



## De-escalating axillary surgery in early-stage breast cancer<sup>☆</sup>

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### ABSTRACT

The role of axillary surgery has evolved over the last three decades from routine axillary lymph node dissection (ALND) to sentinel lymph node biopsy to omission of axillary surgery altogether in select patients. This evolution has been achieved through the design and conduct of multiple clinical trials demonstrating that ALND does not impact survival and is not necessary for local control in patients with early-stage breast cancer and limited nodal involvement. Importantly, this practice-changing shift mirrored the trend towards earlier stage at diagnosis and the recognition of the interplay between local and systemic therapies in maintaining local control. There are numerous clinical scenarios today in which axillary staging can be safely avoided, including (1) DCIS treated with lumpectomy, (2) at the time of contralateral prophylactic mastectomy, and (3) in elderly patients with early-stage, HR+/HER2- clinically node-negative (cN0) disease. Ongoing clinical trials seek to expand the cohorts in which surgical nodal staging can be omitted. These populations include a broader range of early-stage, cN0 patients undergoing upfront surgery, as seen in the SOUND, INSEMA, BOOG 2013–08, SOAPET and NAUTILUS trials. Omission of axillary surgery in cN0 patients with HER2+ or triple-negative disease treated with neoadjuvant chemotherapy is also being tested in the ASICS and EUBREAST-01 trials. Continued advances in imaging and the growing role of genomic assays in selecting patients for systemic therapy are likely to further minimize the need for axillary surgery; thereby further reducing the morbidity of local therapy for women with breast cancer.

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### 1. Introduction

The role of axillary surgery in the management of breast cancer has evolved considerably over the last three decades; moving away from axillary node dissection to sentinel lymph node biopsy (SLNB) and now perhaps to omission of axillary surgery altogether in appropriately selected patients (Fig. 1) [1–25]. This trend towards less aggressive axillary management is supported by robust literature demonstrating reduced patient morbidity without compromising oncologic outcomes. Ongoing efforts now challenge us to consider the true role of axillary staging in the modern era.

It has long been recognized that axillary surgery does not impact survival. This was first demonstrated in the landmark NSABP B-04

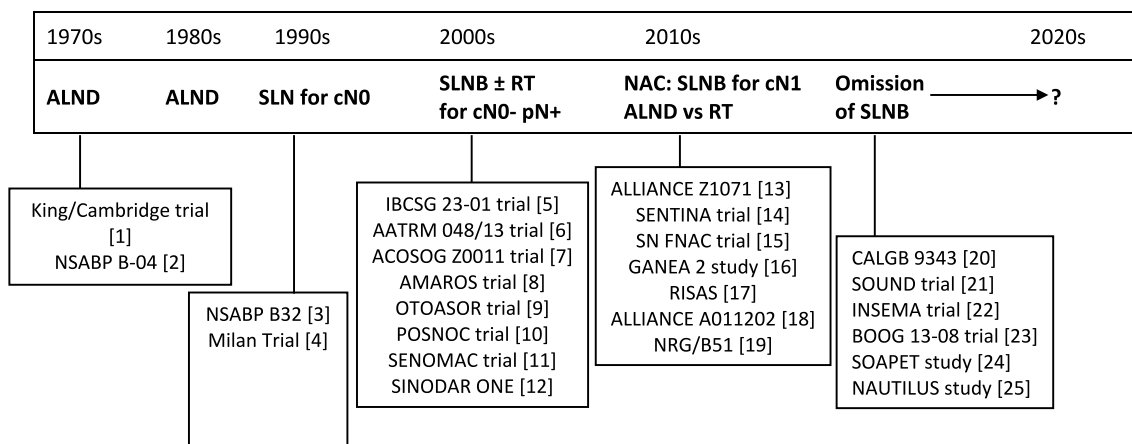
and Kings/Cambridge trials where patients with operable breast cancer and clinically negative axillae (cN0) were randomized to variations of axillary management [1,2]. Notably, in both trials, axillary treatment (surgery or radiation) did not impact overall survival yet did contribute substantially to local control. In the NSABP B-04 trial, rates of axillary recurrence approached 20% in patients who received total mastectomy alone and decreased to 3% or less in patients receiving axillary treatment (surgery or radiation) [2,26]. In parallel to these observations, systemic therapies emerged as a proven modality to reduce breast cancer mortality, with absolute benefits greater among node-positive patients; thus, axillary lymph node dissection (ALND) emerged as the preferred method for axillary staging and local control for the next three decades.

The shift towards earlier stage at diagnosis and the recognition of the interplay between local and systemic therapy in maintaining local control ultimately led to the acceptance of a less invasive approach to staging. The SLNB procedure, initially tested in clinically node-negative breast cancer patients in the NSABP B-32 and

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ALND=axillary lymph node dissection; NAC, neoadjuvant chemotherapy; RT=radiation therapy; SLN=sentinel lymph node; SLNB=sentinel lymph node biopsy

**Fig. 1.** Timeline of major clinical trials examining the role of axillary staging. ALND = axillary lymph node dissection; NAC, neoadjuvant chemotherapy; RT = radiation therapy; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy.

Milan trials [3,4], revolutionized management of the axilla for women with pathologically node-negative disease. For women with clinically negative axillae found to have one or two positive sentinel lymph nodes there is also robust literature comparing SLNB alone versus SLNB plus ALND or axillary radiotherapy (AxRT) demonstrating that the choice of axillary treatment beyond SLNB does not impact local control or survival (Table 1) [5–9,11,27–30]. More recently, trials have demonstrated that among both clinically node-negative and clinically node-positive patients, SLNB after neoadjuvant chemotherapy (NAC) decreases the need for ALND without apparent increased risk of regional recurrence despite reports of false negative rates ranging from 5 to 10% in this setting [16,31–36].

The next frontier is identifying patients who can safely omit axillary surgery altogether. There are several clinical scenarios in which safe omission of SLNB has been demonstrated, yet each has been met with various degrees of acceptance. These include (1) breast conserving therapy (BCT) for ductal carcinoma in situ (DCIS), (2) contralateral prophylactic mastectomy (CPM), and (3) older patients with early-stage clinically node-negative, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative disease where adjuvant therapy decisions will not be impacted by nodal status. There are also a large number of ongoing or planned clinical trials seeking to expand the patient populations where surgical nodal staging can be safely omitted in clinically node-negative patients undergoing upfront surgery and

in select patients post NAC. Here we review the challenges and opportunities for omitting axillary surgical staging.

## 2. Clinical scenarios where SLNB may be omitted

### 2.1. Ductal carcinoma in situ when treated with breast conserving surgery

Since 2005, the American Society of Clinical Oncology (ASCO) clinical practice guideline for SLNB in patients with early-stage breast cancer has recommended SLNB be performed during mastectomy but discouraged its use during lumpectomy [37]. The rationale for omitting sentinel lymph node (SLN) staging during lumpectomy includes the low rate of documented axillary metastases, even if upstaged on final pathology (ranging from 4 to 15%) [38–42], and the ability to return to the operative room should upstaging occur.

Whether axillary staging should be performed in patients undergoing mastectomy for DCIS remains controversial. Although there have been limited reports of successful SLNB after mastectomy, the index operation is the optimal chance to assess the nodes, particularly if immediate breast reconstruction is planned. In studies limited to DCIS patients who have been selected for mastectomy, the rate of upstaging to invasive cancer ranges from 28 to 48% [43], prompting many authors to suggest that SLNB be performed routinely in these cases, as well as when completion

**Table 1**

Overview of randomized controlled trials demonstrating that omission of ALND either in favor of observation or radiation is not associated with significant differences in rates of axillary recurrence.

	Z0011 [7] N = 856	AMAROS [8] N = 1425	OTOASOR [9] N = 474	IBCSG 23–01 [5] N = 933	AATRM [6] N = 233
<b>Additional positive nodes ALND</b>	27.3%	32.8%	38.5%	13%	13%
<b>Axillary recurrence: ALND</b>	0.5%	0.4%	2%	0.2%	1.0%
<b>Axillary recurrence: other treatment<sup>a</sup></b>	1.1%	1.8%	1.7%	1%	1.7%
<b>Median follow-up</b>	9.25yrs	10 yrs	8yrs (mean)	10yrs	5.1yrs
<b>Breast conservation</b>	100%	83%	84%	91%	88%

ALND = axillary lymph node dissection; yrs = years.

<sup>a</sup> Other treatment includes observation or axillary radiation therapy.

mastectomy is performed after attempt at BCT [42,44,45].

The most recent guidelines from the National Comprehensive Cancer Network (NCCN) reaffirm the ASCO guidelines that SLNB should not be performed during breast conserving surgery (BCS) but should be “strongly considered” in patients undergoing mastectomy, in a patient for whom the location of BCS may compromise future SLNB or if there is a high suspicion or risk of upgrade of the lesion on final pathology. Criteria that have been associated with a higher risk of upgrade include the finding of a mass on clinical breast exam or imaging and calcifications spanning  $\geq 5$  cm [46].

Despite these guidelines, there continues to be a trend towards increased use of SLNB in DCIS patients treated with less than mastectomy, exceeding 20% of cases in the U.S. in a 2017 National Surgical Quality Improvement Program (NSQIP) report and 26% of cases in the U.K. in a 2015 audit from the National Health Service (NHS) screening program [42,47].

## 2.2. Contralateral prophylactic mastectomy

Similarly, there is variation in the use of SLNB staging in patients undergoing contralateral prophylactic mastectomy (CPM). The use of CPM in patients who present with unilateral breast cancer undergoing total mastectomy has steadily increased throughout the past two decades in all patient age groups and disease types [48–50]. The rate of occult carcinoma detection at the time of CPM in contemporary series is 3–5%, more than half of which are noninvasive [51–55]. Yet, the finding of occult invasive carcinoma leads to consideration of ALND for staging, thereby prompting many surgeons to consider SLNB at the time of CPM.

Boughey et al. performed a decision-making analysis to assess the need for empiric SLNB [56]. They modeled routine SLNB at the time of prophylactic mastectomy (PM) or directed ALND post-mastectomy for cases with occult disease. Assuming an occult invasive cancer rate of 1.9%, 37 SLNB were performed per one breast cancer detected and 73 SLNB were required to avoid one ALND in a node-negative PM patient. Further, the probability of complications per breast cancer detected were higher with routine SLNB as compared to directed ALND for all projected rates of occult cancer up to 28%, when the rate of complications became equal [56]. Ultimately, the authors concluded that directed ALND was more effective given the complications of SLNB and the overall low risk of identification of occult cancer in PM specimens. Similar work from these authors highlights that patients with a history of invasive lobular cancer or patients greater than 60 years old may have a risk of occult cancer in the PM specimen approaching 10% [57].

McLaughlin et al. sought to quantify the risks and benefits of different approaches for screening of the contralateral breast, such as preoperative MRI before PM [53]. In this retrospective single institution series, 4 of 393 patients (1%) were spared an ALND by routine SLNB. Among those with a preoperative MRI, the sensitivity of MRI for detecting otherwise occult disease was 78%, and the negative predictive value was 98%. Of note, all patients with occult invasive cancer had abnormal MRIs [53]. Nonetheless, routine preoperative MRI may be neither a cost-effective nor practical strategy [58].

Few studies have directly investigated risk factors associated with sentinel node positivity in the contralateral axilla [49,59,60]. In a large retrospective study of 420 patients who underwent CPM, Laronga et al. reported an overall occult cancer rate of 4.3% (18/420) [55]. There were 8 (2%) patients with a positive node in the contralateral axilla, the majority of whom had a locally advanced index cancer suggesting that the contralateral nodal disease likely represented cross metastases.

Collectively, the data do not support routine use of SLNB at the time of CPM; yet the risks and benefits of this approach should be

discussed with patients at increased risk of contralateral cancer such as those with a germline mutation in a breast cancer susceptibility gene.

## 2.3. Patients >70 years old with cT1-2cN0 HR-positive/HER2-negative disease

Age became an integral component of the breast cancer treatment algorithm when the Milan III trial demonstrated that older women had fewer local recurrences, regardless of postoperative radiation therapy (RT) [61]. The elderly demographic, which represents approximately 30% of all invasive breast cancers, typically presents with smaller, low grade and node-negative tumors that are HR positive and responsive to endocrine therapy [62,63]. Several randomized trials have investigated rates of axillary relapse with or without ALND in older patients with favorable tumors (defined as cN0 and estrogen receptor [ER] positive) receiving hormonal therapy with or without RT [64–66]. All trials reported low rates of axillary recurrence, ranging from 1.5% at 10 years of follow up in the CALGB 9343 trial [43] to 5% at 15 years of follow up in the Milan experience [65] with no differences in disease-free survival (DFS), breast cancer mortality, or overall survival based on the performance of an ALND.

The CALGB 9343 trial, a randomized trial of BCS plus tamoxifen with or without RT in women 70 years and older with cT1N0 breast cancer, first published in 2003 and updated in 2013 [40,43], was not designed to address management of the axilla, but rather to test the hypothesis that older women with favorable breast cancer could safely omit RT after BCS. When reported, however, it was determined that approximately 60% of patients in the trial had no axillary staging or treatment. At 10 years, the axillary failure rate was 3% in the tamoxifen only group and 0% in the tamoxifen plus RT group, providing promising data that axillary failure is an uncommon event in this age demographic with early-stage ER-positive breast cancer [20].

Collectively these data led to a statement from the Society of Surgical Oncology as part of the “Choosing Wisely” campaign discouraging routine use of SLNB in clinically node-negative women  $\geq 70$  years of age with early-stage HR-positive, HER2-negative invasive breast cancer where the decision for hormonal therapy has already been made. Importantly, the statement argues against *routine use* and suggests that axillary staging should be considered if the results will impact radiation or systemic therapy recommendations [67].

As described above for patients with DCIS, use of SLNB among the elderly population remains high despite data supporting its diminution, with rates reported from both population-based datasets and single institution series ranging from 80 to 88% in those greater than 70 years of age and 46–76% in patients greater than 80 years old [68–72]. Undoubtedly in patients for whom therapy will be decided based on lymph node status, the selective, individualized use of SLNB is prudent; however, with increasing use of genomic assays in the selection of systemic therapy and low rates of axillary failure in older patients, the omission of SLNB in elderly patients with favorable tumors warrants consideration.

## 3. The future of axillary staging

### 3.1. Early-stage breast cancer

There are now several ongoing trials examining whether SLNB contributes to staging or local control in patients with early-stage, clinically node-negative breast cancer (Table 2) [21–25]. Importantly, these studies are not limited to the elderly population or to patients treated with upfront breast conservation and they are not

**Table 2**  
Select ongoing and planned studies examining SLNB vs. axillary observation in patients with normal axillary imaging.

Trial	Planned Enrollment (N)	Inclusion Criteria	Study Design	Primary endpoint
<b>SOUND (Europe, NCT02167490) [21]</b>	1560	T < 2 cm, BCS + whole breast radiation	SLNB v. observation	DFS at 6 months
<b>INSEMA trial (Germany, NCT02466737) [22]</b>	5940	T < 5 cm, BCS + whole breast radiation	SLNB v. observation in patients with positive SLNB, second randomization to ALND v. no ALND	DFS at 5 years
<b>BOOG 13–08 (Dutch, NCT02271828) [23]</b>	1644	T < 5 cm, planned BCS + whole breast radiation	SLNB v. observation	Regional recurrence at up to 10 years
<b>SOAPET (China, NCT04072653) [24]</b>	1528	T < 5 cm, planned BCS + whole breast radiation	Stage 1: NPV of lymph PET Stage 2: no SLNB in patients with negative preoperative axillary assessment	Stage 1: NPV at 6 months Stage 2: DFS and LRFS at 5 years
<b>NAUTILUS (Korea, NCT04303715) [25]</b>	1734	T < 5 cm, BCS + whole breast radiation + adequate systemic therapy	SLNB v. observation	Invasive DFS at 5 years

ALND = axillary lymph node dissection; BCS = breast conserving surgery; DFS = disease-free survival; LRFS = local recurrence-free survival; NPV = negative predictive value; SLNB = sentinel lymph node biopsy.

limited by molecular subtype. All trials do require negative axillary imaging, predominantly with ultrasound although additional modalities are used in some. Among the major international trials in progress on this topic, the SOUND trial [21] was one of the earliest to open and has completed accrual (n = 1464). This multicenter study designed by the European Institute of Oncology focuses on cT1N0 patients (cN0 status confirmed on preoperative axillary ultrasound [AUS]) planned for BCS with whole breast irradiation. Patients with a negative AUS or negative fine needle aspiration are randomized to either SLNB (with completion ALND in cases with macrometastases) or no axillary surgery. The primary endpoint is 5-year distant DFS. The trial also included an ancillary analysis to examine the impact of SLNB vs no SLNB on post-operative physical function and symptoms of the ipsilateral upper limb using the QuickDASH (Disability of Arm, Shoulder and Hand) validated questionnaire. The authors reported on 176 patients, 94 of whom underwent SLNB and 82 of whom were observed in the setting of BCT. Not surprisingly, SLNB was associated with worse early post-operative physical function and symptoms when compared to the group that did not undergo axillary surgery [73]. While these differences resolved over time, they serve as an important reminder that although SLNB is a less invasive procedure it is still associated with significant patient morbidity.

The INSEMA trial (Germany, NCT02466737) [22], which also recently completed accrual, is a non-inferior trial designed to show that early-stage breast cancer patients managed with reduced extent of axillary surgery do not have inferior 5-year invasive DFS outcomes as compared with the standard treatment arm. cT1-2N0 patients (cN0 defined as negative physical exam and AUS) planned for BCS with whole breast radiation were randomized in a 1:4 ratio to either no axillary surgical intervention or axillary SLNB. Patients with SLNB and pN+(sn) status are secondarily randomized to either SLNB alone or completion ALND in cases with fewer than four involved nodes (1–3 macrometastases). Patients with four or more metastatic sentinel lymph nodes undergo completion ALND.

In the Dutch BOOG 2013–08 trial (Dutch, NCT02271828) [23], cT1-2N0 patients undergoing either upfront BCT or neoadjuvant therapy are randomized to SLNB or no SLNB, with the primary endpoint of regional recurrence at 5 and 10 years. The aim is to decrease the number of breast cancer patients receiving overtreatment of the axilla, in order to positively influence axillary morbidity and quality of life. The SOAPET trial (China, NCT04072653) [24] is a two phase study, the first phase will first evaluate the negative predictive value of pre-operative axillary assessment, including routine imaging examinations and Lymph-PET. In the second phase, SLNB will be spared in patients with

negative preoperative axillary assessment. Finally, the NAUTILUS trial (Korea, NCT04303715) [25], is a prospective, multicenter, randomized trial enrolling cT1-2N0 BCS candidates with negative AUS to SLNB or no SLNB. The primary objective is to examine the necessity of SLNB among patients with clinically node-negative tumors under 5 cm undergoing BCS.

The compilation of these trials will provide robust data to address the role of SLNB for staging and local control in patients with early-stage breast cancer and will have important implications for clinical management with an eye towards reducing axillary morbidity and improving quality of life. Whether nodal status or nodal disease burden will remain critical for adjuvant therapy decisions is a new area of consideration. In HR-positive, HER2-negative patients with cN0 disease that is ultimately pN0 or pN1 (1–3 positive nodes), recent data from the TAILORx [74] and RxPONDER [75] (Positive Node, Endocrine Responsive Breast Cancer [RxPONDER]) trials suggest that SLNB staging may not be necessary for adjuvant therapy decision making. Extrapolating one step further, based on data from ACOSOG Z0011 [7] and EORTC 10981–22023 AMAROS [8] it is unlikely that surgery will be needed for local control in the majority of these patients.

### 3.2. Post neoadjuvant chemotherapy

The role of axillary surgery after NAC remains an area of active investigation. In the cN0 population, SLNB can be reliably used to stage the axilla after NAC and decreases the need for ALND, even in patients with larger tumors where the likelihood of positive nodes is greater [31]. In the cN1 population, more recent attention has been paid to those who experience a good clinical response to NAC with clinical conversion to node-negative status. Several prospective trials have reported the feasibility of SLN staging in this population focusing on the SLN identification rate and the false negative rate (FNR) of the procedure. Two meta-analyses [76,77] have compiled these efforts demonstrating very consistent results; SLN identification rates of 90% and FNR of 13–14% which can be lowered to less than 10% by attention to certain technical details such as the use of dual tracer and the removal of at least 3 SLNs. Early reports of regional and distant recurrences in cN1 patients treated with NAC and deemed pN0 by SLNB alone are reassuring that this is an oncologically safe approach [33–36].

This has inspired efforts to identify predictors of node negativity after NAC (ypN0 status), first in patients who are cN0 prior to treatment, and most notably in those with a high probability of achieving a pathologic complete response (pCR). Patients with HER2-positive breast cancer who receive NAC plus anti-HER2

**Table 3**  
Rate of nodal positivity after NAC in cN0 HER2-positive and TNBC patients with breast pCR.

	Breast pCR	HER2-positive ypN1	TNBC ypN1
<b>Barron et al (NCDB) [82]</b>	5377	1.6%	1.6%
<b>Samiei et al (Netherlands) [83]</b>	986 <sup>a</sup>	ER-positive 1.6% ER-negative 0%	1.5%
<b>Tadros et al (MDACC) [84]</b>	116	0%	0%
<b>Van der Noordaa et al (NKI) [81]</b>	89	0%	0%

ER = estrogen receptor; NAC = neoadjuvant chemotherapy; pCR = pathologic complete response; TNBC = triple-negative breast cancer.

<sup>a</sup> Includes ER-positive/HER2-negative: ypN + rate 6.7%.

therapy achieve a pCR in 65–74% of cases and those with triple-negative breast cancer similarly achieve high rates of pCR in 50–67% of cases [78–81]. When examined further, patients in these subgroups who attain a breast pCR after NAC have very low rates of nodal positivity, approximating less than 2% (Table 3) [81–84].

Collectively, these observations inspired the design of two prospective clinical trials to determine whether SLNB can be omitted altogether after NAC in patients presenting with cN0 disease: the Avoiding Sentinel Lymph Node Biopsy in Breast Cancer Patients After Neoadjuvant Chemotherapy (ASICS) trial in the Netherlands [85] and the EUBREAST-01 Trial [86], a multicenter study by the European Breast Cancer Research Association of Surgical Trialists, both of which are currently underway. The ASICS trial is a non-inferiority, single arm trial open to both BCT and mastectomy patients in which SLNB will be omitted in cT1-3N0 HER2-positive or triple-negative breast cancer (TNBC) patients with a radiographic complete response on MRI after NAC. cN0 status will be confirmed with physical exam, AUS and positron emission tomography (PET). The primary endpoint is 5-year rate of axillary recurrence with a number of secondary endpoints including quality of life, worry and standard survival outcomes. An axillary recurrence rate of <6% at 5 years will be considered acceptable.

The EUBREAST-01 trial is a prospective, non-randomized single arm multicenter trial of cT1c-T3N0 TNBC or HER2-positive breast cancer treated with preoperative NAC in patients planned for BCS with whole breast RT [86]. cN0 status is determined by physical exam and ultrasound prior to NAC and those with a breast pCR after NAC will undergo BCS to ascertain the breast pathologic response. Those who achieve a breast pCR will then be eligible for no further axillary surgery with the primary endpoint of 3-year axillary recurrence-free survival. The measure of success is a 3-year axillary recurrence-free survival rate of at least 98.5%. For patients who do not achieve a breast pCR, SLNB will be performed and subsequent management based on pathologic findings.

#### 4. Conclusions

Opportunities to de-escalate axillary surgery and minimize patient morbidity have been an important area of investigation over the last three decades and remain a high priority for our patients. It is clear that today, SLNB remains the staging procedure of choice both in upfront surgery patients and post NAC patients with cN0 and cN1 disease. Improvements in axillary imaging—in parallel with the expansion of the role of genomic assays in selecting patients for systemic therapy—may obviate the need for axillary surgery to inform most systemic therapy decisions in cT1-2 N0 patients in the future. For early-stage breast cancer patients, routine axillary imaging to rule out unsuspected, high-volume disease will likely diminish the need for axillary surgery for staging and control. Overall, the increasing role of biology over anatomy in systemic therapy decisions are likely to supersede SLNB as a staging procedure. For more advanced disease, response to therapy

will likely be the primary determinant of the extent of axillary treatment.

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#### Declaration of competing interest

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