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Upfront Axillary Surgical Management: Remaining Questions

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ABSTRACT

Early breast cancer is treated with curative intent by a network of incredibly interconnected disciplines. There are certain points in each discipline's decision-making that can affect one of the others, and one such point is axillary surgery. Because removing all the lymph nodes from the cancer-containing historically provided the most accurate lymph node information to other disciplines, standard-of-care axillary surgery had been removal of all axillary lymph nodes with an axillary lymph node dissection (ALND). The benefit of an accurate ALND was soon outweighed, though, by its plethora of associated morbidities. This sparked numerous landmark clinical trials that ultimately demonstrated the safety of ALND omission. Following these trials there has been a trend toward de-escalating axillary surgery whenever possible. This review will explore the remaining questions in upfront axillary surgical management, specifically focusing on hormone receptor-positive (HR+) breast cancer patients, and the accompanying challenges for systemic therapy administration decisions.

Introduction

Early breast cancer refers to breast cancer that has not metastasized and is treated with curative intent. This curative treatment is accomplished by a network of incredibly interconnected disciplines (i.e., radiology, pathology, surgical oncology, medical oncology, and radiation oncology) that work together to obtain the best outcomes for the patients. There are certain points in each discipline's decision-making that can affect one of the others, and one such point is axillary surgery.

Upfront axillary surgical management is the axillary surgery performed when surgery is the first treatment received, i.e., the patient is not treated with any pre-operative systemic therapy or radiation therapy. Early on in breast cancer evidence-based practice, it was proven that lymph node involvement conferred poorer outcomes[1]. During this time, the presence of single lymph node metastasis was a major indication for treating a patient with chemotherapy and soon became an indication for radiation therapy as well[2,3]. Although there have been advances since then (i.e., it is no longer a "yes/no" decision), information obtained by axillary surgery (i.e., the number of lymph node metastases) still guides systemic and radiation therapy recommendations. Because removing all the lymph nodes from the cancer-containing breast provides the most accurate lymph node information to other disciplines, standard-of-care axillary surgery has been removal of all axillary lymph nodes with an axillary lymph node dissection (ALND).

The benefit of an accurate ALND was soon outweighed, though, by its plethora of associated morbidities, including lymphedema, range of motion issues, paresthesia, and pain[4]. A more selective approach toward axillary surgery, the sentinel lymph node biopsy (SLNB), was then tested, and despite a 10% false negative rate, the SLNB appeared safe[5-7]. This was shown in a number of studies whereby patients who were randomized to SLNB and subsequent ALND only if positive lymph nodes were detected fared as well as patients who underwent automatic ALND. Later, it was proven that patients with positive sentinel lymph nodes may not need an ALND, and the body of literature has grown to support ALND omission for most clinically node-negative (cN0, i.e., no evidence of nodal disease by physical exam or axillary imaging, if obtained) but pathologically node-positive breast cancer patients [REF][8-12]. Although this has been beneficial for patients and their quality of life, medical oncologists have been faced with the difficult task of having to make systemic therapy recommendations based on less pathological nodal information. This narrative review will explore the remaining questions in upfront axillary surgical management, specifically focusing on hormone receptor-positive (HR+) breast cancer patients, and the accompanying challenges for systemic therapy administration decisions.

Clinically lymph node-negative patients

The cN0 patient has seen the most success in avoiding unnecessary axillary surgery. Several landmark clinical trials have shown that ALND omission is safe in cN0 patients with 1-2 positive sentinel lymph nodes on pathology (pN1(sn))[8-12]. IBCSG 23-01 was a multicenter randomized trial that found that cN0 women with sentinel node micrometastatic disease derived no benefit from cALND, and that ALND led to significantly worse adverse effects[8]. Similar results were shown in AATRM trial, whereby there was no difference in disease-free survival among women with micrometastatic sentinel node disease who underwent SLNB alone versus SLNB with cALND[9]. ACOSOG Z0011 compared cALND to no further treatment after SLNB among patients with pN1(sn) disease; at 10-year follow-up, SLNB alone was noninferior to cALND in terms of overall survival[10]. Finally, in both the AMAROS and OTOASOR trial, women with cN0 pN1(sn) breast cancer were randomized to cALND versus RNI, with results from both trials showing that RNI was as effective as cALND[11,12].

The omission of ALND was proven safe, first in ACOSOG Z0011 patients who underwent upfront

surgery with breast conservation followed by whole breast irradiation, then over time trial eligibility broadened to include mastectomy patients (i.e., IBCSG 23-01 and AMAROS)[8,10,11]. However, many patient groups were still underrepresented. For example, though mastectomy patients were included in IBCSG 23-01 and AMAROS, they only comprised 9-17% of the trial populations. In a recent publication of the SENOMAC trial, SLNB alone was found to be non-inferior to cALND in a more inclusive cohort, and now patients with extracapsular extension, relatively higher volume lymph node metastases, and those who undergo mastectomy are well-represented[13].

The most recent landmark clinical trial among cN0 patients, the Sentinel Node vs Observation After Axillary Ultra-Sound or "SOUND" trial, reported that omission of axillary surgery altogether can be safe[14]. This has been previously reported in an older, frail population, but the SOUND trial enrolled patients of any age to SLNB or no axillary surgery[14,15]. All patients had to have a negative axillary ultrasound, and if there were suspicious lymph nodes on imaging, they had to be biopsy-proven negative. Comparing 708 patients enrolled to SLNB and 697 enrolled to no axillary surgery, 5-year distant disease-free survival was similar at 97.7% and 98.0%, respectively (non-inferiority p = 0.02)[14]. Some institutions have implemented the SOUND trial, while others are awaiting results from the INSEMA trial (NCT02466737), which has a similar design but a much larger sample size of 7,095.

Clinically lymph node-positive patients

The last group that is undergoing frequent ALND is the clinically lymph node-positive (cN1) patient. The most common way to avoid ALND in the cN1 patient is to administer pre-operative or neoadjuvant chemotherapy, perform SLNB to assess response, and omit ALND for patients whom neoadjuvant chemotherapy has managed to completely eradicate the pathologic nodal disease[16-20]. There are several weaknesses to this approach for patients with HR+ breast cancer. First, there is level I evidence that many HR+ patients will not gain survival benefit from chemotherapy based on genomic assay results; therefore, it is difficult to recommend chemotherapy just to clear the axilla[21,22]. That is accepting the morbidities of chemotherapy to avoid the morbidities of ALND – which seems like jumping from the frying pan to the fire. Second, HR+ breast cancer exhibits low rates of nodal clearance after neoadjuvant chemotherapy. Several studies show axillary lymph node pathologic complete response rates range from 10-35% only[23-25]. This is much lower in comparison to the higher risk breast cancer subtypes, e.g., HR-negative HER2-positive (HER2+) breast cancer patients, which may experience nodal pathologic complete response rates as high as 97%[23]. Taken together, this strategy involves giving toxic chemotherapy to achieve nodal clearance, but it only works less than a quarter of the time.

There is another way to avoid ALND in the cN1 population. The patients could be taken to upfront surgery if there were algorithms to safely omit ALND in this setting. Creation of algorithms requires clinical trial data. The "Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer" or "TAXIS" trial (NCT03513614) is enrolling cN1 patients being treated with either upfront surgery or with preoperative chemotherapy then surgery, to targeted axillary surgery (i.e., removing the palpable/concerning lymph node disease only) versus ALND. Accrual to TAXIS is ongoing, and other trials will be needed before we can de-escalate ALND for cN1 patients.

Challenges for systemic therapy decisions – the real remaining questions

The breast surgery community has known since NSABP B-04 that omission of ALND is safe and does not impact overall or disease-free survival [REF][26]. In this trial, 1079 patients with cN0 disease

were randomized to one of three groups: total mastectomy alone without any axillary treatment (n=365), total mastectomy plus axillary radiation (n=352), or radical mastectomy (n=362). After 25 years of follow-up, there were no significant differences in terms of overall or disease-free survival between groups[27]. However, NSABP B-04 was performed at a time when chemotherapy decisions were "simple" – all or none. Most patients received chemotherapy, especially if a lymph node was involved. While axillary surgery has been de-escalated, there has also been a push to de-escalate chemotherapy to avoid toxicities, including but not limited to peripheral neuropathy, cardiomyopathy, and alopecia. The most impactful clinical trials to de-escalate chemotherapy to date are the TAILORx and RxPONDER trials[21,28]. These trials used genomic assay results to stratify patients into risk groups and randomize certain groups to endocrine versus chemoendocrine therapy[29]. The TAILORx trial treated pathologically node-negative HR+ HER2- breast cancer patients with 21-gene recurrence scores (RS) indicating a low risk of systemic recurrence (RS 0-10) with endocrine therapy alone, and randomized the patients with intermediate risk (RS 11-25) to endocrine versus chemoendocrine therapy[30]. Among the 6,711 women with intermediate risk of systemic recurrence, the addition of chemotherapy provided no added benefit compared to endocrine therapy alone, especially in women over 50 years of age[28]. RxPONDER had a similar design to TAILORx, this time randomizing pathologically node-positive patients with a low-to-intermediate risk of recurrence (RS 0-25) to endocrine versus chemoendocrine therapy, but only if they had just 1-3 positive lymph nodes[21]. RxPONDER similarly found that many patients with low-to-intermediate risk of recurrence did not benefit from chemotherapy, specifically post-menopausal patients. However, patients with 4 or more positive lymph nodes were excluded from the trial, so these patients are routinely treated with chemotherapy and are thought to glean benefit.

While chemotherapy is being de-escalated, other systemic treatments are being escalated. For example, optimizing endocrine therapy regimens with the addition of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors has emerged as an effective and less toxic therapeutic strategy for HR+ breast cancer patients. Notably, the monarchE trial showed that patients with "high-risk" HR+ breast cancer who were treated with a combination of adjuvant endocrine therapy and 2 years of the CDK4/6 inhibitor abemaciclib had improved invasive disease-free survival (hazards ratio 0.664 [95% confidence interval 0.578-0.762, $p < 0.0001$) compared to patients treated with endocrine therapy alone[31]. Patients were considered high-risk if they had 4 or more positive lymph nodes, or if they had 1-3 positive nodes and at least one high-risk feature (tumors > 5cm, grade 3 disease, or Ki67 staining level ≥ 20%). Of the 5,637 patients enrolled, most had prior chemotherapy either in the adjuvant or neoadjuvant setting, and hazards ratios in both subgroups significantly favored abemaciclib.

With the simultaneous de-escalation of axillary surgery and chemotherapy, there was concern that patients may be erroneously treated with de-escalated systemic regimens because the surgeon did not provide enough lymph node information, i.e., among patients with 1-3 positive sentinel lymph nodes, if ALND is not performed the medical oncologist may be apprehensive about chemotherapy omission because additional positive lymph nodes may be present, just not detected. Additionally, to determine suitability for abemaciclib administration, complete nodal information; if 4 nodes are present but not detected, the patient may not be eligible for CDK4/6 inhibition. This led to many providers suggesting a return to ALND for patients who were able to avoid it previously, previously when chemotherapy was given to patients for just 1 positive lymph node.

What empowered the medical oncologists? Growing comfort with using genomic assay results to guide therapy, and rigorous research from both fields. One way to provide reassurance to medical oncologists would be to prove that anatomic information is less important than the prognostic

information provided by genomic assays. The 8th edition American Joint Commission on Cancer staging system has provided some comfort for very low risk patients. Patients with an OncotypeDX recurrence score < 11 are stage IA regardless of their tumor size up to 5cm because there is ample evidence that the genomically-derived prognostic information is more accurate than anatomic information[32]. More work needs to be done among node-positive patients, though, such as hypothesis-generating work from the National Cancer Database comparing the prognostic impact of genomic assay results versus the prognostic impact of number of positive lymph nodes[33].

Another way to assuage fears would be to prove that it is unlikely that a patient has 4 or more positive lymph nodes. Shortly after the publication of RxPONDER, Kantor et al. examined the National Cancer Database and their institutional database for patients with cN0 disease and discovered that of patients who underwent ALND, only 12.0% and 4.9%, respectively, had greater than pN1 disease[34]. Thus, only a small proportion of patients who "need" chemotherapy would potentially be missed if an ALND was not performed, and authors concluded that ALND should not be performed for cN0 patients strictly to determine systemic therapy. A similar study by Farley et al. examined their institutional database and of 2,532 post-menopausal patients with cN0 breast cancer, only 2.4% had 4 or more positive lymph nodes[35]. For cN0 patients, the Italian National Association of Breast Surgeons put out a position statement that routine ALND should not be performed to determine systemic therapy recommendations[36]. Among patients with cN1 disease, Weber et al., the principal investigator and team of the TAXIS trial, examined adjuvant systemic therapy among the upfront surgery cohort from TAXIS in a pre-planned secondary analysis; analysis revealed no difference in type of endocrine therapy administered or proportion of patients treated with chemotherapy between treatments arms (i.e., with or without ALND)[37]. Unfortunately, they did not assess CDK4/6 inhibition use.

The SENOMAC trialists did examine ALND and resulting nodal information, and indirectly its impact on CDK4/6 inhibitor use. The trialists recently published an interesting pre-planned exploratory analysis from their trial[38]. This trial enrolled the highest risk cN0 patient group to date, including patients with 1-2 lymph nodes containing macrometastases, and even additional nodes with micrometastases allowed, and randomized them to SLNB or ALND, with nearly all patients treated with RNI. Thirty-five percent of patients in the ALND group had additional non-sentinel positive lymph nodes[38]. Despite this additional nodal disease that remained in the evenly matched SLNB group, there was no difference in recurrence-free survival (hazards ratio 0.89 [95% confidence interval 0.66-1.19, p < 0.001 below the non-inferiority margin])[13]. The trialists then determined the number needed to treat with ALND to prevent one invasive disease-free event at 5 years per the monarchE trial data: 104 patients. One-hundred and four patients would need to be treated with ALND in order to prevent one disease event, and of those 104, 9 patients would develop severe, or very severe arm symptoms at 1 year[38]. It is the authors' opinions that an ALND should not be performed solely to provide anatomic information for systemic therapy decision-making[38].

Another development that will help avoid ALND as a means to obtain an accurate count of positive lymph nodes is the recent September 17, 2024 Federal Drug Administration approval of ribociclib as adjuvant therapy for HR+ node-positive breast cancer based on the European Society of Medical Oncology presentation of NATALEE's 4 year follow-up data which showed a 5% absolute improvement in disease-free survival among patients taking endocrine therapy plus ribociclib over endocrine therapy alone[39,40]. Similar to monarchE, the NATALEE trial (NCT03701334) included patients who were at an elevated risk of recurrence, but in contrast to monarchE even just one positive node was considered high-risk.

Now that we have established that we do not need an ALND to make systemic therapy decisions, do

we need SLNB? In a single institution series of 1,786 patients with HR+ cN0 breast cancer who underwent SLNB, only 14% had 1-3 positive lymph nodes and only 1% had 4 or more positive lymph nodes[41]. Among patients randomized to the SLNB/axillary surgery arm in the SOUND trial, these percentages were nearly identical. Only 13.7% had involved lymph nodes and the patients with cancer-containing lymph nodes then underwent ALND (per pre-Z0011 treatment algorithms) and ultimately 0.6% had 4 or more positive lymph nodes.[14] This suggests that very few patients would miss out on chemotherapy if SLNB is omitted. It is important to remember, though, that 88% of SOUND patients were HR+ [REF][14]. Omitting SLNB is not currently recommended for HER2+ or triple negative breast cancer because systemic therapy will be administered if there is lymph node involvement, and in these populations the exact number of involved lymph nodes is not crucial.

Special groups – extremes of age

Among the elderly, the Choosing Wisely guidelines have endorsed omission of SLNB among cN0 patients for several years[42]. Choosing Wisely was based on clinical trials comparing ALND to no axillary surgery in elderly patients that revealed equivalent survival; additionally, 45% of the patients enrolled to the CALGB 9343 clinical trial examining the omission of radiation did not undergo SLNB and outcomes were good[15,43]. Lastly, the elderly are far less likely to be treated with chemotherapy, so axillary staging information is not needed. If there was any question before, the SOUND results should eliminate any doubt that omitting SLNB for the elderly is good practice. Although SOUND technically enrolled women of any age, the median age was 60 years, so we are left with questions regarding younger patients[14].

At the other end of the spectrum, there is an increasing population of young breast cancer patients. Xu et al. have shown that there is a significant increase in HR+ disease among them[44]. Oddly, we often "do more" for young patients, including performing more ALNDs, because we worry about axillary recurrence when a patient has decades to live; however, they do have longer to live, and this means they also have longer to suffer from the morbidities[45-47]. The picture is a little mixed for pre-menopausal patients. RxPONDER showed that pre-menopausal patients benefited from chemotherapy if they even had just 1 lymph node positive, so RxPONDER did not successfully de-escalate chemotherapy in this population[21]. On the bright side, one would not need an ALND to determine an accurate lymph node count for chemotherapy decisions. Regarding CDK4/6 inhibition, another ESMO presentation showed that the benefit of ribociclib was consistent among both post-and pre-menopausal patients[48]. Thus, it appears an ALND would not be necessary to make CDK4/6 inhibitor decisions among pre-menopausal patients, either, and should be avoided.

Conclusions

There is no question that ALND should be avoided when there are safer, better tolerated alternatives like SLNB and axillary radiation. The real remaining question facing breast cancer patients, surgeons, and multi-disciplinary colleagues is how to make adjuvant treatment decisions based on limited information. The extent of axillary surgery will continue to decrease, and we will increasingly be faced with this scenario. Future work should focus on identifying additional non-invasive biomarkers that may predict lymph node burden, or prognosis in the absence of pathologic lymph node information.

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