not impact overall mortality, it reduces local recurrences, critical for preventing progression to invasive disease affecting survival[23-33].

Rationale and evidence

- **Epidemiological and prognostic data:** Reconstructed studies and observational data indicate that, while many low-grade DCIS cases are low-risk, invasive recurrence rates increase over time. Studies by Ryser et al. and Wright et al. show that DCIS treatment reduces local recurrence rates, though no mortality difference is observed in 10-year follow-ups[24,25].
- **Comparative approaches:** Active surveillance (monitoring without immediate surgical or radiotherapeutic intervention) has been explored in trials like the COMET, but its long-term validity remains uncertain due to short follow-up[29]. Standard treatment, typically involving breast-conserving surgery (with or without radiotherapy and/or hormone therapy), effectively reduces local events and progression to invasive cancer[23-33].
- **Expert opinion:** As per the provided survey data, 84% of panelists favor standard treatment for low-grade DCIS, with only 16% supporting active surveillance.

Voting results

- Standard treatment: 84%
- Active surveillance: 16%

Practical recommendations

- **Standard treatment:** For most patients with low-grade DCIS, standard treatment is recommended including breast-conserving surgery (wide excision with adequate margins) and, where appropriate, radiotherapy to reduce local recurrence risk. While not impacting mortality, reducing invasive recurrences is critical for preventing progression and preserving quality of life.
- **Active surveillance:** Active surveillance may be considered in experimental settings or tightly monitored clinical protocols, but current evidence and expert consensus support standard treatment as safe and effective.
- **Individualized approach:** Therapeutic decisions should involve a multidisciplinary team, considering clinical, histological, and patient preferences. Patients should be informed of the risks and benefits, noting that standard treatment reduces local recurrence even if it does not alter short- to medium-term mortality.

Conclusion

Based on evidence and expert consensus (84% for standard treatment vs. 16% for active surveillance), the guideline recommends standard treatment for low-grade DCIS to reduce the risk of progression to invasive cancer and control local recurrences. Active surveillance, while promising in some contexts, lacks long-term validation and should not replace standard treatment outside well-structured clinical trials. This guideline integrates current evidence and expert consensus, guiding clinical practice for low-grade DCIS management with an emphasis on standard therapeutic intervention to prevent recurrence and progression.

CONCLUSIONS

The established guidelines reflect the current state of knowledge in the preventive and therapeutic management of breast cancer. There is no conclusive evidence that GLP-1RAs reduce breast cancer risk; their use should focus on metabolic benefits, with prospective studies needed. Risk-reducing surgery is strongly recommended for young BRCA mutation carriers due to its significant survival impact, with strong consensus (92%). Liquid biopsy is a valuable tool for monitoring metastatic cases, despite limitations and absence of formal consensus (74% in favor), and should be integrated into multidisciplinary decisions. Standard treatment for low-grade DCIS is preferred (84% in favor) to prevent progression, with active surveillance limited to clinical trials. These recommendations underscore the importance of evidence-based decisions, personalized treatment, and the need for further research to address unresolved issues.

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AUTHORS' CONTRIBUTION

ECP: Conceptualization, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. FB: Investigation, Validation, Visualization, Writing – review & editing. MM: Investigation, Methodology, Validation, Writing – review & editing. JTAN: Investigation, Resources, Validation, Writing – review & editing. GMT: Investigation, Supervision, Writing – review & editing. FB: Investigation, Validation, Visualization, Writing – review & editing. BBG: Investigation, Writing – original draft, Writing – review & editing. DAB: Conceptualization, Investigation, Validation, Writing – review & editing. CC: Investigation, Methodology, Validation, Writing – review & editing. ALCB: Investigation, Visualization, Writing – review & editing. PT: Investigation, Validation, Writing – review & editing. PM: Investigation, Writing – review & editing. ATH: Conceptualization, Supervision, Writing – review & editing.

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