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## Letter to the Editor

# The INSEMA trial: redefining axillary surgery in early breast cancer

Sir,

We read with great interest the INSEMA (Intergroup-Sentinel-Mamma) trial published in the New England journal of medicine in 2025, which evaluates the oncologic safety of omitting sentinel lymph node biopsy (SLNB) in clinically node-negative early breast cancer.[1] This landmark study represents a major step toward surgical de-escalation; however, important limitations must be carefully considered before widespread implementation, particularly in resource-limited settings.

The trial enrolled 5,154 patients in the intention-to-treat population, predominantly postmenopausal (90% ≥50 years), with favorable tumor biology: 90% had T1 tumors, 98.5% were hormone receptor (HR) positive, 96.4% HER2-negative, and 96.4% grade 1-2. Only 3.6% had grade 3 disease or HER2-positive tumors, and 1.2% had triple-negative breast cancer, reflecting highly selective inclusion of excellent-prognosis patients. Preoperative axillary ultrasound excluded those with suspicious nodes, creating a strictly clinically node-negative cohort. At a median follow-up of 6 years, the estimated 5-year invasive disease-free survival was comparable between omission and SLNB groups (91.9% vs. 91.7%; HR 0.91, 95% CI 0.73-1.14), meeting non-inferiority criteria. Axillary recurrence remained low (1.0% vs. 0.4%), while omission significantly reduced morbidity including lymphedema (1.8% vs. 5.7%), pain (2% vs. 4.2%), and impaired arm mobility (2% vs. 3.5%).

Notably, 15.7% of SLNB patients were node positive, with macrometastases comprising 75% of these, yet axillary recurrence remained low in the omission group, underscoring the effectiveness of systemic therapy and radiotherapy in controlling microscopic disease. All breast-conserving surgery patients received whole-breast radiotherapy (WBRT). Chemotherapy usage was modest (10.4% vs. 12.9%) and was nodal-status driven in the SLNB arm, while endocrine therapy predominated in HR-positive patients, although specific regimens were not reported.

Several critical limitations warrant discussion. The exclusion of aggressive subtypes (HER2-positive, triple-negative, grade 3) limits generalizability to high-risk populations. WBRT likely contributed to axillary control, as axillary level I receives approximately 85% and level II approximately 15% of the prescribed breast radiation dose, potentially confounding the independent effect of surgical omission.[2] The absence of outcome reporting by radiation field further obscures interpretation. The trial also lacks data on ductal carcinoma in situ, lymphovascular invasion, and perineural invasion, all known predictors of recurrence. Furthermore, although 851 events were targeted, only 525 were reported, reducing statistical power to detect small survival differences. The 1:4 randomization ratio and per-protocol non-inferiority design (margin HR <1.271), while methodologically sound, further necessitate caution when interpreting secondary endpoints. Additional limitations include unreported imaging protocols for recurrence detection and absence of long-term (>10-year) outcome data.

In resource-limited settings such as India, where patients often present with larger T1-T2 tumors and access to consistent high-quality radiotherapy may be constrained, the applicability of INSEMA becomes challenging. The trial's dependence on optimal WBRT and high-quality axillary imaging emphasizes the need for standardized ultrasound training and simplified radiation delivery protocols to facilitate safe implementation.

To conclude, the INSEMA trial marks a paradigm shift, proving axillary surgery omission is safe for carefully selected low-risk patients (HR+/HER2-, grade 1-2, stringent staging). While the trial convincingly demonstrates reduced morbidity without compromising short-term survival in carefully selected low-risk patients, its applicability remains limited for high-risk disease, and its reliance on adjuvant therapies obscures the independent role of axillary surgery omission. Nevertheless, INSEMA marks an important paradigm shift toward biologically guided de-escalation.

Future studies should include diverse tumor biology, report long-term outcomes, and integrate genomic risk stratification tools such as oncotype DX to refine patient selection.[3] If validated across broader populations, INSEMA may ultimately support guideline updates endorsing omission of axillary surgery in selected low-risk patients.

**Reshma R. Balachandran, Mayank Tripathi***

Department of Surgical Oncology, Mahamana Pandit Madan Mohan Malaviya Cancer Centre and Homi Bhabha Cancer Hospital, Homi Bhabha National Institute, Varanasi, Uttar Pradesh, India

***Correspondence to**
Dr. Reshma R. Balachandran,
E-mail: resh.bala12@gmail.com

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