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# Axillary Nodal Management Following Neoadjuvant Chemotherapy

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## Abstract

**Importance—**The increasing use of neoadjuvant chemotherapy (NAC) for operable breast cancer has raised questions about optimal local therapy for the axilla.

**Observations—**Sentinel lymph node biopsy (SLNB) after NAC in patients presenting with clinically negative nodes has an accuracy similar to upfront SLNB and reduces the need for axillary lymph node dissection (ALND) compared to SLNB prior to NAC. In patients presenting with node-positive disease, clinical trials demonstrate that SLNB after NAC is accurate when ≥3 sentinel nodes are obtained, but long-term outcomes are lacking. The relative importance of pre- and post-NAC stage in predicting risk of locoregional recurrence remains an area of controversy.

**Conclusion and Relevance—**NAC reduces the need for ALND, and SLNB is an accurate method of determining nodal status post NAC.

## Introduction

Neoadjuvant chemotherapy (NAC) is increasingly used for patients with operable breast cancer to allow more limited surgery in the breast and axilla.[1-5] Although NAC does not improve survival compared to adjuvant therapy[6], a survival benefit has been demonstrated for the use of additional chemotherapy in patients who fail to achieve a pathologic complete response (pCR)[7] with NAC. The paradigms for local therapy of the breast and axilla were developed based on trials of initial surgical treatment. The increasing use of NAC has raised questions about the optimal approach to the axilla, including accuracy and timing of sentinel lymph node biopsy (SLNB) in patients who are clinically node negative (cN0) at presentation, use of NAC to avoid axillary lymph node dissection (ALND) in patients presenting with node-positive disease, and the relative importance of pre-and post-NAC stage in predicting the risk of locoregional recurrence (LRR). Here we review the controversies and unanswered questions regarding axillary management in patients receiving NAC.

## Concerns regarding feasibility of SLNB post NAC

Initially, there was concern that fibrosis in lymphatic channels as tumor emboli responded to treatment would result in altered lymphatic drainage in the breast and that a non-uniform

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response to treatment in the axillary nodes would cause an unacceptably high false-negative rate (FNR) for SLNB after NAC. Early studies reporting SLN identification rates following NAC ranging from 63% to 100%, as well as FNRs of 0% to 33%[8-11], substantiated these concerns. There was wide variation in the stage of patients included in these reports, and bulky nodal disease at presentation or persistent adenopathy following NAC significantly impact the accuracy of SLNB. Subsequent studies examining more well-defined patient subsets established the feasibility of SLNB post-NAC.

## Clinically node-negative patients

Studies examining the accuracy of SLNB after NAC in patients presenting with cN0 disease report similar identification rates and FNRs to those seen in the upfront surgery setting. The GANEA study was a prospective multi-institutional European trial assessing the feasibility of SLNB following NAC in both cN0 and node-positive (cN+) cohorts. Among 130 cN0 patients, the SLN identification rate was 95% with a FNR of 9%; the 82% identification rate seen among cN+ patients (p=0.008) was significantly lower.[12] A single-institution retrospective study of cN0 patients from MD Anderson Cancer Center (MDACC) included 3171 patients undergoing upfront surgery and 575 patients who had SLNB following NAC. SLN identification rates and FNRs were not significantly different, with identification rates of 99% and 97%, and FNRs of 4% and 6%, respectively.[13] Several study-level meta-analyses including more than 5000 patients treated with SLNB after NAC report SLN identification rates of 90–94% and FNRs of 7–12%.[8, 9, 14, 15] A persistent finding in studies comparing upfront SLNB to SLNB after NAC is a lower rate of nodal positivity in the post-NAC group. In the 1097 cN0 patients enrolled in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial comparing preoperative versus postoperative doxorubicin and cyclophosphamide (AC) chemotherapy, there was a significant reduction in node-positive disease in women undergoing NAC (33% versus 48%, p<0.001).[2] Subsequently, NSABP B-27 reported significantly greater reductions in nodal involvement in women receiving preoperative docetaxel and AC compared to those receiving neoadjuvant AC alone (40% vs 49%, p<0.001).[1] In the MDACC experience, a statistically significant reduction in nodal metastases was seen for T2 and T3 tumors, with a similar trend observed for T1 tumors (13% vs 19%, p=0.2)[13] (Table 1).[1, 2, 13] In aggregate, these studies support the feasibility of SLNB following NAC in cN0 patients and highlight the potential to downstage microscopic nodal disease and avoid ALND.

While the FNRs of SLNB appear similar among cN0 patients staged prior to NAC versus those undergoing SLNB following NAC, the long-term consequence of leaving lymph nodes with potentially chemo-resistant disease in situ has raised concern. Information to address this question is limited since the majority of studies of SLNB after NAC required completion ALND to establish the accuracy of the procedure. In the MDACC series, 409 of 444 women with a negative SLN following NAC were managed with a SLNB alone. With a median follow-up of 47 months, the 1.2% rate of regional recurrence did not differ significantly from the 0.9% rate observed in 3171 patients having a negative upfront SLNB.[13] In a second study including 15 women with a negative SLNB following NAC, no axillary recurrences were observed at a median follow-up of 52 months.[16]

## Timing of SLNB—pre- or post-neoadjuvant chemotherapy

There has been persistent variation regarding the preferred timing of axillary staging among women undergoing NAC[17], and both the 2008 National Cancer Institute statement of the science concerning NAC and current National Comprehensive Cancer Network (NCCN) guidelines support the use of SLNB either before or after NAC among cN0 patients.[18, 19] Pre-treatment SLNB provides accurate axillary staging, identifying node-negative patients who may avoid ALND as well as node-positive patients who would benefit from nodal irradiation. The major drawbacks of upfront SLNB include the need for two separate surgical procedures with a delay in initiation of NAC to allow wound healing. Most importantly, axillary staging pre-NAC eliminates the benefit of downstaging the axilla to avoid ALND in patients who achieve a nodal pCR. The SENTinel NeoAdjuvant (SENTINA) study evaluated axillary surgery strategies among four patient subgroups, including a group of cN0 patients who underwent SLNB prior to NAC, had a positive SLN, and underwent repeat SLNB following completion of NAC. The SLN identification rate on repeat SLNB (n=64) was 61% with a FNR of 52%[20], indicating that repeat SLNB post-NAC is not a viable strategy. Based on these data, ALND remains standard for patients with an upfront positive SLNB, regardless of response to treatment.

A series of single-institution studies reporting results of patients with a positive pre-treatment SLNB followed by post-chemotherapy ALND[21-24] demonstrate that 33–69% of patients have no additional positive axillary lymph nodes at completion ALND. Studies examining node-positive patients diagnosed by needle biopsy who undergo NAC report nearly identical rates of nodal pCR, ranging from 35% to 68% (Table 2).[25-30] Performance of SLNB prior to NAC eliminates the potential to avoid ALND in patients who have a nodal pCR. An early argument for the performance of pre-NAC SLNB was that knowledge of nodal status pre-treatment was necessary to determine the need for adjuvant radiotherapy. Data published by Mamounas and colleagues from the NSABP B-18 and B-24 trials demonstrate that residual disease in the breast and axilla following NAC is a more important predictor of LRR than pre-treatment stage.[31] Among cN0 patients undergoing breast-conserving surgery following NAC, rates of regional recurrence at 10 years were low (≤2%), regardless of final pathologic status. Conversely, among cN+ patients, those achieving a nodal pCR had low rates of regional recurrence (≤2%), while those who remained pathologically node positive had the highest rates of regional recurrence (8–9%). For patients undergoing mastectomy post-NAC, lack of a nodal pCR was the strongest predictor of 10-year LRR (HR 4.5, 95% confidence interval [CI] 1.6–12.2, p<.001). These results suggest that the post-treatment pathological response to NAC may allow a more personalized radiotherapy treatment plan than that derived from a pre-treatment SLNB, and eliminate much of the rationale for pre-NAC axillary staging, whether by ultrasound and fine needle aspiration or SLNB in cN0 patients. In the opinion of the authors, axillary staging prior to NAC should be reserved for the unusual circumstance where the identification of nodal metastases would provide the indication for NAC.

## Clinically node-positive disease

The decrease in nodal metastases in cN0 patients undergoing post-NAC axillary staging and the increasing rates of pCR in the breast in patients treated with current chemotherapy regimens led to the study of SLNB among patients presenting with cN+ disease. Table 3[20, 25, 32] summarizes data from three prospective, multi-institutional trials assessing the accuracy of SLNB after NAC among node-positive patients.

As mentioned, the SENTINA study was a four-arm study undertaken at 103 centers across Germany and Austria between 2009 and 2012. Patients were stratified based on both pre- and post-chemotherapy clinical nodal status, which was assigned by physical exam and axillary ultrasound. Histologic confirmation of metastases in clinically suspicious nodes was not mandatory. Patients converting from cN+ to cN0 following NAC (n=592) had a SLN detection rate of only 80%, with improved detection with the use of dual radiocolloid and blue dye compared to radiocolloid alone (88% versus 77%). The overall FNR was 14%; dual tracer mapping versus radiocolloid alone resulted in FNRs of 9% versus 16%, respectively, although mapping technique was not significantly associated with the FNR on multivariate analysis (p=0.15). The FNR with removal of 3 or more SLNs was 7% or less, compared to 19% with 2 nodes removed and 24% with only one SLN removed (p=0.008).[20]

The American College of Surgeons Oncology Group (ACOSOG) Z1071 trial also assessed the feasibility of SLNB following NAC in patients presenting with cN+ disease confirmed by biopsy.[32] The primary study endpoint was a FNR of 10% or less. Unlike the SENTINA study, conversion from cN+ to cN0 was not mandated, but patients were required to have ≥2 SLNs identified to be included in the calculation of the FNR. Surgery was completed by 649 patients with cN1 disease at presentation. Following NAC, 83% were cN0 by physical exam, 13% had residual palpable adenopathy, and clinical axillary status was unknown in 4%. At least 1 SLN was identified in 639 (93%) of all patients. The FNR among women who had ≥2 SLNs excised was 13% and failed to meet the pre-defined 10% rate to consider the procedure successful. In unplanned, exploratory analyses, a significant reduction in the FNR was seen with the use of dual tracer mapping (dual tracer FNR 11% versus 20% with single agent, p=0.05) and with the removal of ≥3 SLNs (FNR 9% ≥3 SLNs, 21% 2 SLNs, p=.007). On multivariable modeling, only number of SLNs excised (2 versus ≥3) remained significantly associated with the FNR.

Similar in design, the Sentinel Node Biopsy Following Neoadjuvant Chemotherapy (SN FNAC) study enrolled biopsy-proven node-positive patients to examine the technical success of SLNB following NAC with a predefined optimal identification rate of 90% and a FNR of ≤10%. Pathologic evaluation of the SLNs was performed with immunohistochemistry (IHC) as well as routine staining. The trial closed early following accrual of 51% of the target population (n=153) given the findings of the SENTINA and AGOCOSG Z1071 trials. Results included an overall identification rate of 88% and a FNR of 8% when isolated tumor cells (ITCs) were considered node positive. The FNR was 13% when ITCs were not considered metastases as is standard in the upfront surgical setting.[25]

The overall FNRs greater than 10% in the SENTINA and ACOSOG Z1071 trials were felt to be unacceptably high, and they were considered negative trials. However, technical modifications, including use of dual tracer and retrieval of al least 3 SLNs, resulted in clinically acceptable FNRs of <10% (Table 4).[20, 25, 32] The need to identify 3 or more SLNs for accurate post-NAC staging potentially limits the use of SLNB given that the median number of SLNs retrieved in trials in the primary surgical setting was 2.[33-35] In ACOSOG Z1071 and SENTINA, only 56% and 34% of patients had ≥3 SLNs removed.[20, 32] Mamtani et al examined the likelihood of identifying >2 SLNs after NAC in a prospective, consecutive cohort of 155 patients with biopsy-proven cN1 disease. Following NAC, 132 converted to cN0 and underwent SLNB with dual agent mapping. ALND was performed for any residual nodal tumor. Routine IHC was not used. A SLN was identified in 98% of cases, and ≥3 SLNs were retrieved in 110 cases (86%). ALND was performed for positive SLNs (n=54), failed mapping (n=3), fewer than 3 SLNs identified (n=9), or based on intraoperative findings (n=4). Based on this algorithm, 47% of cN1 patients who converted to cN0 following NAC were spared ALND.[30]

## Additional techniques to optimize SLNB following NAC

Marking abnormal axillary lymph nodes at the time of needle biopsy with either a clip or by tattooing to allow for localization and excision of the known metastatic node following NAC has been suggested as a strategy to reduce the FNR.[27, 36-39] Studies examining the combination of SLNB and excision of the clipped node report that the clipped lymph node is not a SLN in 9% to 24% of cases and that the combination of SLNB with targeted excision of the clipped node reduces the FNR.[27, 36, 40] One caveat in evaluating the benefit of clipping nodes is variability in the SLNB techniques utilized and failure to control for the number of SLNs removed, making it difficult to determine the benefit of nodal clipping when SLNB technique and pathologic evaluation are optimized. Clear evidence of benefit of nodal clipping is important, since clipped nodes require localization with either a wire or a radioactive seed. Wires in the axilla may be difficult to place and are uncomfortable, while clips not centrally placed in nodes may fall out when the node responds to chemotherapy, leading to placement of a radioactive seed in the axillary fat, which may be difficult to retrieve. Although retained seeds are not harmful, they are reportable radiation safety events in some states.

Another approach to documenting removal of nodes that were positive prior to NAC is the identification of post-treatment changes in the node on pathologic examination. Barrio et al identified treatment effect in 94% (192/204) of nodal specimens in patients with documented metastases pre-NAC who had a nodal pCR. Factors significantly associated with the likelihood of identifying treatment effect include tumor subtype (83% hormone receptor+/HER2-, 96% triple negative, 96% of HER2+ tumors, p=0.05) and the pathologic response in the breast (treatment effect present in 97% compared to 89% of those with and without a breast pCR, respectively, p=0.05). Among SLNB patients, SLNs with treatment effect were retrieved in 88% of women with ≥3 SLNs removed without marking the biopsied node.[41] However, even among patients undergoing ALND, treatment effect was not seen in 3%.

A major unanswered question regarding the use of SLNB alone in patients who convert from cN+ to cN0 is the rate of nodal recurrence. Although FNRs of 5–10% in the primary surgical setting are associated with axillary failure in <1% of patients[42-44], residual disease after NAC is by definition drug resistant and may result in higher rates of regional recurrence. Information on nodal recurrence is not available from the prospective studies discussed since all required ALND to determine the FNR.[20, 25, 32] In spite of this, growing numbers of surgeons are comfortable omitting ALND among women after a nodal pCR.[45] Available data suggest that some combination of techniques (dual mapping, retrieval of >2 SLNs, nodal marking) should be considered when utilizing SLNB among node-positive patients who convert to cN0 following NAC to minimize the FNR. Current NCCN guidelines endorse the use of post-NAC SLNB for axillary staging in node-positive patients who convert to clinically node negative following systemic therapy.[18] In our practice, SLNB following NAC with dual tracer mapping and retrieval of 3 or more negative SLNs are required to eliminate ALND in patients presenting with nodal metastases who become cN0.

## Role of regional radiation therapy

While nodal irradiation after SLNB has been proven as a safe alternative to ALND among patients with 1–2 positive nodes undergoing primary surgery[46], the optimal combination of surgery and radiation therapy after NAC remains unknown. Traditionally, the pre-NAC stage has been the determinant of the need for nodal irradiation. A National Cancer Database retrospective review of 1560 cN+ patients with nodal pCR following NAC evaluated the role of post-mastectomy radiation therapy (PMRT) among this cohort. PMRT was administered to 58% of patients, with PMRT significantly more common among patients with higher T or N stage and hormone receptor negativity. At a median follow-up of 56 months, no statistical difference in overall survival was observed between groups. On subgroup analyses, PMRT was associated with a significant improvement in overall survival for patients with clinical stage IIIB/IIIC disease, or residual invasive disease in the breast following NAC ($p<0.05$).[47] As previously discussed, in a retrospective analysis of data from the NSABP trials of NAC in which PMRT was prohibited and node field irradiation was not used after BCT, Mamounas et al noted that residual disease in the axillary nodes after NAC was the strongest predictor of LRR, and that risk was low in patients with negative nodes and residual disease in the breast.[31]

Prospective data addressing the need for radiotherapy after nodal pCR will come from the NSABP B-51 trial, a randomized trial enrolling patients with stage II-III breast cancer with biopsy-confirmed nodal metastases who convert to ypN0 (staged by SLNB or ALND) following NAC.[48] Mastectomy patients are randomized to chest wall and regional nodal irradiation versus no radiation, while lumpectomy patients are randomized to whole breast irradiation with or without nodal treatment.

The need for ALND in women with residual nodal disease after NAC is addressed in the ALLIANCE A011202 trial[49] comparing overall survival, LRR, and lymphedema outcomes after ALND versus axillary nodal irradiation among women who undergo SLNB and have residual nodal disease. It is possible that the effectiveness of RT without ALND will vary based on the hormone receptor and HER2 status of the tumor, given that failure to achieve

pCR in patients with triple-negative breast cancer is strongly associated with a poor outcome[50], while the same relationship is not seen in patients with estrogen receptor positive cancers who have the benefit of 5–10 additional years of endocrine therapy.[50] Together, these 2 studies address the ability to individualize a patient's axillary management based on response to NAC to both maximize regional control and minimize therapeutic morbidity. While awaiting the results, ALND remains standard for patients with tumor in the axillary nodes post-NAC, including those with micrometastases. In determining the need for nodal and chest wall irradiation in patients who have a nodal pCR, we consider the presenting stage, presence of pCR in the breast, and other factors known to influence local control such as age, lymphovascular invasion, hormone receptor status, and HER2 status to identify low-risk women unlikely to benefit from RT.

## Neoadjuvant therapy versus initial surgery: Selecting the optimal pathway to avoid ALND

From a patient and surgeon perspective, the safe avoidance of ALND and the associated lymphedema risk is desirable. With current axillary management strategies for clinically node-negative patients, there is a question as to which approach, initial surgery or NAC, minimizes the likelihood of ALND. In patients undergoing primary breast-conserving surgery, ALND is necessary only for 3 or more nodal metastases[44, 46], while in patients receiving NAC, the presence of any nodal disease post treatment is an indication for ALND. Although approximately 25% of cN0 patients harbor nodal metastases[34, 35], fewer than 6% have metastases in ≥3 SLNs%.[51]

In a prospective, consecutive series of 287 patients with positive SLNs who met ACOSOG Z0011 eligibility, only 16% had indications for ALND for either ≥3 positive SLNs or gross extracapsular extension.[52] Subsequently, the same group reported a cohort of 701 consecutive cT1-2N0 patients with a positive SLN and found no difference in the likelihood of ALND among high-risk patients, defined as women 50 years of age or younger, or with triple-negative or HER2 amplified tumors compared to postmenopausal women with estrogen receptor positive cancers, with 13% and 12% of each group having ≥3 positive SLNs (p=0.82).[53] While these results indicate a minority of cN0 women undergoing breast-conserving therapy require ALND, it may be possible to reduce this rate among selected patients, and, importantly, these results do not apply to women undergoing mastectomy. Rates of nodal pCR with NAC differ based on tumor subtype[18], ranging from 40% to 60% overall, and approaching 70% to 80% among patients with triple-negative and HER2 amplified tumors (Table 5).[26, 27, 29, 30, 48, 54] cN0 patients with these subtypes, even when undergoing breast-conserving surgery, may have a higher likelihood of avoiding ALND with definitive axillary staging following NAC, a concept that warrants further study. In cN+ patients, it is clear that NAC offers the only possibility of avoiding ALND.

## Conclusion

The demonstration that SLNB accurately stages the axilla after NAC regardless of the presenting nodal stage (cN0, cN1) provides an important rationale for the use of NAC for axillary downstaging in patients who are candidates for breast-conserving surgery at

presentation or who desire mastectomy. SLN identification rates and FNRs in those who are cN0 are similar to those seen with initial SLN surgery, and nodal recurrence after a negative SLNB is uncommon. In patients with cN1 disease, modification of the SLNB technique is needed to minimize the FNR, and the optimal method remains under study, but should include dual tracer mapping and removal of >2 sentinel nodes. The rate of regional recurrence in patients with proven nodal metastases who have a pCR and undergo SLNB alone is uncertain. A major unresolved question is the relative importance of the pre-NAC nodal stage versus the post-NAC nodal stage in determining the risk of LRR and the need for radiotherapy. Ongoing clinical trials will address this issue. For cN0 patients with estrogen receptor positive, HER2 negative cancers undergoing breast-conserving therapy, initial surgery is the path most likely to avoid ALND. The optimal approach to cN0 patients with triple negative or HER2 overexpressing cancers is uncertain, but for patients undergoing mastectomy, and those with biopsy-proven nodal metastases, NAC reduces the likelihood of ALND.[13, 30]

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## Table 1

**Rates of Nodal Positivity Among Women Undergoing Axillary Staging Prior to Systemic Therapy Versus Following Neoadjuvant Chemotherapy**

| Study, year | Upfront surgery | NAC | P value |
|---|---|---|---|
| NSABP B-18, 1997 | 48% | 33% | <0.001 |
| NSABP B-27, 2003 | 49% | 40% | <0.001 |
| Hunt et al, 2009 | | | 0.04 |
| T1 | 19% | 13% | |
| T2 | 37% | 21% | |
| T3 | 51% | 30% | |

Abbreviations: NAC, neoadjuvant chemotherapy; NSABP, National Surgical Adjuvant Breast and Bowel Project

## Table 2

**Rates of Nodal Pathologic Complete Response Following Neoadjuvant Chemotherapy in Biopsy-Proven Node-Positive Patients**

| Author, year | Number biopsy proven pN+ | Number who convert to ypN0 post-NAC | pCR rate |
|---|---|---|---|
| **Boughey, 2014**[26] | 525 | 215 | 41% |
| **Boileau, 2015**[25] | 145 | 50 | 35% |
| **Kim, 2015**[29] | 415 | 159 | 38% |
| **Mamtani, 2016**[30] | 195 | 96 | 49% |
| **Diego, 2016**[27] | 30 | 19 | 63% |
| **Enokido, 2016**[28] | 143 | 68 | 48% |

Abbreviations: NAC, neoadjuvant chemotherapy; pCR, pathologic complete response

**Table 3**

**Studies Evaluating the Identification Rate and False-Negative Rate Among Clinically Node-Positive Patients Undergoing SLNB Following Neoadjuvant Chemotherapy**

| Study | Population cN1-N2 | Biopsy required | cN0 post NAC | Identification rate | False-negative rate |
|---|---|---|---|---|---|
| SENTINA | 592 | No * | 100% * | 80% | 14% |
| ACOSOG Z1071 | 689 | Yes | 83% | 93% | 13% |
| SN FNAC Study | 153 | Yes | Unknown * | 88% | 13% ** |

* Ultrasound performed in all patients

** False-negative rate excluding immunohistochemially detected isolated tumor cells

Abbreviations: SLNB, sentinel lymph node biopsy; NAC, neoadjuvant chemotherapy; SENTINA, Sentinel Neoadjuvant; ACOSOG, American College of Surgeons Oncology Group; SN FNAC, Sentinel Node Biopsy Following Neoadjuvant Chemotherapy

**Table 4**

**Factors Impacting the SLNB False-Negative Rate in the SENTINA, ACOSOG Z1071, and SN FNAC Studies**

| Study | Number SLNs removed | | | P value | Tracer used | | P value |
|---|---|---|---|---|---|---|---|
| | 1 | 2 | ≥3 | | Single tracer | Dual tracer | |
| SENTINA | 24% | 19% | 7% | 0.008 | 16% | 9% | 0.15 |
| ACOSOG Z1071 | - | 21% | 9% | .007 | 20% | 11% | .05 |
| SN FNAC study* | 18% | 5%** | | | 16% | 5% | |

*False negative rates reported here consider immunohistochemially detected isolated tumor cells node positive

**False negative rate 5% with ≥2 SLNs removed

Abbreviations: SLNB, sentinel lymph node biopsy; SENTINA, Sentinel Neoadjuvant; ACOSOG, American College of Surgeons Oncology Group; SN FNAC, Sentinel Node Biopsy Following Neoadjuvant Chemotherapy; SLNs, sentinel lymph nodes

**Table 5**

**Rates of Axillary Nodal Pathologic Complete Response (ypN0) by Tumor Subtype**

| Author, year | N, stage | HR+/HER2- | HER2+ | Triple negative | Chemotherapy regimen |
|---|---|---|---|---|---|
| Zhang, 2013[54] | 301, stage II-III | 46% | 72% | 69% | 51% taxane based, 95% HER2+ received trastuzumab |
| Boughey, 2014[26] | 756, pN+ | 21% | 65% | 49% | 75% Anthracycline and taxane, 89% HER2+ received trastuzumab |
| Kim, 2015[29] | 415, pN+ | 29% | 49% | 54% | 86% Anthracycline and taxane, 10% HER2 + received trastuzumab |
| Mamtani, 2016[30] | 195, pN+ | 21% | 82% | 47% | 97% ddACT, 9% carboplatin. 100% HER2+ received trastuzumab + pertuzumab |
| A L-Tweigeri, 2016[51] | 80, Stage II-III | 50% | 79% | 73% | FEC, cisplatin/docetaxel, 100% HER2+ received trastuzumab |
| Diego, 2016[27] | 30, pN+ | 0% | 69% | 67% | Chemotherapy regimen unknown, 100% HER2+ received trastuzumab |