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Lymph Node Surgery – Stepwise Retirement for the Breast Surgeon?

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Keywords

Breast cancer · Sentinel lymph node · Lymph node dissection

Summary

Axillary lymph node dissection (ALND) has been standard of care for all patients with breast cancer until the 1990s. The stepwise retreat of breast surgeons from the axilla began after the introduction of the sentinel lymph node procedure. The evidence based clinical trend toward the omission of ALND has advanced to include patients with affected nodes, and several ongoing randomized controlled trials are evaluating the remaining indications for ALND. Conflicting with this trend toward less axillary surgery, indication and extent of regional nodal irradiation are currently broadened, equally supported by evidence from randomized trials. The present review summarizes this conflicting evidence, presents ongoing trials, and discusses the current and future optimal regional management of patients with affected nodes.

Evolution of Axillary Surgery

Since the 1900s, axillary lymph node dissection (ALND) was standard of care for all patients with breast cancer. Many decades later, NSABP B04 was one of the first prospective studies to address axillary treatment. It randomized patients with clinically negative nodes into a group with total mastectomy and ALND – the current standard at the time – versus total mastectomy and regional irradiation versus total mastectomy alone without any axillary treatment [1]. Even though there was no difference in overall survival between the 3 groups, ALND remained standard of care for all patients, primarily for staging and regional control. Due to the morbidity associated with the procedure and the decreasing axillary node involvement over time, a series of randomized controlled trials (RCTs) have been initiated in the 1990s and early 2000s to question this paradigm in patients with clinically negative axillary lymph nodes. These trials can be divided into 4 categories: 1) omission of any surgical axillary staging in selected patients [2–5], 2) omission of axillary dissection in all patients with negative sentinel lymph nodes (SLN) [6–8], 3) omission of axillary dissection in selected patients with limited nodal disease in the SLN [9–11], and 4) axillary radiation versus axillary dissection [12, 13] or observation [14]. The trial findings supported the trend in clinical practice toward decreased rates of axillary dissection [15, 16] and established axillary radiation as valid alternative to dissection in selected patients.

Residual Axillary Disease after Surgery

The NSABP B04 trial showed that even in the absence of any surgical or adjuvant treatment, less than half of all axillary metastases progress to regional recurrence [1]. With the introduction of adjuvant radiation and systemic treatment, many more residual nodal metastases were treated and regional recurrence became rare. In 2010 for example, the NSABP B-32 study was published as the largest randomized surgical trial in breast cancer thus far [6]. In one arm, ALND was only performed when the sentinel node was positive. In the other arm, back-up ALND was performed in all patients and showed that the rate of false-negative sentinel nodes was 9.8%. The trial demonstrated a rate of regional recurrence of 0.4% after ALND and only 0.7% without ALND despite the high false negative rate.

During the same randomization period from 1999 to 2004, patients with metastases in 1 or 2 sentinel nodes undergoing breast conserving surgery and adjuvant treatment were eligible for ACO-

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Table 1. Ongoing clinical trials in axillary surgery

Country/Name	Population	Randomization	Endpoint	Start
Italy SOUND IEO S637/311 NCT02167490	cT1cN0 US negative	SLN vs. observation	DDFS	Jan 2012
Germany INSEMA NCT02466737	cT1–2 cN0 US negative	1. SLN vs. observation 2. 1–2 SLN+ → ALND vs. no ALND	DFS	Sept 2015
France SERC/IPC 2012-001 NCT01717131	cT1–2 cN0	ALND vs. no ALND	DFS	July 2012
China Z0011-China NCT01796444	cT1–2 cN0 1–2 SLN+	ALND vs. no ALND	DFS	Jan 2013
Sweden SENOMAC NCT02240472	cT1–2 cN0 cT1–2 iN1 1–2 SLN+	ALND vs. no ALND	BCSS	Jan 2015
United Kingdom POSNOC NCT02401685	cT1–2 1–2 SLN+	ALND or axillary radiotherapy vs. no axillary treatment	axillary recurrence	Jan 2014
Netherlands BOOG 2013-07 NCT02112682	cT1–2 cN0 1–3 SLN+ Mastectomy	ALND or axillary radiotherapy vs. no axillary treatment	RRR	June 2014
USA Alliance A011202 NCT01901094	cT1–3 cN1 (S)LN+ after NACT	ALND + extended regional nodal irradiation vs. axillary radiotherapy + extended regional nodal irradiation	IBC-RFI	Feb 2014

NCT = ClinicalTrials.gov identifier, cT1 = clinical stage T1, cN0 = clinical stage N0 (no palpable lymph nodes), US = ultrasound, SLN = sentinel lymph node, DDFS = distant disease-free survival, ALND = axillary lymph node dissection, DFS = disease-free survival, SLN+ = SLN affected, iN1 = nodal disease detected by imaging, BCSS = breast cancer specific survival, RRR = regional recurrence rate, (S)LN = lymph node (sentinel or non-sentinel), NACT = neoadjuvant chemotherapy, IBC-RFI = invasive breast cancer recurrence-free interval.

SOG Z0011 [10, 11]. They were randomized into one arm with ALND and one arm with no axillary-specific treatment. Despite the finding of residual nodal disease in 27% of patients treated by ALND in the control arm, the axillary recurrence rate was below 1% in the experimental arm without ALND. Taken together, these trials showed that most residual axillary lymph node metastases do not progress. The underlying reasons for this phenomenon most likely include regional control by host factors that are still poorly understood, and effective adjuvant radiation and systemic treatment.

Conflicting Clinical Trends in Regional Management

Conflicting with the trend toward less axillary surgery, radiation oncologists are broadening the indication for post-mastectomy irradiation in patients with positive nodes, based – among others – on confirming recent data from the latest Lancet overview [17]. In this EBCTCG meta-analysis, postmastectomy radiotherapy has been shown to reduce breast cancer mortality for women with 1–3 affected axillary lymph nodes (risk ratio (RR) 0.80; 95% confidence interval (CI) 0.67–0.95; log-rank 2, p = 0.01). If given, post-mastectomy radiotherapy includes the chest wall and regional nodes in most patients [18]. Moreover, radiation oncologists are currently establishing the concept of extended regional lymph node irradiation based on evidence from 2 large phase III RCTs [19–21]. The majority of patients in MA.20 and more than half of the patients in EORTC 22922/10925 had positive axillary lymph nodes. Even though both trials showed improved loco-regional and distant control for extended radiation to the internal mammary and medial supraclavicular nodes, none of them achieved a significant overall survival benefit at 10 years. However, an improvement in overall survival of 3.7% at 8 years was shown for internal mammary nodal irradiation in a large population-based cohort study of patients with early-stage node-positive breast cancer (adjusted hazard ratio for death 0.82, 95% CI 0.72–0.94; p = 0.005) [22].

Ongoing Randomized Controlled Trials

Several surgical trials have been initiated to provide further evidence for the safety of omitting axillary surgery in selected clinically node-negative patients (table 1). Two of them investigate the omission of any surgical axillary staging, i.e. the omission of the SLN procedure, in patients with a negative preoperative ultrasound of the axilla. Until now, axillary ultrasound is used to identify axillary disease in clinically node-negative patients to omit the SLN procedure and proceed directly to axillary dissection. In the ACOSOG Z0011 era, this indication has become controversial inasmuch

as patients with a positive preoperative axillary ultrasound may still undergo the SLN procedure without axillary dissection [23]. The results of the following 2 trials have the potential to establish a new indication for axillary ultrasound as a procedure to exclude high-volume axillary disease and spare patients any axillary surgery. The SOUND trial randomizes clinically node-negative patients with small breast cancers (≤ 2 cm) who are candidates for breast conserving surgery and irradiation into one group with the SLN procedure versus one group with no surgical axillary staging (observation arm). The SLN procedure is followed by axillary dissection in all patients with SLN macrometastases, which is perceived as overtreatment by many clinicians who apply the Z0011 protocol. The INSEMA trial has a similar first randomization, but includes patients with a clinical tumor size of up to 5 cm and randomizes patients with 1 or 2 positive SLN with macrometastases into one arm with ALND versus one arm without ALND. Therefore, the second randomization is designed to validate the findings of Z0011.

Several other ongoing RCTs primarily aim at validating the Z0011 protocol in different countries. Z0011-China strictly applies the Z0011 protocol to the same patient population in China. The other validation trials broadened the inclusion criteria compared with the original Z0011 protocol. The SERC/IPC 2012–001 trial in France, for example, randomizes all patients with positive SLN into one arm with ALND and one arm without ALND. The inclusion of patients with more than 2 positive SLN will add valuable evidence to clinical practice, since these patients were excluded from Z0011. A prospective study of a consecutive cohort of patients who met the Z0011 criteria at the time of initial surgery at the Memorial Sloan-Kettering Cancer Center showed that 29 of 287 patients (10.1%) underwent completion ALND for ≥3 positive SLNs [24]. On the other hand, the randomization of patients with isolated tumor cells or micrometastases into the ALND arm is nowadays considered overtreatment by many, at the latest since the publication of IBCSG 23–01 [9]. SENOMAC largely follows the Z0011 protocol in Sweden, but allows the inclusion of patients undergoing mastectomy and those with nodal disease detected by ultrasound. POSNOC investigates the Z0011 protocol in the United Kingdom, but allows axillary radiotherapy as alternative to ALND in the control arm. Similarly, BOOG 2013–07 from the Netherlands allows axillary radiotherapy or ALND to complete axillary treatment in the control arm, but includes patients with 1–3 positive SLN undergoing mastectomy. Notably, this trial allows randomization of mastectomy patients with SLN micrometastases into the axillary treatment arm, a patient population eligible for – but underrepresented in – IBCSG 23–01 [9].

The most progressive ongoing clinical trial of axillary management is Alliance A011202. It compares ALND with axillary radiation in patients with residual disease after chemotherapy, which was an exclusion criterion in both the AMAROS and the Z0011 trials. Eligibility criteria include initially clinically node-positive breast cancer that converted into clinically node-negative disease and at least 1 metastasis greater than 0.2 mm in sentinel or non-sentinel lymph nodes after chemotherapy. Patients in the ALND arm undergo extended regional nodal irradiation excluding the dissected axilla, while patients in the axillary radiation arm receive extended regional nodal irradiation including the full axilla. The trial tests the hypothesis that the AMAROS protocol in combination with extended regional nodal irradiation works in these patients without ALND inasmuch as chemotherapy-resistant lymph node metastases are as radiosensitive as chemotherapy-naive disease.

Open Debates

As in all clinical trials in oncology, patients are treated according to the standards that are in use when they are included. During follow-up, more effective treatment options may become available, potentially compromising the applicability of the findings to a contemporary patient population. The same is true for rigid in- and exclusion criteria, which are often necessary in terms of feasibility of the trial and later jeopardize its generalizability. Finally, methodological issues are frequent, and must be critically reviewed when determining the quality of the evidence. Many recent non-inferiority trials were limited by lower-than-expected event rates resulting in a lack of statistical power. This is good for the patients in those studies, but problematic for trialists and, of course, clinicians trying to apply their results. Prominent examples are IBCSG 23–01, ACOSOG Z0011, and EORTC AMAROS [9–12]. Nevertheless, many of those landmark trials still managed to change clinical practice in selected pioneering centers of excellence, before their corroborative prospective surveillance data convinced critics that the protocols work and can be more widely adopted.

There is little controversy on the optimal management of sentinel node-negative patients and those with 4 or more positive nodes. However, for patients with 1–3 affected nodes, individualizing and optimizing treatment based on the available evidence is challenging. For example, the dramatic improvement in locoregional control for post-mastectomy and regional nodal irradiation and its impact on survival in patients with 1–3 positive nodes shown in the EBCTCG meta-analysis were based on a baseline 5-year local-regional recurrence rate of 17%, far in excess of what we see today. Generalized application of these data to today's patients disregards both relevant improvements in systemic therapy and the adverse effect of radiotherapy on complication rates after contemporary immediate breast reconstruction [25].

ACOSOG Z0011, EORTC-AMAROS, MA.20, and EORTC 22922/10925 suggested fundamentally different approaches for similar patient populations [10–12, 20, 21]. ACOSOG Z0011 showed that many of these patients can be managed with no specific axillary treatment. EORTC-AMAROS validated axillary and medial supraclavicular radiation as equally effective and a potentially less harmful alternative to ALND in these patients. Finally, MA.20 and EORTC 22922/10925 suggested that some of these patients may benefit from extended regional nodal irradiation.

The main limitations of the MA.20 and EORTC 22922/10925 trials are that all patients underwent ALND and that many patients did not receive current systemic treatments, such as taxane chemotherapy, trastuzumab, and more effective endocrine strategies [26].

One limitation of ACOSOG Z0011 was the lack of standardization and detailed documentation of adjuvant radiation fields and the angles of the tangents, which makes it impossible to determine how much of the axilla was irradiated [27]. Since the no-axillary dissection arm in Z0011 was categorized as 'no further axillary treatment' and defined by 'no axillary dissection and no third-field nodal irradiation', this question became relevant. However, an attempt to reconstruct the radiation fields of Z0011 resulted in the receipt of only 30% of detailed radiotherapy records for centralized review [28]. Critics of ACOSOG Z0011 felt reassured by this publication inasmuch as a substantial amount of patients received directed regional nodal radiotherapy using ≥3 fields. However, the facts that most patients treated in Z0011 received tangential radiotherapy alone and some did not receive radiotherapy at all make it very unlikely that the very low regional recurrence rate of 0.9% (4/436) in the SLN alone arm at a median follow-up of 6.3 years was observed due to protocol-prohibited nodal fields. Another limitation of Z0011 was the limited duration of follow-up, a self-resolving issue since 10-year follow-up results are expected soon. Finally, particularly in Europa, there is still no uniform consensus on the application of the Z0011 data to several subgroups, such as young patients with estrogen receptor-negative or high-grade breast cancer, due to a relative underrepresentation of these patients in the trial [29]. Corroborative prospective surveillance data from centers that adopted the Z0011 protocol more than 5 years ago and pending results from various Z0011 validation trials will close that debate in the near future.

Current and Future Axillary Treatment

To date, most patients with invasive breast cancer should undergo the SLN procedure; however, SOUND and INSEMA may challenge this paradigm within the next decade or two. Patients with micrometastases or isolated tumor cells can forego ALND [9–11]. Most patients with macrometastases in 1 or 2 sentinel nodes undergoing breast conserving surgery, adjuvant whole-breast irradiation, and systemic treatment should not undergo ALND [10, 11, 30]. They can be treated according to the Z0011 protocol without axilla-specific treatment or according to EORTC AMAROS with axillary radiotherapy; the optimal patient selection for one or the other remains a subject for further study. In the absence of a trial of extended regional nodal irradiation following the sentinel node procedure alone, individualized treatment decisions on the extent of irradiation should be based on the patient's baseline risk of recurrence.

The remaining indications for ALND include confirmed node-positive breast cancer with a large primary (>5 cm) or high-volume nodal disease (≥3 positive SLN, gross extranodal disease, palpable lymph node metastases), residual nodal disease after neoadjuvant chemotherapy, and patients with at least one sentinel node macrometastasis undergoing mastectomy. The latter, however, is only valid if the number of positive nodes removed by ALND is needed to evaluate the indication for post-mastectomy radiotherapy. If post-mastectomy radiotherapy including the regional nodes is indicated according to local protocols due to the positive SLN per se, ALND can be safely omitted, a lesson learned from EORTC AMAROS [12, 31]. Finally, potential predictors of high nodal disease volume are sometimes used in clinical practice to indicate ALND; the most common are lymph node metastases detected by imaging before surgery and microscopic extranodal disease in the SLN [32–34]. While the extent of extracapsular extension may influence the need for ALND [35], a positive imaging-guided axillary lymph node needle biopsy does not accurately predict the need for ALND [23]. BOOG 2013–07 from the Netherlands, SERC/IPC 2012–001 from France and the Alliance trial A011202 may eliminate most of the remaining indications for ALND, potentially leaving only confirmed palpable lymph node metastases as the last absolute indication for ALND in the near future. With decreasing use of ALND, opportunities for junior staff, fellows, and residents to practice this procedure will continue to decline. In parallel, the technical complexity of performing ALND will continue to increase in the more advanced, chemotherapy-resistant, or recurrent disease. Therefore, breast surgeons will not retire from lymph node surgery; instead, they will be challenged by performing more difficult procedures with less experience.

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