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From Axillary Dissection to Sentinel Node Biopsy: Three Decades Redefining Axillary Surgery in Early Breast Cancer – A Narrative Review

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Abbreviations:
BCS: breast-conserving surgery;
ALND: axillary lymph node dissection;
SLNB: sentinel lymph node biopsy;
SLN: sentinel lymph node;
ASCO: American Society of Clinical Oncology;
RCT: randomized controlled trial;
NCCN: National Comprehensive Cancer Network;
OS: overall survival;
DFS: disease-free survival;
ESMO: European Society for Medical Oncology;
OSNA: one-step nucleic acid amplification;
ICG: indocyanine green.

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Rezumat

De la limfadenectomia axilară la biopsia ganglionului santinelă: trei decenii de evoluție și redefinire a chirurgiei axilare în cancerul mamar precoce - un review narativ

Introducere: Timp de peste un secol, limfadenectomia axilară (LA) a constituit standardul de aur în stadializarea axilară a cancerului mamar. Introducerea biopsiei ganglionului santinelă (BGS) în anii 1990 a marcat o schimbare fundamentală de paradigmă, oferind o alternativă minim invazivă cu acuratețe diagnostică echivalentă și morbiditate substanțial redusă. De atunci, o serie de studii clinice randomizate de referință au demonstrat în mod convergent că limfadenectomia axilară de completare poate fi omisă în siguranță la paciente selectate cu ganglioni santinelă pozitivi, fără a compromite rezultatele oncologice. Prezentul review narativ își propune să traseze evoluția de la limfadenectomia axilară sistematică la biopsia ganglionului santinelă, să evalueze critic studiile clinice pivotale care au fundamentat practica curentă și să analizeze controversele nerezolvate și direcțiile emergente în managementul axilar al cancerului mamar în stadiu precoce.
Material și Metodă: S-a efectuat o căutare sistematică a literaturii în bazele de date PubMed/MEDLINE, Scopus și Web of Science, utilizând termenii „sentinel lymph node biopsy", „axillary lymph node dissection", „breast cancer" și „axillary management". Au fost identificate, selectate și analizate studiile clinice randomizate de referință, review-urile sistematice, meta-analizele și ghidurile de practică clinică actuale.
Rezultate: Studiul NSABP B-32 a validat BGS ca instrument de stadializare cu acuratețe echivalentă LA. Studiul ACOSOG Z0011 a demonstrat absența oricărui beneficiu în supraviețuire al LA de completare la pacientele cu 1-2 ganglioni santinelă metastatici tratate prin chirurgie conservatoare a sânului. Studiul AMAROS a evidențiat că radioterapia axilară asigură un control locoregional comparabil cu LA, asociind o morbiditate semnificativ inferioară. Studiul IBCSG 23-01 a confirmat că LA poate fi omisă în prezența micrometastazelor la nivelul ganglionului santinelă. Cel mai recent, studiul SENOMAC a extins aceste concluzii la o populație mai largă de paciente cu 1-2 macrometastaze ganglionare.
Concluzii: BGS a înlocuit LA ca standard terapeutic pentru stadializarea axilară în

cancerul mamar precoce cu axilă clinic negativă. De-escaladarea progresivă a intervenției chirurgicale axilare a fost susținută în mod constant de evidențe științifice de nivel înalt, fără compromiterea supraviețuirii. Cercetările viitoare vor stabili fezabilitatea unei de-escaladări suplimentare, în special în contextul chimioterapiei neoadjuvante.

Cuvinte cheie: cancer mamar, chirurgia ganglionilor limfatici axilari, biopsia ganglionului santinelă, de-escaladare chirurgicală, ACOSOG Z0011

Abstract

Introduction: Axillary lymph node dissection (ALND) has been the gold standard for axillary staging in breast cancer for over a century. The introduction of sentinel lymph node biopsy (SLNB) in the 1990s offered a minimally invasive alternative with comparable staging accuracy and significantly reduced morbidity. Multiple landmark randomized controlled trials have since demonstrated that completion ALND can be safely omitted in selected patients with positive sentinel lymph nodes without compromising oncologic outcomes. This narrative review aims to examine the evolution from ALND to SLNB, critically evaluate the landmark trials that shaped current practice, and discuss ongoing controversies and future directions in axillary management in early breast cancer.

Materials and Methods: A comprehensive literature search was performed using PubMed/MEDLINE, Scopus, and Web of Science databases. Search terms included "sentinel lymph node biopsy", "axillary lymph node dissection", "breast cancer", and "axillary management." Landmark randomized controlled trials, systematic reviews, meta-analyses, and current clinical practice guidelines were identified and reviewed.

Results: The NSABP B-32 trial validated SLNB as an accurate staging tool equivalent to ALND. The ACOSOG Z0011 trial demonstrated no survival benefit from completion ALND in patients with 1-2 positive sentinel lymph nodes undergoing breast-conserving surgery. The AMAROS trial demonstrated that irradiation of the axilla provides equivalent locoregional disease control compared to surgical dissection, while carrying a substantially more favorable morbidity profile.The IBCSG 23-01 trial confirmed that ALND can be omitted for sentinel node micrometastases. Most recently, the SENOMAC trial extended these findings to patients with 1-2 macrometastases in a broader population.

Conclusions: SLNB has become the established standard for axillary staging in early breast cancer with a clinically negative axilla, superseding ALND entirely. Progressive de-escalation of axillary surgery has been consistently supported by high-level evidence without compromising survival. Future research will determine the feasibility of further de-escalation, particularly after neoadjuvant chemotherapy.

Keywords: breast cancer, axillary lymph node surgery, sentinel lymph node biopsy, surgical de-escalation, ACOSOG Z0011

Introduction

Breast cancer remains the most commonly diagnosed malignancy among women worldwide, with an estimated 2.3 million new cases diagnosed annually (1). Accurate staging of the axilla is a cornerstone of breast cancer management, guiding treatment decisions regarding adjuvant systemic therapy and locoregional treatment. For over a century, axillary lymph node dissection (ALND) served as the gold standard for axillary staging, providing crucial prognostic information but at the cost of significant morbidity (2,3).

The introduction of sentinel lymph node biopsy (SLNB) in the 1990s by Giuliano et al. (4) and Krag et al. (5) represented a paradigm shift in the surgical management of the axilla. By identifying and removing only the first lymph node(s) receiving lymphatic drainage from the primary tumor, SLNB offered a minimally invasive alternative with equivalent staging accuracy and substantially reduced morbidity. Since then, multiple landmark randomized controlled trials have progressively demonstrated that the extent of axillary surgery can be safely de-escalated without compromising oncologic outcomes (6-10).

This narrative review aims to examine the historical evolution from ALND to SLNB, critically evaluate the landmark clinical trials that have shaped current practice, summarize current guidelines, and discuss ongoing controversies and future directions in axillary management in early breast cancer.

Historical Background of Axillary Lymph Node Dissection

The history of axillary surgery in breast cancer is inseparable from the legacy of William Stewart Halsted,

who, in 1882, introduced the radical mastectomy, a procedure consisting on the principle that oncologic cure demanded the en bloc removal of the breast, both pectoral muscles, and all regional lymphatic tissue (2). Within this framework, axillary lymph node dissection encompassing levels I and II, and occasionally extending to level III, became the undisputed standard for both staging and regional treatment, a role it maintained unchallenged for over a century (2,3). The procedure was performed routinely in all patients with invasive breast cancer, regardless of preoperative clinical examination or imaging findings of the axilla, reflecting the prevailing belief that complete axillary clearance was indispensable for accurate prognostication and adequate locoregional control (3). Indeed, the metastatic lymph node count obtained through ALND emerged as one of the strongest independent predictors of overall survival, disease-free survival, and recurrence risk, and became the cornerstone of the pathological TNM staging system upon which adjuvant treatment strategies were built (1,3). Beyond its undeniable value as a staging tool, ALND was also regarded as a direct therapeutic benefit, predicated on the hypothesis that the systematic excision of clinically occult nodal metastases could interrupt the locoregional cascade of disease spread and reduce the incidence of axillary recurrence (2). Nevertheless, by the late 20th century, Bernard Fisher and other investigators had compellingly demonstrated that breast cancer behaves as a systemic disease from its inception, fundamentally challenging the Halstedian paradigm of locoregional containment. This conceptual shift, together with the growing efficacy of adjuvant systemic and radiation therapies, progressively undermined the rationale for routine complete axillary dissection and set the stage for the development of less invasive axillary staging strategies

While ALND fulfilled a critical role in axillary staging throughout most of the modern surgical era, it was invariably accompanied by a significant burden of procedure-related morbidity that adversely affected both physical function and long-term quality of life. In a landmark prospective analysis of surgical complications among patients enrolled in the ACOSOG Z0011 trial, Lucci et al. (11) provided robust evidence that ALND was associated with substantially higher rates of postoperative adverse events compared to SLNB alone, including wound infections, seroma requiring aspiration, and clinically significant lymphedema. Lymphedema represents the most clinically consequential long-term complication, reported in 15-25% of patients following ALND, manifesting as chronic progressive swelling of the ipsilateral upper extremity that impairs daily activities and often necessitates lifelong compression therapy and physiotherapy (11). Furthermore, the extensive dissection inherent to ALND carries a well-documented risk of injury to the intercostobrachial nerve, leading to persistent sensory disturbances, including numbness, dysesthesia, and neuropathic pain, along the medial aspect of the upper arm and axilla, as well as shoulder dysfunction with restricted range of motion that may limit the patient's ability to perform overhead activities (11). Collectively, these complications underscore the disproportionate morbidity of ALND relative to its staging benefit and provided the strongest clinical argument for the development of less invasive axillary assessment strategies (4,11).

The substantial morbidity associated with ALND became increasingly difficult to justify as accumulating evidence revealed that a significant proportion of patients subjected to complete axillary clearance ultimately harbored no nodal metastases, thus deriving no therapeutic benefit from a procedure that nonetheless exposed them to considerable long-term sequelae (3,6). This clinical reality was further compounded by the conceptual revolution initiated by Bernard Fisher through the NSABP B-04 trial, which fundamentally challenged the previous paradigm by demonstrating that variations in the extent of locoregional surgical intervention; including the omission of routine axillary dissection, failed to produce significant differences in distant disease-free survival or overall survival at 25-year follow-up (3). These findings lent powerful support to the emerging view that breast cancer behaves as a systemic disease from its inception, rather than one that spreads exclusively through orderly, contiguous locoregional extension. Together, these converging lines of evidence: the unnecessary morbidity inflicted upon node-negative patients and the evolving biological understanding of breast cancer dissemination, created a compelling scientific rationale for the development of a more selective, less morbid approach to axillary staging. It was within this context that the sentinel lymph node hypothesis was conceptualized, proposing that the metastatic status of the first lymph node receiving direct lymphatic drainage from the primary tumor could accurately predict the pathological condition of the entire axillary basin, thereby sparing node-negative patients the consequences of a complete dissection (4,5). The successful translation of this concept into clinical practice by Giuliano et al. (4) using vital blue dye and independently by Krag et al. (5) using a radioactive tracer catalyzed what is now widely recognized as one of the most consequential paradigm shifts in the surgical management of this disease.

Development of Sentinel Lymph Node Biopsy

Genesis and early clinical evidence

The sentinel lymph node hypotesis is predicated on the observation that lymphatic drainage from a primary tumor follows an orderly, predictable anatomic pathway, arriving first at one or a small group of lymph nodes before reaching the remainder of the regional basin. This principle was first described by Cabanas (17) in 1977, who identified a consistent pattern of lymphatic drainage from penile carcinomas to a specific inguinal node whose pathological status reflected the involvement of the entire nodal basin. The concept was subsequently extended to cutaneous melanoma by Morton et al. (18) in 1992, who demonstrated that intraoperative injection of vital blue dye could reliably map the lymphatic channels and identify the sentinel node draining the primary tumor site. Recognizing the potential applicability of this approach to breast cancer, Giuliano et al. (4) published their landmark experience in 1994, reporting that intraoperative lymphatic mapping using isosulfan blue dye injected at the primary tumor site successfully identified the sentinel lymph node in 114 of 174 procedures (65.5%), with the sentinel node accurately predicting the axillary nodal status in 95.6% of identified cases. Importantly, the authors documented a clear learning curve, with all false-negative results concentrated in the early phase of the study and 100% predictive accuracy achieved in the final 87 consecutive procedures (4). In a parallel but independent line of investigation, Krag et al. (19) described in 1993 an alternative technique utilizing peritumoral injection of technetium-99m labeled sulfur colloid followed by intraoperative localization with a handheld gamma probe, achieving successful sentinel node identification in 18 of 22 patients and demonstrating that sentinel node metastatic status correctly predicted the pathological condition of the remaining axilla in all node-positive cases. These two complementary approaches, vital blue dye mapping and radiocolloid-guided gamma probe detection, were subsequently combined into the dual-tracer technique that became the standard method for sentinel node identification in breast cancer, with mature series consistently reporting detection rates exceeding 95% (5,12).

Technique

The sentinel lymph node biopsy technique relies on the injection of one or both of two complementary tracers, a vital blue dye (isosulfan blue, patent blue V, or methylene blue) and a radiopharmaceutical agent (technetium-99m labeled sulfur colloid or nanocolloid) into the breast parenchyma via peritumoral or subareolar routes. The blue dye is taken up by afferent lymphatic channels and visually stains the sentinel node, enabling its identification through a small axillary incision, while the radiocolloid is detected intraoperatively using a handheld gamma probe that directs the surgeon toward the node with the highest radioactive uptake. Although each tracer independently achieves acceptable identification rates, the combination of both modalities in a dual-mapping approach consistently yields sentinel node identification rates exceeding 95% with false-negative rates below 10%, figures that proved sufficiently robust to establish SLNB as a clinically reliable staging procedure capable of replacing the diagnostic function of complete axillary dissection (5,6,12).

Validation: NSABP B-32

Definitive confirmation that sentinel lymph node biopsy could serve as a self-sufficient staging method was furnished by the NSABP B-32 trial, which remains the largest randomized surgical investigation ever performed in breast cancer (6). This phase III multicenter trial, conducted across 80 centers in the United States and Canada between 1999 and 2004, enrolled 5,611 women with clinically node-negative invasive breast cancer who were randomized to sentinel lymph node resection followed by mandatory axillary lymph node dissection (Group 1), or sentinel lymph node resection alone with completion ALND performed only if the sentinel node contained metastatic disease (Group 2). Among 3,986 evaluable patients whose sentinel nodes were free of metastatic disease, outcomes were statistically indistinguishable between the two treatment arms across all primary endpoints. With approximately eight years of median follow-up, overall survival as estimated by Kaplan-Meier analysis was 91.8% in the combined SLNB-and-ALND group versus 90.3% in the SLNB-only group (HR 1.20; 95% CI 0.96–1.50; p=0.12), while disease-free survival showed a comparable pattern at 82.4% versus 81.5% (HR 1.05; 95% CI 0.90–1.22; p=0.54) (6). Crucially, axillary recurrence was an exceptionally rare event in both arms (8 versus 14 events; p=0.22), reinforcing the conclusion that omitting complete axillary clearance in sentinel-node-negative patients carries no detectable penalty in regional control. On the strength of these results, SLNB was firmly established as the reference procedure for axillary evaluation in clinically node-negative breast cancer. By demonstrating that an uninvolved sentinel node reliably excludes significant residual axillary disease, the trial validated an approach that avoids the substantial

morbidity of complete dissection in most patients without incurring any oncologic cost.

Landmark Clinical Trials

The following trials collectively transformed the management of the axilla in early breast cancer, progressively de-escalating surgical intervention while maintaining oncological safety.

ACOSOG Z0011

While the NSABP B-32 trial established SLNB as an accurate and safe staging alternative to ALND in sentinel-node-negative patients, the more fundamental clinical question remained un-resolved: whether completion ALND could be safely omitted even when the sentinel node harbored metastatic disease, thereby challenging the century-old surgical axiom that identified nodal metastases must be removed. The ACOSOG Z0011 trial took on this unresolved question directly, generating what has been widely considered the most consequential shift in surgical practice for breast cancer in the modern era (7,8).

The trial, a phase III noninferiority study spanning 115 centers from 1999 to 2004, assigned 891 women to completion ALND or no additional axillary treatment. Eligibility required clinical T1-T2 invasive breast cancer, absence of palpable axillary adenopathy, and hematoxylin and eosin-confirmed metastatic disease in one or two sentinel lymph nodes. Protocol requirements stipulated that all patients receive breast-conserving surgery with tangential whole-breast irradiation alongside systemic adjuvant treatment. Intentional irradiation of the axillary and supraclavicular nodal stations was categorically excluded by trial design, a provision intended to isolate the therapeutic contribution of surgical dissection from that of radiation. Survival without axillary recurrence was the central question, operationalized through a noninferiority design with an overall survival hazard ratio cap of 1.3. Across two successive analyses, the first at 6.3 years (7), the second and definitive report at 9.3 years of median follow-up (8), the absence of completion dissection conferred no detectable oncological penalty. Ten-year overall survival stood at 86.3% among patients who underwent sentinel node biopsy alone compared with 83.6% among those who received ALND (HR 0.85; noninferiority p=0.02), while freedom from locoregional failure was virtually indistinguishable at 94.1% and 93.2%, respectively (p=0.36) (8). Perhaps most remarkably, pathological analysis of the ALND specimens revealed that 27% of patients in the dissection arm harbored additional metastatic non-sentinel nodes; disease that was, by definition, left undisturbed in the SLNB-alone arm yet produced no detectable detriment to survival or regional control. This observation fundamentally challenged the long-held premise that all identifiable nodal disease requires surgical extirpation, lending further support to the systemic disease paradigm first articulated by Fisher and suggesting that adjuvant systemic therapy and tangential breast irradiation may effectively sterilize low-volume residual axillary disease.

The clinical impact was swift and transformative. Within years of publication, the rate of completion ALND among Z0011-eligible patients declined from over 70% to below 20% at major academic centers, representing one of the most rapid de-escalation shifts in modern surgical oncology (8). International guidelines from NCCN, ASCO, and ESMO incorporated the Z0011 criteria into their recommendations, fundamentally altering the standard of care for patients with limited sentinel node metastases. However, the trial carried well-recognized limitations that constrained its generalizability. Enrollment closed prematurely at 891 of a planned 1,900 patients due to a lower-than-anticipated event rate, limiting statistical power and precluding definitive subgroup analyses. The eligibility criteria were narrowly defined, restricted to patients undergoing breast-conserving surgery with tangential whole-breast irradiation, and subsequent review of radiation records revealed that a substantial proportion of patients received high tangential fields or supraclavicular irradiation that may have incidentally treated the lower axilla, introducing an uncontrolled therapeutic variable. Critically, patients undergoing mastectomy, those with three or more positive sentinel nodes, and those receiving neoadjuvant chemotherapy were excluded, leaving these increasingly prevalent clinical populations without direct evidence from the trial and creating the impetus for subsequent studies, most notably the SENOMAC trial, to address these unresolved questions (13).

AMAROS Trial

While the Z0011 trial demonstrated that completion ALND could be omitted entirely in selected patients with limited sentinel node disease, it left unanswered a complementary question of considerable clinical relevance: for patients with a positive sentinel node who warrant further axillary treatment, could radiotherapy replace surgical dissection as the means of achieving regional control, and would such a substitution meaningfully reduce treatment-related morbidity? The EORTC 10981-22023 AMAROS trial, a multicenter phase III noninferiority study conducted

across 34 centers in nine European countries between 2001 and 2010, directly addressed this question (9,20). Of 4,806 patients with clinically T1-T2 node-negative breast cancer enrolled in the trial, 1,425 with a positive sentinel node, approximately 60% of whom harbored macrometastases, were randomized to completion ALND (n=744) or axillary radiotherapy (n=681). The initial 5-year results reported by Donker et al. (9) and the preplanned 10-year update published by Bartels et al. (20) yielded remarkably concordant findings. At 10 years, the cumulative incidence of axillary recurrence was 0.93% after ALND versus 1.82% after axillary radiotherapy — a nonsignificant difference (HR 1.71; p=0.365) — with comparable overall survival (84.6% versus 81.4%; HR 1.17; p=0.26) and disease-free survival (75.0% versus 70.1%; HR 1.19; p=0.11) (20). Notably, the axillary recurrence rates in both arms were far lower than the protocol-anticipated 2% for ALND and 4% threshold for noninferiority, rendering the planned formal non-inferiority analysis underpowered, though this limitation paradoxically reinforced the central message of the trial: axillary recurrence after either modality was an exceedingly rare event. The most clinically consequential finding, however, was not oncological equivalence but the pronounced divergence in treatment-related morbidity. Lymphedema, assessed by a clinician-measured arm circumference increase of at least 10%, was approximately twice as prevalent after ALND at every time point evaluated: at 5 years, 28% of patients who underwent ALND reported lymphedema compared with 14% after axillary radiotherapy (p<0.0001), a difference that persisted at 10 years, with patients in the surgical arm continuing to report significantly worse arm swelling and reduced mobility on quality-of-life assessments (9,20). The AMAROS trial thus expanded the therapeutic options available for sentinel-node-positive breast cancer in a fundamentally different manner than Z0011. Where Z0011 established that selected patients require no further axillary intervention, AMAROS demonstrated that when treatment of the axilla is deemed necessary, radiation achieves equivalent regional control to surgical dissection with substantially less morbidity, offering clinicians and patients a nonsurgical alternative that proved particularly valuable for those who fell outside the narrow Z0011 eligibility criteria. The trial did identify a higher incidence of second primary cancers in the radiotherapy arm (11.0% versus 7.7%), driven predominantly by contralateral breast cancers, though the investigators considered a causal relationship with axillary irradiation unlikely (20). A further acknowledged limitation is that the radiation fields employed in AMAROS were broader than what current techniques would require, suggesting that contemporary axillary radiotherapy may achieve similar regional control with even less collateral morbidity.

IBCSG 23-01

The advent of enhanced pathological techniques for sentinel node evaluation: serial sectioning, immunohistochemistry, and molecular assays had substantially increased the detection of minimal nodal disease, particularly micrometastases (tumor deposits ≤ 2 mm), whose prognostic significance and therapeutic implications remained incompletely defined. While Z0011 enrolled patients with both micro- and macrometastatic sentinel node involvement, its subgroup analyses lacked the power to draw definitive conclusions about micrometastases specifically. The IBCSG Trial 23-01, a multicenter phase III noninferiority study conducted across 27 institutions between 2001 and 2010, addressed this question directly by restricting enrollment exclusively to patients with clinically node-negative breast cancer (tumors ≤ 5 cm) whose sentinel nodes harbored only micrometastatic disease without extracapsular extension (10,21). A total of 934 patients were randomized to completion ALND or no further axillary treatment. Unlike Z0011, the trial was not restricted to patients undergoing breast-conserving surgery, providing evidence applicable across the full spectrum of breast surgical approaches. At a median follow-up of 9.7 years, the 10-year update confirmed and reinforced the initial 5-year findings: disease-free survival was 76.8% in the no-dissection group versus 74.9% in the ALND group (numerically favoring observation) with no significant difference in overall survival and axillary recurrence remaining an exceptionally rare event in both arms (10,21). The investigators explicitly noted the concordance of these results with the 10-year Z0011 data, concluding that together these trials provide high-level evidence supporting the omission of completion ALND when sentinel node tumor burden is minimal or moderate (21). The clinical ramification of IBCSG 23-01 was both specific and far-reaching: it established definitively that sentinel node micrometastases; findings that had become increasingly common with refined pathological techniques and that had historically prompted reflexive completion axillary dissection, do not warrant further surgical intervention, thereby sparing a substantial proportion of patients from a morbid procedure of no demonstrable oncological benefit.

SENOMAC trial

The collective evidence from Z0011, AMAROS, and IBCSG 23-01 had shifted clinical practice decisively

toward axillary de-escalation, yet each trial carried limitations that left important questions unresolved and fueled persistent skepticism in certain clinical scenarios. Z0011 excluded patients undergoing mastectomy and was potentially confounded by incidental axillary irradiation from high tangential fields; AMAROS, though it included mastectomy patients, comprised only 17% in that subgroup and substituted radiation for surgery rather than omitting axillary treatment entirely; and IBCSG 23-01 was restricted to micrometastatic disease. The SENOMAC trial, a Scandinavian-led international phase III noninferiority study published by de Boniface et al. in the New England Journal of Medicine in 2024, was designed from its inception to be the definitive confirmatory trial, enrolling a larger, broader, and more contemporary population than any of its predecessors while addressing their acknowledged design limitations head-on (13). Conducted across 67 centers in Sweden, Denmark, Germany, Greece, and Italy between 2015 and 2021, SENOMAC randomized 2,540 patients (per-protocol population) with clinically node-negative T1-T3 breast cancer (confirmed by mandatory preoperative axillary ultrasound) and one or two sentinel node macrometastases to sentinel node biopsy alone (n=1,335) or completion ALND (n=1,205). The trial population was deliberately representative of real-world practice in a way that prior trials had not been: over a third underwent mastectomy, over a third had extracapsular extension of nodal metastases, tumors ranged up to T3 stage, and the full spectrum of molecular subtypes was represented (13). Most critically, approximately 89% of patients received, in both arms, deliberate regional nodal irradiation administered according to contemporary national guidelines; not the incidental low-axillary coverage of tangential fields of Z0011, but intentional, protocol-specified nodal treatment, thereby clarifying the role of radiation as the therapeutic partner to sentinel node biopsy in the post-ALND era. At a median follow-up of 46.8 months, sentinel node biopsy alone proved robustly noninferior to completion ALND: the estimated 5-year recurrence-free survival was 89.7% versus 88.7% (HR 0.89; 95% CI, 0.66–1.19; non-inferiority p<0.001), and 5-year overall survival was 92.9% versus 92.0% (13). No examined subgroup, including patients who underwent mastectomy, those with extracapsular extension, and those with T3 disease, demonstrated any benefit from axillary dissection, effectively dismantling the residual argument that these clinical features necessitate more aggressive surgical management of the axilla. Taken together with the concordant long-term data from Z0011, AMAROS, and IBCSG 23-01, the SENOMAC results represent the culmination of two decades of evidence confirming that in clinically node-negative breast cancer with limited sentinel node macrometastases, completion ALND can be safely omitted when adequate systemic therapy and regional nodal irradiation are administered — a conclusion that has now been endorsed by updated guidelines from ASCO, NCCN, and ESMO (13,14,15,16).

Summary of landmark trials

Taken together, these five landmark trials mentioned in *Table 1* (spanning two decades and over 12,000 randomized patients) deliver a remarkably consistent message: progressive de-escalation of axillary surgery does not compromise survival or regional disease control, while substantially reducing the burden of treatment-related lymphedema, shoulder dysfunction, and sensory impairment. This convergence of evidence from independently conceived studies with complementary populations and differing comparator strategies has fundamentally recast the role of axillary intervention in breast cancer, transforming it from a therapeutic procedure intended to eradicate regional disease into a staging tool whose primary purpose is to inform systemic treatment decisions rather than deliver local control.

Current Guidelines and Clinical Practice

The evidence generated by these trials has been uniformly incorporated into the clinical practice guidelines of all major oncological societies.

The NCCN (Version 1.2026), ASCO (2025 guideline

Table 1. Summary of landmark randomized controlled trials in axillary management of early breast cancer

Trial	Year	Population	Comparison	Key Finding
NSABP B-32	2010	Clinically node-negative	SLNB + ALND vs. SLNB alone	SLNB validated as accurate staging
ACOSOG Z0011	2011	1-2 positive SLNs, T1-T2	SLNB alone vs. completion ALND	No survival difference; ALND safely omitted
IBCSG 23-01	2013	SLN micrometastases	ALND vs. no ALND	No benefit from ALND for micrometastases
AMAROS	2014	Positive SLN	ALND vs. axillary radiation	Equivalent control; less morbidity with RT
SENOMAC	2024	1-2 SLN macrometastases	SLNB alone vs. completion ALND	SLNB alone non-inferior

update), and ESMO (2024 clinical practice guideline) now converge on the following core recommendations: a robust body of trial evidence now supports SLNB as the only axillary staging procedure required in early breast cancer with no clinical suspicion of nodal involvement. For patients treated with breast-conserving surgery and tangential whole-breast irradiation, metastatic disease confined to one or two sentinel nodes is no longer regarded as justification for proceeding to complete axillary clearance. Prompted by the SENOMAC findings, this conservative approach has been broadened to encompass the mastectomy setting as well: in patients with clinically negative axillae, tumors of 5 cm or less, and no more than two positive sentinel nodes, completion ALND can be safely omitted provided that postmastectomy radiation with intentional coverage of the regional nodal basins is incorporated into the treatment plan (14,15,22). ESMO additionally endorses axillary radiotherapy as a less morbid alternative to ALND for patients requiring axillary treatment, based on the AMAROS evidence (15).

Perhaps most remarkably, the concept of de-escalation has now reached the sentinel node biopsy itself. On the basis of the INSEMA trial data, the 2026 NCCN guidelines have sanctioned the omission of any axillary surgical staging in a rigorously selected subset of patients: postmenopausal women aged 50 years or older harboring small (≤ 2 cm), low-grade, hormone receptor-positive and HER2-negative breast cancers with a sonographically unremarkable axilla, for whom breast-conserving therapy constitutes the planned treatment strategy (14). The pace of guideline evolution over the past decade, from mandating ALND for all node-positive patients, to permitting its omission, to now questioning the necessity of sentinel node biopsy itself in select cases, underscores how profoundly the accumulating trial evidence has reshaped the paradigm of axillary management.

The adoption of these recommendations in clinical practice has been broadly consistent across Western Europe and North America but more heterogeneous in other regions. In Romania, SLNB was introduced in 2003 at the Alexandru Trestioreanu Oncology Institute in Bucharest and has since expanded progressively, as documented by several institutional series and reviews published in this journal (23-26). However, the transition from routine ALND to selective sentinel-node-based management remains constrained by later-stage disease presentation, limited nuclear medicine infrastructure outside major academic centers, and the need for ongoing surgical training in the technique. The present review, encompassing the complete evidence through SENOMAC and the 2025 ASCO guideline update, aims to provide Romanian surgeons with a current, comprehensive framework for implementing evidence-based axillary de-escalation in their practice.

Ongoing Controversies and Future Directions

SLNB after neoadjuvant chemotherapy

The application of SLNB to patients who present with clinically node-positive (cN+) disease and convert to clinically node-negative (ycN0) status after neoadjuvant chemotherapy remains one of the most actively debated areas in contemporary axillary management. Concerns center on potentially altered lymphatic drainage and non-uniform tumor regression within the axillary basin, which may compromise the accuracy of sentinel node identification. Three prospective studies addressed this question simultaneously.

The SENTINA trial cast a critical light on the limitations of sentinel node biopsy in the post-neoadjuvant setting. Among patients whose nodal disease was downstaged to clinically negative status after chemotherapy, the sentinel node was successfully identified in only four out of five cases, and the overall FNR stood at 14.2%. The number of nodes harvested proved to be the single most decisive determinant of staging accuracy: when only one sentinel node was recovered, nearly one quarter of metastatic axillae escaped detection (FNR 24.3%), whereas retrieval of three or more nodes brought the FNR down to an acceptable 7.3% (15). The ACOSOG Z1071 trial, enrolling 756 women with biopsy-proven cN1–N2 disease across 136 institutions, found an FNR of 12.6% among patients with cN1 disease in whom at least two sentinel nodes were examined; exceeding the prespecified acceptability threshold of 10% (29). The Canadian SN FNAC study achieved an FNR of 8.4% with mandatory immunohistochemistry and classification of isolated tumor cells as positive; without immunohistochemistry, the FNR would have risen to 13.3% (30). Across all three trials, subgroup analyses consistently identified technical factors that reduced the FNR below 10%: use of dual-tracer mapping (radiocolloid combined with blue dye), retrieval of three or more sentinel nodes, and confirmation that the biopsy-proven metastatic node was among those retrieved. Building on these findings, Caudle et al. (16) introduced targeted axillary dissection (TAD), whereby a radiopaque clip is placed in the biopsy-proven metastatic node at diagnosis and selectively localized and excised alongside standard SLNB after completion of chemotherapy; this approach reduced the FNR to approximately 2%. Notably, the clipped node was not identified among the sentinel nodes in

approximately 23% of cases, indicating that conventional SLNB alone would have missed the index node in nearly one quarter of patients. Current NCCN and ESMO guidelines now endorse SLNB after neoadjuvant chemotherapy in initially cN1 patients who convert to ycN0, provided that dual tracers are used, at least three sentinel nodes are retrieved, and the clipped node is confirmed among the excised specimens.

TAD is increasingly adopted as a refinement that further improves staging accuracy in this challenging population, though its implementation remains variable across centers.

Omission of axillary surgery in complete responders

Following the established safety of reduced axillary intervention after neoadjuvant chemotherapy, the next investigational frontier concerns the complete omission of axillary surgery in patients whose nodal disease has been fully eradicated by systemic treatment. This scenario arises most frequently in HER2-positive and triple-negative subtypes, where current neoadjuvant protocols achieve complete pathological response in the axillary nodes in approximately six to seven out of every ten patients. Several randomized trials are addressing this question: the NSABP B-51/RTOG 1304 trial is evaluating whether regional nodal irradiation can be omitted in patients who convert from cN1 to ypN0, while the Alliance A011202 trial compares axillary radiotherapy versus completion ALND in patients with residual sentinel node disease after chemotherapy (31,32). Parallel efforts are investigating whether advanced imaging; axillary ultrasound, MRI, and PET-CT, or minimally invasive percutaneous biopsy of the clipped node can identify complete responders with sufficient accuracy to forgo surgical staging altogether; however, no imaging modality or combination has yet achieved the negative predictive value required to replace histological confirmation. Until these trials report mature results, axillary surgery remains the standard for confirming nodal response after neoadjuvant chemotherapy, but the direction of ongoing research suggests that selected complete responders may be safely spared any axillary intervention in the near future.

Novel technologies

Several emerging technologies have the potential to refine or replace conventional methods for sentinel node detection and intraoperative assessment. Indocyanine green (ICG) fluorescence imaging is the most clinically mature alternative. ICG, a near-infrared fluorescent dye, enables real-time transcutaneous visualization of lymphatic channels and sentinel nodes without ionizing radiation or nuclear medicine infrastructure. Meta-analyses have demonstrated pooled sentinel node detection rates of 98%, comparable to or exceeding combined radiocolloid and blue dye, with a lower false-negative rate than blue dye alone and no significant adverse effects (33,34).

These properties make ICG particularly attractive for resource-variable settings where access to nuclear medicine is limited, and several European and Asian institutions have adopted it as a standalone tracer or as a component of combined mapping protocols. In intraoperative sentinel node assessment, the one-step nucleic acid amplification (OSNA) assay offers a standardized molecular alternative to frozen section histology. OSNA quantifies cytokeratin 19 mRNA copy numbers in homogenized lymph node tissue via automated isothermal amplification, delivering results within 30-40 minutes. Pooled analyses report a 96% concordance rate with definitive histopathology and a negative predictive value exceeding 97% (35). By analyzing the entire node rather than representative sections, OSNA reduces sampling error inherent to frozen section and provides semiquantitative total tumor load data that may predict non-sentinel node involvement. Its principal limitation is the destruction of tissue during homogenization, precluding subsequent histopathological review.

Superparamagnetic iron oxide (SPIO) nanoparticles represent a further radiation-free alternative. Injected peritumorally, SPIO particles are detected intraoperatively using a handheld magnetometer, with the SentiMAG multisite trial reporting detection rates equivalent to the radiocolloid technique (36). However, iron-induced discoloration of nodes and potential interference with subsequent imaging have limited broader adoption. Finally, artificial intelligence, specifically deep learning applied to digitized whole-slide images, is emerging as a tool for histopathological assessment of lymph node specimens. The CAMELYON16 challenge demonstrated that the best-performing algorithms achieved an area under the receiver operating characteristic curve of 0.994 for detecting nodal metastases, exceeding the diagnostic performance of pathologists operating under simulated clinical time constraints (37). Subsequent studies have confirmed that algorithm-assisted pathologists achieve higher sensitivity for micrometastasis detection than either the algorithm or the pathologist alone, while significantly reducing review time. Although these tools remain in the validation phase, they hold substantial promise for standardizing nodal assessment, reducing interobserver variability, and improving the detection of low-volume metastatic disease.

Conclusions

Three decades of methodical investigation have fundamentally redefined the role of axillary surgery in early breast cancer. SLNB has established itself as the uncontested standard for axillary staging in clinically node-negative disease, and five seminal randomized trials, NSABP B-32, ACOSOG Z0011, AMAROS, IBCSG 23-01, and SENOMAC have together assembled an evidence base of remarkable consistency and strength, demonstrating that completion ALND can be judiciously withheld in a progressively expanding population of patients whose sentinel node disease is limited in volume. This body of evidence has simultaneously confirmed two inseparable truths: that oncological safety, measured by both survival and regional disease control, is preserved in its entirety, and that the considerable toll of complete axillary clearance: lymphedema, impaired shoulder function, and persistent pain can be averted for the majority of patients who would previously have borne it. The frontier of de-escalation now extends to the post-neoadjuvant setting, where targeted axillary dissection has reduced false-negative rates to clinically acceptable levels, and to the emerging question of whether axillary surgery can be omitted entirely in patients who achieve a complete nodal response. Novel technologies, including ICG fluorescence mapping, OSNA molecular assessment, magnetic tracers, and artificial intelligence-assisted pathological evaluation, are poised to further refine patient selection, improve intraoperative decision-making, and broaden the applicability of minimally invasive staging strategies. Taken together, the evidence accumulated over the past two decades supports a continued, evidence-driven transition from radical axillary clearance toward individualized, biology-guided management in which the extent of axillary intervention is calibrated to each patient's disease biology and treatment context rather than dictated by anatomic convention.

Conflicts of Interest

The authors have no conflict of interest to disclose.

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