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Patterns of local-regional management following neoadjuvant chemotherapy in breast cancer: Results from ACOSOG Z1071 (Alliance)

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Abstract

Purpose/Objective(s)—AXXXXX ZXXXX was a prospective trial evaluating the false negative rate of sentinel node (SLN) surgery after neoadjuvant chemotherapy (NAC) in breast cancer patients with initial node-positive disease. Radiation therapy (RT) decisions were at the discretion of treating physicians, providing an opportunity to evaluate variability in practice patterns following NAC.

Methods and Materials—Of 756 patients enrolled from July 2009 to June 2011, 685 met all eligibility requirements. Surgical approach, RT, and radiation field design were analyzed based on presenting clinical and pathologic factors.

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Results—Of 401 node-positive patients, mastectomy was performed in 148 (36.9%), mastectomy with immediate reconstruction in 107 (26.7%), and breast-conserving surgery (BCS) in 146 (36.4%). Of the 284 pathologically node-negative patients, mastectomy was performed in 84 (29.6%), mastectomy with immediate reconstruction in 69 (24.3%) and BCS in 131 (46.1%).

Bilateral mastectomy rates were higher in women undergoing reconstruction compared to those without (66.5% vs 32.2%, $p<0.0001$). Usage of internal mammary RT was low (7.8%–11.2%) and did not differ between surgical approaches. Supraclavicular-RT rate ranged from 46.6% to 52.2% and did not differ between surgical approaches but was omitted in 193/408 (47.3%) of node-positive patients. Rate of Axillary-RT was more frequent in patients who remained node-positive ($p=0.002$). However, 22% of patients who converted to node-negative still received Axillary RT. Post-mastectomy RT was more frequently omitted after reconstruction compared to mastectomy (23.9% vs 12.1%, $p=0.002$), and was omitted in 19 of 107 (17.8%) patients with residual node-positive disease in the reconstruction group.

Conclusion—The majority of clinically node-positive patients treated with NAC undergoing mastectomy receive RT. RT was less common in patients undergoing reconstruction. There is wide variability in RT fields. These practice patterns conflict with expert recommendations and ongoing trial guidelines. There is a significant need for greater uniformity and guidelines regarding RT following NAC.

Keywords

breast cancer; neoadjuvant; radiation; surgery

Introduction

Neoadjuvant chemotherapy (NAC) is commonly used in locally advanced and increasingly in the management of stage II breast cancer^{1–3}. Randomized trials comparing NAC to standard adjuvant chemotherapy demonstrate similar overall survival and disease-free survival rates, but more patients were able to undergo BCS after NAC and a substantial proportion with complete clinical and pathologic responses^{4–6}. The increased utilization of NAC can be attributed to a number of practical clinical advantages. Response to NAC is a powerful prognostic factor that can help the treating physicians evaluate tumor response and guide future systemic approaches and multimodality treatment recommendations⁷. Evaluation of response to NAC also provides an efficient approach for evaluating novel drugs in clinical trials⁸.

The increasing use of NAC has, however, introduced questions regarding appropriate local-regional management, given that local-regional decision-making has traditionally been based on clinical and pathologic factors after upfront surgery^{3, 9, 10}. With the broad range of responses to NAC, clinicians are faced with many decisions including appropriate imaging modalities in evaluating response, the optimal surgical approach to the breast, reliability of SLN surgery versus axillary lymph node dissection (ALND), the type and timing of reconstruction in anticipation of the need for radiation, and the appropriate use of regional nodal or post-mastectomy radiation (PMRT). Some of these issues are currently being addressed in ongoing randomized trials, such as NRG-9353/NSABPB-51/RTOG1304

(NRG_B-51) which is addressing the issue of potentially omitting regional nodal and PMRT in patients converting from node-positive to node-negative disease following NAC, and Alliance A011202, which is addressing whether axillary radiation alone is non-inferior to ALND in patients who remain SLN positive after NAC^{11–13}.

American College of Surgeons Oncology Group (AXXXXX is now part of the Alliance for Clinical Trials in Oncology) ZXXXX was a phase II, multicenter trial enrolling patients with node-positive disease treated with NAC¹⁴ to determine the false negative rate of SLN surgery following NAC. All patients had biopsy proven node-positive breast cancer at diagnosis and then had SLN surgery followed by completion ALND after NAC. Since the primary endpoint of ZXXXX was solely to determine the false negative rate of SLN surgery, local-regional management (beyond the required ALND) was left to the discretion of the treating physicians. Decisions regarding BCS or mastectomy, reconstruction, subsequent systemic therapy and RT were based on standard practices as determined by the treating physicians, with no specific guidelines within the trial regarding RT indications or field design. ZXXXX therefore offers a unique opportunity to evaluate contemporary practice patterns of local-regional therapy after NAC to assess variability in practice to inform gaps in education and the need for practice guidelines.

The current study examined local-regional treatment after NAC in patients enrolled in ZXXXX, with specific attention to surgical approaches, use of reconstruction after mastectomy, and utilization of post-mastectomy and regional nodal irradiation, as a function of clinical factors, nodal status and response to NAC.

Methods and Materials

AXXXXX ZXXXX was approved by the institutional review boards of participating institutions and participants provided written informed consent. All patients had T0–T4, N1–N2, M0 primary invasive breast cancer, ECOG performance status 0 or 1, and underwent NAC. Nodal metastasis at initial diagnosis was confirmed by fine needle aspirate or core biopsy. Surgery was performed within 84 days of completion of NAC, and all patients underwent appropriate treatment of the primary tumor by BCS, mastectomy, or mastectomy with immediate reconstruction, based on clinical judgement, patient and physician preference. All patients underwent SLN surgery followed by completion ALND. Further details of the trial with respect to the false negative rate of SLN have been previously published¹⁴. As noted above there were no specific guidelines or central review related to RT as the intent of the trial was limited to determining the false negative rate of the SLN surgery.

The records of patients enrolled in AXXXX ZXXXX were reviewed with specific attention to local-regional management details following NAC. For the current analysis, surgical and radiation details as a function of clinical presentation, nodal status, and response to NAC were documented from the original case report forms in an effort to determine practice variability, needs for practice guidelines and potential issues for future trials.

Statistical analysis

Categorical variables were summarized as frequencies and percentages. Comparisons of categorical variables between groups were made with a chi-square test or Fisher's exact test if expected cell sizes were too small for the chi-square test. All tests were two-sided, and p-values less than 0.05 were considered to be statistically significant. Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center. Analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina) on a dataset frozen on March 13, 2013.

Results

A total of 756 women were enrolled in ZXXXX from July 2009 to June 2011, of whom 701 met all eligibility requirements, underwent the mandated SLN surgery and completion ALND. Nodal status following NAC was not documented in one patient, and surgical details were not available in 15 patients, leaving 685 patients eligible for the current analysis.

Clinical characteristics of patients in the trial by surgical management of the primary tumor are summarized in Table 1. All patients who underwent immediate reconstruction or an expander for subsequent reconstruction were classified as mastectomy with immediate reconstruction.

Local-regional management (breast surgical procedure and radiation fields) following NAC for the 685 patients is summarized in Figures 1A (node-positive following NAC) and 1B (node-negative following NAC). Of the 685 patients, 401 (58.5%) remained node-positive following chemotherapy, and 284 (41.5%) converted to node-negative.

Surgical approach

Of the 401 node-positive patients, mastectomy was performed in 148 (36.9%), mastectomy with immediate reconstruction in 107 (26.7%), and BCS in 146 (36.4%). Of the 284 node-negative patients, mastectomy was performed in 84 (29.6%), mastectomy with immediate reconstruction in 69 (24.3%) and BCS in 131 (46.1%).

The rates of BCS were higher in patients with triple-negative and HER2-positive breast cancer, 79/170 (46.5%) and 89/212 (42.0%), respectively, compared to those patients with hormone-receptor-positive, HER2-negative disease (39.4%, $p=0.024$).

BCS was more commonly performed in those patients presenting with smaller primary tumors, with 82.7% of BCS cases having clinical stage cT0-cT2 disease at presentation. Patients undergoing BCS had higher rates of pathologic complete response in both the primary tumor (43.0% pathologically T0 or Tis) and nodes (47.3% pathologically node-negative) compared to patients undergoing mastectomy with or without immediate reconstruction ($p < 0.0001$; see Table 1). RT was omitted in 10.7% of patients after BCS.

Of the patients who underwent mastectomy, a higher portion undergoing immediate reconstruction presented with earlier clinical stages of disease (Table 2). Use of immediate reconstruction was higher in patients presenting with cT0-2 tumors than those with cT3-4

disease ($p < 0.0001$). However, there were no significant differences in the final pathologic T-stage or N-stage between the patients undergoing mastectomy without reconstruction compared with those having immediate reconstruction.

Bilateral mastectomy rates were significantly higher in women undergoing immediate reconstruction compared to women without immediate reconstruction (66.5% vs 32.2%, $p < 0.0001$).

Radiation Approach

As demonstrated in Figure 1, whether nodes remained positive or converted to node-negative after NAC, RT was employed in the vast majority of patients, regardless of the treatment of the primary tumor.

RT details are summarized in Tables 3–5. RT was more frequently used in patients undergoing mastectomy without reconstruction [204/232 (87.9%)] compared to patients undergoing mastectomy with reconstruction [134/176 (76.1%), $p = 0.002$]. Of patients who remained node-positive following NAC, RT was employed in 133/148 (89.9%) of the mastectomy patients compared to 88/107 (82.2%) of the mastectomy with reconstruction patients ($p = 0.077$). Although not statistically significant, PMRT was omitted more frequently in the mastectomy with reconstruction patients compared to the patients undergoing mastectomy without reconstruction, despite the fact that the final pathologic T-stage and N-stage did not differ between these two groups.

In those patients converting to node-negative after NAC (Figure 1B), PMRT was employed in 71/84 (84.5%) of the mastectomy patients compared to 46/69 (66.7%) of those undergoing mastectomy with reconstruction ($p < 0.001$).

Although PMRT was omitted more frequently in patients undergoing reconstruction, the majority of mastectomy patients in both the node-negative (76%) and node-positive (87%) cohorts did receive PMRT.

For all surgical approaches, regional nodal irradiation in some form was employed in the majority of node-positive and node-negative patients.

Internal mammary radiation use was low, ranging from 7.8% to 11.2%, and did not differ by surgical approach, pathological tumor stage or nodal response. Similarly, rates of supraclavicular radiation ranged from 46.6% to 52.2% and did not differ between surgical approaches, pathological tumor stage or nodal response. Notably, supraclavicular radiation was omitted in 193/408 (47.3%) of patients with residual node-positive disease after NAC.

The use of axillary radiation was variable in this group of patients, all of whom underwent completion ALND. Axillary radiation was used more frequently in those patients remaining node-positive after NAC ($p = 0.002$, Table 4) as well as those with residual disease in the breast ($p = 0.025$). Axillary radiation was used less frequently in those undergoing BCS, consistent with the higher rate of pN0 patients in the BCS cohort. Of note, 22% (62/284) of patients who converted to pathologic node-negative disease and underwent completion ALND received axillary radiation.

Discussion

The increasing use of NAC has significantly impacted local-regional decision-making for patients and their treating physicians.^{3, 9–12} Surgical decision-making in patients undergoing NAC is complex, and involves consideration of response to therapy, patient and clinician preferences, and clinical judgement.

As expected, BCS was more common among women with higher response rates to NAC¹⁵. However, a significant proportion of patients with a good response to NAC still elect to undergo mastectomy. The decision-making is multifactorial and may reflect factors at presentation despite a good response to NAC, and difficulties with interpretation of imaging modalities to evaluate extent of residual disease.¹⁵ Details on family history and genetic testing were not available for the current study population and could also have impacted decision-making.

Of those patients in ZXXXXX undergoing mastectomy after NAC, 43% underwent immediate reconstruction. Bilateral mastectomy was more common in those women electing reconstruction. This is in keeping with previous studies that have reported immediate reconstruction is associated with higher rates of bilateral mastectomy for breast cancer¹⁶. This has been attributed to improved symmetry with bilateral reconstruction compared with unilateral reconstruction and a contralateral symmetrisation procedure¹⁷

The high rate of mastectomy with immediate reconstruction in this cohort of women who presented with node-positive disease demonstrates a paradigm shift from earlier time periods where immediate reconstruction was not favored if PMRT was anticipated. This may in part be due to increasing rates nationally of immediate reconstruction in women undergoing mastectomy for breast cancer.¹⁶

While patients undergoing mastectomy without reconstruction presented with higher stages of disease compared to the immediate reconstruction group, the post-treatment pathologic T and N stages of these two groups were similar. Although pathologic data would usually not be available until several days after the surgery, these data suggest that the initial clinical stage may still be an important driver in decision-making regarding immediate reconstruction rather than the response to therapy. This may also be a reflection of the fact that currently available imaging modalities cannot fully assess response to therapy, as reported in a previous analysis of ZXXXXX¹⁵. Improvements in imaging and predictors of pathologic complete response could aid in patient counselling and decision-making. During the time of receiving NAC patients may also gain additional information regarding genetic testing results, reconstructive options and experiences of other breast cancer patients, all of which may influence individual treatment decisions.

Local-regional management practice patterns following NAC from patients enrolled in ZXXXXX confirm a lack of uniformity with wide variations in practice, stressing the need for clinical trials, practice guidelines or consensus statements in this setting. Although NCCN guidelines do recommend PMRT following NAC for advanced breast cancer, more detailed practice statements and targeted education of the surgical, medical and radiation oncology community can serve to lower practice variability¹⁸. In addition, this variability highlights

the importance of detailed guidelines regarding radiation field design and dose constraints, with centralized review and quality assurance. Close collaboration of all members of the multidisciplinary team, including the radiation oncologist, is essential in patients with advanced breast cancer regardless of response to NAC.

Two ongoing trials may help address several unresolved issues. Both trials have similar radiation field design and dose constraint guidelines that can be helpful in driving more uniformity in the delivery of radiation. Even for patients ineligible or unwilling to participate in the trials, the RT guidelines and dose constraints provide a useful resource for local-regional treatment after NAC. Alliance A011202 will address whether axillary radiation is non-inferior to ALND following NAC. NRG_B-51 will determine the need for PMRT or regional nodal irradiation in patients who convert to node-negative after NAC¹².

There are some clinical data suggesting that in women who experience a complete response with NAC, omission of PMRT or elimination of regional nodal irradiation after BCS and radiation may be an option^{10, 19–21}. Therefore NRG_B-51 randomizes mastectomy patients who convert to node-negative after NAC to PMRT or no further radiation, and patients undergoing BCS to breast radiation only or breast and regional nodal irradiation. Our data confirm wide variability in practice, reflecting the need for this trial. Of patients treated with BCS who converted to node-negative, it is interesting that regional nodal irradiation was employed in just over 50% reflecting uncertainty of the appropriate approach to regional nodal irradiation in this setting of true equipoise supporting the need for a randomized trial. Over 70% of patients treated with mastectomy who converted to node-negative received PMRT in our cohort, suggesting that the current most commonly practiced standard is to perform PMRT even with complete response. However 24% omitted PMRT, indicating variability across practices. The ongoing NRG_B-51 has the potential to significantly change practice if it demonstrates equivalence in omission of radiation in this setting.

Our data also revealed variations in radiation field design, often conflicting with the current radiation guidelines in the NRG and Alliance trials and conflicting with NCCN recommendations¹⁸. Although our data were retrieved from the original case report forms as opposed to centralized film review, introducing some uncertainty regarding the delivered radiation volumes, a previous analysis of AXXXXX Z0011 fields demonstrated excellent concordance between the case data report forms and centralized film review²².

Despite persistent node-positive disease following NAC, among patients receiving RT, supraclavicular radiation was omitted in 47% of patients. The benefit of regional nodal irradiation has recently been demonstrated in two randomized trials in patients with early stage node-positive or high-risk node-negative disease following upfront surgery.^{23, 24} For patients with node-positive disease that persists even after NAC, the potential benefit may be greater and supraclavicular radiation is prudent and should be strongly recommended.

Internal mammary radiation was low in our cohort, reflecting a reluctance to recognize deliberate targeting of internal mammary nodes as a significant contribution to the benefits of regional nodal irradiation. Several trials have attempted to address this issue with conflicting reports, although most trials demonstrating an advantage to regional nodal

irradiation employed internal mammary radiation, including two recent trials published in patients with earlier stage disease^{23–25}. Furthermore, the recent Danish DBCG-IMN prospective study demonstrated an advantage to internal mammary radiation²⁶. While we cannot comment on the benefit of internal mammary radiation from our data, it is clear that its use is limited and additional justification and educational resources will be required to increase its utilization.

Management of the axilla in node-positive disease is complex, requiring close coordination among the multidisciplinary team²⁷. The accuracy of SLN surgery and the false negative rate from the ZXXXX trial have been previously reported¹⁴. Whether axillary radiation can replace ALND in those patients who remain SLN positive is being addressed in Alliance A011202, which randomizes patients who are SLN positive following NAC to ALND plus radiation to the undissected Level II/III nodes, or full axillary and nodal radiation without further surgery¹³. The AMAROS trial demonstrated equivalent regional control in patients who underwent axillary radiation compared to ALND for the group of patients treated with upfront surgery who were SLN positive, with decreased morbidity associated with axillary radiation²⁸. However, patients who remain SLN positive after NAC are a higher risk group and the Alliance A011202 trial will address whether axillary radiation can replace ALND in this setting¹².

Variability in the use of axillary radiation after completion ALND is expected, and often depends on a number of factors including the extent of ALND, residual nodal burden, initial nodal status, physician biases and preferences, and clinical judgement³. However, in patients who undergo completion ALND, as was done in all patients in this cohort, axillary radiation should typically be employed selectively in patients with a heavy residual nodal burden or inadequate dissection. Both the NRG_B-51 and Alliance A011202 trials discourage axillary radiation in patients undergoing completion ALND, except in the circumstances of an inadequate sampling or heavy tumor burden. In the current series it is notable that 22% of patients with complete axillary response (pN0) and completion ALND also received axillary radiation. This also demonstrates a gap in knowledge and need for clinical practice guidelines.

Omission of radiation in patients undergoing immediate reconstruction also raises concerns. While it is expected that there is variability and lack of consensus regarding the need for PMRT, particularly in those patients converting to node-negative, it is generally accepted that patients with persistently node-positive disease after NAC should receive PMRT.⁹ Furthermore, NRG_B-51 excludes patients who remain node-positive after NAC as experts felt uncomfortable omitting radiation in this setting. Omission of PMRT in nearly 20% of patients with persistently node-positive disease in the current study also points to the need for education and guidance. It is interesting that PMRT was employed less frequently in reconstructed patients than in patients without reconstruction, despite the fact that there was no significant difference in the pathologic T or N stages between these groups, suggesting that immediate reconstruction and cosmetic issues may have influenced oncologic decision-making. Prior consultation with radiation oncologists regarding the use of immediate reconstruction is recommended, so that the patient can be fully informed and the radiation oncologist can be involved with the multidisciplinary decision-making.

In conclusion, results from XXXXXX ZXXXX demonstrate wide variability in local-regional practice patterns following NAC in patients with initial node-positive disease. While ongoing trials will help to address several unanswered questions, there is a need for more uniformity, practice guidelines and education to fill gaps in knowledge and alter practice patterns. While controversies and uncertainties will remain with some necessary variation in practice, several areas that deserve attention include factors that drive oncologic decision-making in the setting of immediate reconstruction and appropriate radiation field selection and design after NAC.

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Summary

Local-regional management following neoadjuvant chemotherapy in ACOSOG 1071 were reviewed. All patients had node positive breast cancer treated with neoadjuvant chemotherapy, sentinel node and completion axillary dissection. Review of the records revealed wide variability in practice, particularly regarding administration of radiation therapy, often conflicting with practice recommendations and guidelines. The study emphasizes the need for education, clinical practice statements and trials to address these issues and reduce variability in practice.

Local Regional Management from Z1071
Node Negative After Preoperative System Therapy

Local Regional Management from Z1071
Node Positive After Preoperative System Therapy

Figure 1.
Figure 1A. Local-regional management of node-positive patients following chemotherapy from AXXXXX ZXXXX
RNI, regional nodal irradiation; RT, radiation therapy
*Regional Nodal Irradiation
Figure 1B. Local-regional management of node-negative patients following chemotherapy from AXXXXX ZXXXX
RNI, regional nodal irradiation; RT, radiation therapy
*Regional Nodal Irradiation

Table 1
Clinical characteristics of the patient population (N = 685) by primary surgical approach

	Breast conserving surgery	Mastectomy without reconstruction	Mastectomy with immediate reconstruction	p-value
Number of patients	277 (40.4%)	232 (33.9%)	176 (25.7%)	
Clinical tumor stage at presentation				<0.0001
cT0/Tis	3 (1.1%)	1 (0.4%)	3 (1.7%)	
cT1	38 (13.7%)	23 (9.9%)	28 (16.0%)	
cT2	188 (67.9%)	98 (42.2%)	94 (53.7%)	
cT3	44 (15.9%)	84 (36.2%)	48 (27.4%)	
cT4	4 (1.4%)	26 (11.2%)	2 (1.1%)	
Unknown	0	0	1	
Clinical nodal stage at presentation				0.37
cN1	266 (96.0%)	214 (93.4%)	163 (93.7%)	
cN2	11 (4.0%)	15 (6.6%)	11 (6.3%)	
Unknown	0	3	2	
Clinical stage				<0.0001
II	220 (79.4%)	115 (50.2%)	118 (68.2%)	
III	57 (20.6%)	114 (49.8%)	55 (31.8%)	
Unknown	0	3	3	
Pathological tumor stage at surgery				<0.0001
pT0/is	119 (43.0%)	59 (25.6%)	50 (28.7%)	
pT1	99 (35.7%)	85 (37.0%)	64 (36.8%)	
pT2	54 (19.5%)	50 (21.7%)	41 (23.6%)	
pT3	5 (1.8%)	34 (14.8%)	18 (10.3%)	
pT4	0	2 (0.9%)	1 (0.6%)	
Unknown	0	2	2	
Pathological nodal stage at surgery				0.0003
pN0	131 (47.3%)	84 (36.2%)	69 (39.2%)	

		Breast conserving surgery	Mastectomy without reconstruction	Mastectomy with immediate reconstruction	p-value
	pN1 pN2 pN3 Unknown	100 (36.1%) 39 (14.1%) 7 (2.5%) 0	72 (31.0%) 51 (22.0%) 25 (10.8%) 0	63 (35.8%) 36 (20.4%) 8 (4.6%) 0	
Approximated tumor subtype	Triple negative HER2 positive HR positive, HER2 negative Unknown	79 (28.5%) 89 (32.1%) 109 (39.4%) 0	49 (21.1%) 70 (30.2%) 113 (48.7%) 0	40 (22.7%) 48 (27.3%) 88 (50.0%) 0	0.11
Laterality of surgery	Unilateral Bilateral Unknown	n/a	156 (67.8%) 74 (32.2%) 2	59 (33.5%) 117 (66.5%) 0	<0.0001
Radiation therapy	Yes No Unknown	242 (89.3%) 29 (10.7%) 6	204 (87.9%) 28 (12.1%) 0	134 (76.1%) 42 (23.9%) 0	0.0002

HER2, human epidermal growth factor receptor 2; HR, hormone receptor

Table 2

Comparison of mastectomy patients (N = 408) with or without immediate reconstruction

		Mastectomy without reconstruction	Mastectomy with immediate reconstruction	p-value
Number of patients		232 (56.9%)	176 (43.1%)	
Clinical tumor stage at presentation				<0.0001
	cT0/Tis	1 (0.4%)	3 (1.7%)	
	cT1	23 (9.9%)	28 (16.0%)	
	cT2	98 (42.2%)	94 (53.7%)	
	cT3	84 (36.2%)	48 (27.4%)	
	cT4	26 (11.2%)	2 (1.1%)	
	Unknown	0	1	
Clinical nodal stage at presentation				0.93
	cN1	214 (93.4%)	163 (93.7%)	
	cN2	15 (6.6%)	11 (6.3%)	
	Unknown	3	2	
Clinical stage at presentation				0.0003
	II	115 (50.2%)	118 (68.2%)	
	III	114 (49.8%)	55 (31.8%)	
	Unknown	3	3	
Pathological tumor stage at surgery				0.71
	pT0/is	59 (25.6%)	50 (28.7%)	
	pT1	85 (37.0%)	64 (36.8%)	
	pT2	50 (21.7%)	41 (23.6%)	
	pT3	34 (14.8%)	18 (10.3%)	
	pT4	2 (0.9%)	1 (0.6%)	
	Unknown	2	2	
Pathological nodal stage at surgery				0.12
	pN0	84 (36.2%)	69 (39.2%)	
	pN1	72 (31.0%)	63 (35.8%)	
	pN2	51 (22.0%)	36 (20.4%)	
	pN3	25 (10.8%)	8 (4.6%)	
	Unknown	0	0	
Approximated tumor subtype				0.80
	Triple negative	49 (21.1%)	40 (22.7%)	
	HER2 positive	70 (30.2%)	48 (27.3%)	
	HR positive, HER2 negative	113 (48.7%)	88 (50.0%)	
	Unknown	0	0	

		Mastectomy without reconstruction	Mastectomy with immediate reconstruction	p-value
Laterality of surgery	Unilateral	156 (67.8%)	59 (33.5%)	<0.0001
	Bilateral	74 (32.2%)	117 (66.5%)	
	Unknown	2	0	
Radiation therapy	Yes	204 (87.9%)	134 (76.1%)	0.002
	No	28 (12.1%)	42 (23.9%)	
	Unknown	0	0	
		Radiation	No Radiation	p value
Pathological complete response	Yes	64 (18.9%)	26 (37.1%)	0.0008
	No	274 (81.1%)	44 (62.9%)	
	Unknown	0	0	
Pathological T stage	pT0/is	82 (24.6%)	27 (38.6%)	<0.0001
	pT1	123 (36.8%)	26 (37.1%)	
	pT2	80 (24.0%)	11 (15.7%)	
	pT3	49 (14.7%)	3 (4.3%)	
	pT4	0	3 (4.3%)	
	Unknown	4	0	
Pathological N stage	pN0	117 (34.6%)	36 (51.4%)	0.008
	pN1-3	221 (65.4%)	34 (48.6%)	
	Unknown	0	0	
Approximated tumor subtype	Triple negative	73 (21.6%)	16 (22.9%)	0.63
	HER2 positive	95 (28.1%)	23 (32.9%)	
	HR positive, HER2 negative	170 (50.3%)	31 (44.3%)	
	Unknown	0	0	

HER2, human epidermal growth factor receptor 2; HR, hormone receptor

Table 3

Radiation therapy by surgical approach

		Breast conserving surgery (N = 277)	Mastectomy without reconstruction (N = 232)	Mastectomy with immediate reconstruction (N = 176)	
Breast RT	Yes	242 (89.3%)	NA	NA	NA
	No	29 (10.7%)			
Chest Wall RT	Yes	NA	179 (77.2%)	100 (56.8%)	<0.0001
	No		53 (22.8%)	76 (43.2%)	
Axillary RT	Yes	64 (23.6%)	64 (27.6%)	57 (32.4%)	0.12
	No	207 (76.4%)	168 (72.4%)	119 (67.6%)	
Supraclavicular RT	Yes	134 (49.4%)	121 (52.2%)	82 (46.6%)	0.54
	No	137 (50.6%)	111 (47.8%)	94 (53.4%)	
Internal Mammary RT	Yes	21 (7.8%)	26 (11.2%)	16 (9.1%)	0.41
	No	250 (92.2%)	206 (88.8%)	160 (90.9%)	

RT, radiation therapy

Table 4

Axillary radiation

		Axillary radiation received		
		Yes	No	p value
Type of breast surgery	Breast conserving surgery	64 (34.6%)	207 (41.9%)	0.12
	Mastectomy without reconstruction	64 (34.6%)	168 (34.0%)	
	Mastectomy with reconstruction	57 (30.8%)	119 (24.1%)	
	Unknown	7	6	
Clinical tumor stage at presentation	cT0/Tis	4 (2.1%)	6 (1.2%)	0.85
	cT1	26 (13.5%)	63 (12.6%)	
	cT2	105 (54.7%)	274 (54.9%)	
	cT3	50 (26.0%)	131 (26.2%)	
	cT4	7 (3.6%)	25 (5.0%)	
	Unknown	0	1	
Clinical nodal stage at presentation	cN1	179 (94.2%)	469 (94.4%)	0.94
	cN2	11 (5.8%)	28 (5.6%)	
	Unknown	2	3	
Clinical stage	II	127 (66.8%)	326 (65.7%)	0.78
	III	63 (33.2%)	170 (34.3%)	
	Unknown	2	4	
Pathological tumor stage at surgery	pT0/is	54 (28.6%)	176 (35.3%)	0.025
	pT1	62 (32.8%)	187 (37.5%)	
	pT2	55 (29.1%)	93 (18.6%)	
	pT3	18 (9.5%)	40 (8.0%)	
	pT4	0	3 (0.6%)	
	Unknown	3	1	
Pathological nodal stage at surgery	pN0	62 (32.3%)	222 (44.4%)	0.002
	pN1	65 (33.8%)	174 (34.8%)	
	pN2	48 (25.0%)	81 (16.2%)	
	pN3	17 (8.8%)	23 (4.6%)	
	Unknown	0	0	
Approximated tumor subtype	Triple negative	48 (25.0%)	120 (24.0%)	0.13
	HER2 positive	48 (25.0%)	163 (32.6%)	
	HR positive, HER2 negative	96 (50.0%)	217 (43.4%)	
	Unknown	0	0	

HER2, human epidermal growth factor receptor 2; HR, hormone receptor

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Table 5

Supraclavicular radiation

		Supraclavicular radiation received		
		Yes	No	p value
Type of breast surgery	Breast conserving surgery	134 (39.8%)	137 (39.9%)	0.54
	Mastectomy without reconstruction	121 (35.9%)	111 (32.5%)	
	Mastectomy with reconstruction	82 (24.3%)	94 (27.4%)	
	Unknown	8	5	
Clinical tumor stage at presentation	cT0/Tis	6 (1.7%)	4 (1.2%)	0.036
	cT1	38 (11.0%)	51 (14.7%)	
	cT2	187 (54.4%)	192 (55.3%)	
	cT3	103 (29.9%)	78 (22.5%)	
	cT4	10 (2.9%)	22 (6.3%)	
	Unknown	1	0	
Clinical nodal stage at presentation	cN1	319 (93.0%)	329 (95.6%)	0.14
	cN2	24 (7.0%)	15 (4.4%)	
	Unknown	2	3	
Clinical stage	II	217 (63.4%)	236 (68.6%)	0.15
	III	125 (36.6%)	108 (31.4%)	
	Unknown	3	3	
Pathological tumor stage at surgery	pT0/is	109 (32.0%)	121 (34.9%)	0.20
	pT1	126 (37.0%)	123 (35.4%)	
	pT2	81 (23.8%)	67 (19.3%)	
	pT3	25 (7.3%)	33 (9.5%)	
	pT4	0	3 (0.9%)	
	Unknown	4	0	
Pathological nodal stage at surgery	pN0	130 (37.7%)	154 (44.4%)	0.13
	pN1	121 (35.1%)	118 (34.0%)	
	pN2	75 (21.7%)	54 (15.6%)	
	pN3	19 (5.5%)	21 (6.0%)	
	Unknown	0	0	
Approximated tumor subtype	Triple negative	84 (24.4%)	84 (24.2%)	0.99
	HER2 positive	105 (30.4%)	106 (30.6%)	
	HR positive, HER2 negative	156 (45.2%)	157 (45.2%)	

		Supraclavicular radiation received		
		Yes	No	p value
	Unknown	0	0	

HER2, human epidermal growth factor receptor 2; HR, hormone receptor

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