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ORIGINAL ARTICLE – BREAST ONCOLOGY

Neoadjuvant Chemotherapy and Nipple-Sparing Mastectomy: Timing and Postoperative Complications

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ABSTRACT

Background. As the demand for nipple-sparing mastectomy (NSM) increases and surgeons expand the eligibility criteria, a subset of patients may become candidates following neoadjuvant chemotherapy (NACT). However, the impact of NACT on postoperative complications remains unclear as the current literature is discordant.

Methods. A single-institution, retrospective chart review was performed on patients undergoing NSM from 1989 to 2017. Patient demographics, surgical intervention, systemic treatment, and complication rates were collected. Primary outcomes were 30-day postoperative complications, including nipple-areolar necrosis, skin flap necrosis, infection, wound dehiscence, hematoma, and seroma. Secondary outcomes included characterization of the timing between chemotherapy and surgical intervention, and the impact on complication rates. Each breast was considered independently for analysis, and breasts undergoing either NACT or primary surgery (PS) were compared.

Results. Of the 832 breasts included, 88 (10.6%) received NACT and 744 (89.4%) underwent PS. Baseline complication rates were not significantly different between the NACT group and the PS group (5.7% vs. 10.6%; $p = 0.119$). When controlling for age, body mass index (BMI), smoking, and prior radiation, NACT was not a predictor of complications. Time from completion of NACT to PS occurred at a median of 40.5 days (interquartile range 31.3–55.3), and decreased intervals were not associated with increased complication rates.

Conclusions. Postoperative complications following NSM in patients completing NACT are comparable with those receiving PS. Patients undergoing NACT do not have a significantly increased risk of necrosis, unintended reoperations, or nipple loss. NACT should not be considered a contraindication for NSM.

Nipple-sparing mastectomy (NSM) is an oncologically safe intervention for women with breast cancer or for prophylactic management in high-risk patients.[1] NSM provides improved cosmetic results and a psychosocial benefit to the patient by leaving an intact nipple-areolar complex (NAC).[2] While NSM was previously restricted to women with small to moderate breast size and minimal ptosis, eligibility criteria continue to expand to accommodate the high demand in non-ideal patients.[3,4] NSM has now been proposed as an acceptable surgical option for women completing neoadjuvant chemotherapy (NACT) in the setting of locally advanced disease.[5–7]

As eligibility for NSM in patients completing NACT is a more recent surgical option, evidence-based guidelines and consensus regarding risks and timing of NACT and NSM are lacking. The timing interval between chemotherapy and surgery requires balancing the patient's return from an immunocompromised state with potentially impaired wound healing, while considering the potential risk of tumor rebound from delaying surgery.[8] On the oncologic side, NSM following NACT demonstrates comparable rates of locoregional recurrence to traditional skin-sparing mastectomy.[9] However, the impact on rates of surgical complications requires further investigation to ultimately guide recommendations and appropriate patient selection.

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The handful of studies exploring NACT in NSM, specifically, have come to different conclusions regarding whether NACT increases rates of NAC necrosis,[6,10,11] a particularly important indicator of NSM success. In addition, no study has examined how the timing interval between chemotherapy and surgery may affect rates of acute postoperative complications following NSM.

At our institution, NSM is now offered to women with favorable eligibility, independent of completion of NACT. In order to better characterize the effect of NACT on NSM, this study describes our institutional experience with rates of surgical complications, as well as the timing between chemotherapy and surgical intervention.

METHODS

Study Population

All patients undergoing NSM at MedStar Georgetown University Hospital from 1989 to December 2017 were identified with Institutional Review Board approval. Patient demographics, surgical intervention, systemic treatments, and surgical complication rates were retrieved retrospectively from electronic medical records. Patients receiving NACT followed by surgical intervention were compared with patients undergoing primary surgical intervention (PS), with or without adjuvant chemotherapy.

Outcomes

The primary outcome was the development of a composite 30-day postoperative complication consisting of nipple-areolar necrosis, skin flap necrosis, infection, wound dehiscence, hematoma, and seroma. Necrosis was determined based on requiring operative debridement, the infection required administration of antibiotics, and the hematoma/seroma required operative intervention. Secondary outcomes included an analysis of the timing between chemotherapy and surgical intervention, complication rates related to the timing interval, rates of unintended reoperations, and rates of NAC excision for reasons including cosmesis, pathology, or ischemic complications. The decision for NACT was made at the discretion of the medical oncologist in accordance with the most recent National Comprehensive Cancer Network guidelines at the time.

Statistical Analysis

Each breast was considered independently for analysis. Breasts receiving NACT were compared with those receiving primary surgical intervention. Chi square analysis or Fisher's exact test when appropriate were used to compare the rates of postoperative complications. In addition, multivariate logistic regression was used to determine the odds of developing surgical complications while controlling for body mass index (BMI), age, macromastia (cup size larger than C), history of smoking, and history of radiation. The two-sample t-test was used to evaluate the effect of the number of days between chemotherapy and surgery on the rates of postoperative complications. Timing was additionally examined in three categories: < 4 weeks, 4–6 weeks and > 6 weeks. Statistical analysis was performed using JMP version 13.1.0.[12]

RESULTS

Patient Demographics

A total of 832 breasts were included in the final cohort, of which 88 (10.6%) received NACT and 744 (89.4%) received PS. Patients undergoing NACT were significantly younger (41.7 vs. 46.0; $p < 0.001$). When comparing the NACT and PS groups, the rates of prior irradiation (4.6% vs. 5.8%; $p = 0.810$), smoking (1.1% vs. 4.2%; $p = 0.240$), and macromastia (25.0 vs. 20.9%; $p = 0.422$) were comparable. A more thorough cohort description is detailed in Table 1.

Postoperative Complications

The rate of any surgical complication across the entire cohort was 10.1%, with no significant difference between the NACT group (5.7%) and the primary surgery group (10.6%; $p = 0.119$). When examining individual complications (Table 2), rates were also comparable across the NACT and PS cohorts for NAC necrosis (0% vs. 2.7%; $p = 0.256$), skin flap necrosis (2.3% vs. 3.9%; $p = 0.764$), infection (4.6% vs. 3.5%; $p = 0.548$), wound dehiscence (2.3% vs. 1.5%; $p = 0.639$), and hematoma/seroma (0% vs. 2.3%; $p = 0.242$). Hyperbaric oxygen therapy (HBOT) was used in 5.9% of breasts in the NACT cohort and 3.0% of the PS cohort ($p = 0.199$). When controlling for BMI, smoking, prior radiation, age, and macromastia, NACT was not a significant predictor of the composite surgical complication outcome (odds ratio [OR] 0.63, 95% confidence interval [CI] 0.24–1.66; $p = 0.352$). However, BMI (OR 1.09, 95% CI 1.03–1.16; $p = 0.005$), history of radiation (OR 3.15, 95% CI 1.37–7.20; $p = 0.006$), and history of smoking (OR 1.84, 95% CI 1.09–3.10; $p = 0.022$) significantly increased the odds of postoperative complications. Completion of NACT was not a significant predictor of any individual postoperative complications included in the composite measure.

TABLE 1 Patient demographics of those undergoing neoadjuvant chemotherapy or primary surgery

Variable	Neoadjuvant chemotherapy [$n = 88$]	Primary surgery [$n = 744$]	p-Value	N
Age, years	41.7 (7.9)	46.0 (9.7)	< 0.001	832
BMI	23.6 (3.6)	23.4 (3.8)	0.694	832
Smoker at diagnosis [n (%)]	1 (1.1)	31 (4.2)	0.240	832
Former smoker [n (%)]	24 (27.3)	199 (27.1)	0.974	822
Diabetes mellitus [n (%)]	0	15 (1.8)	0.390	831
Radiation history [n (%)]	4 (4.6)	43 (5.8)	0.810	825
Breast size [n (%)]				
A	5 (6.6)	102 (15.5)	0.015	735
B	21 (27.6)	239 (36.3)		
C	31 (40.8)	180 (27.3)		
D+	19 (25.0)	138 (20.9)		
Bilateral NSM [n (%)]	72 (81.8)	611 (82.1)	0.944	832
Reconstruction [n (%)]			0.009	824
TE	50 (56.8)	526 (71.5)		
DTI	38 (43.2)	177 (24.0)		
Autologous	0	27 (3.7)		
None	0	6 (0.8)		

BMI Body mass index, *NSM* nipple-sparing mastectomy, *TE* tissue expander, *DTI* direct to implant

TABLE 2 Rates of 30-day postoperative complications following nipple-sparing mastectomy in the neoadjuvant and primary surgery cohorts

Surgical complication	Total [$n = 832$] (%)	Neoadjuvant [$n = 88$] (%)	Primary surgery [$n = 744$] (%)	p-Value
Skin flap necrosis	3.7	2.3	3.9	0.764
Nipple-areolar complex necrosis	2.4	0	2.7	0.256
Hematoma/seroma	2.0	0	2.3	0.242
Infection	3.6	4.6	3.5	0.234
Wound dehiscence	1.6	2.3	1.9	0.639
Composite complication	10.1	5.7	10.6	0.119

Rates of unintended reoperations were identical between the two cohorts, i.e. 9.1% in the NACT group and 9.1% in the PS group, while rates of NAC excision were 0% in the NACT cohort and 3.9% in the PS cohort. NACT was not a significant predictor of unintended reoperations in multivariate analysis.

Timing of Neoadjuvant Chemotherapy and Impact on Postoperative Complications

Time from the date of last chemotherapy to primary surgery was recorded for patients undergoing NACT; the exact dates of completion of chemotherapy were unavailable for three patients (four breasts). The median interval was 40.5 days (interquartile range 31.3–55.3), with a range of 20–165 days.

There was no effect of time interval between chemotherapy and surgical intervention on the rates of postoperative complications in either the univariate or multivariate analysis. Among the NACT cohort, patients with a complication had a mean NACT-to-surgery interval of 57.0 days (standard deviation [SD] 36.1), and the no complication group had a mean of 53.6 days (SD 38.3; $p = 0.875$). Time interval bins for analysis included 19.0% of patients at < 4 weeks, 41.7% at 4–6 weeks, and 39.3% at > 6 weeks between chemotherapy and surgery. Rates of complications were not significantly different ($p = 0.333$) between the < 4 weeks group (12.5%), 4–6 weeks group (2.9%), and the >6 weeks group (6.1%). Multivariate analysis demonstrated no effect ($p = 0.141$) of time interval on complication rates.

DISCUSSION

Patients completing NACT should be considered as appropriate candidates for NSM. This study demonstrated no increased risk of 30-day postoperative complications, including nipple necrosis, which is a particularly important

indicator of NSM success. This result remained when controlling for factors known to cause complications, including age, BMI, smoking, breast size, and prior history of irradiation.[13–16]

A small number of studies have previously explored the effects of systemic chemotherapy in the neoadjuvant setting on the rates of postoperative NSM complications.[6,10,11] In the first study to examine NACT in NSM, Santoro et al. demonstrated similar complication rates between groups completing NACT and PS, including nipple loss either due to necrosis (4% vs. 4%) or positive margins (18% vs. 10%), flap complications (6% vs. 7%), and implant explanation (10% vs. 5%). However, the rates of locoregional recurrence (6% vs. 0%) were significantly higher in the NACT group, but comparable with those seen in a high-risk setting.[11] Santoro et al. ultimately concluded that NACT was not a contraindication to NSM. However, Frey et al. [10] demonstrated significantly increased rates of nipple necrosis in NACT patients (10.7% vs. 1.8%), cautioning the use of NSM in this cohort. However, no attempt was made to account for known factors affecting the rates of nipple necrosis, such as BMI, which differed significantly between the two comparison groups. Additionally, this result included patients who received both adjuvant chemotherapy and NACT, without a clear description and analysis of the time frame between surgical intervention and systemic therapy, which is often institution-dependent.

The effect of timing between NACT and surgery has been proposed to have an effect on surgical complications and potential for tumor rebound.[8] This is the first study to examine the effect of time interval specifically in NSM, and to demonstrate no difference in complication rates in our cohort and patients undergoing surgery following chemotherapy ranging from 20 to 165 days (median 40.5 days). While it is standard practice to have patients undergo NSM approximately 1 month after completion of NACT at our institution, larger-scale studies should examine this effect on ischemic complications to NAC. Similarly, Frey et al.[10] reported the timing of NACT to surgery had a mean of 37.2 days, but did not examine this as a factor in complication rates.

Our study is limited by the retrospective nature of the chart review, the relatively small sample size of NACT patients and the low complication rates within this cohort, variation in the chemotherapy regimens used by patients due to guideline changes over time, and the grouping of patients across a decade of progress with regard to advancements in biomaterials and technique.[17] Due to the timeframe of investigation, this analysis focused on acute complications rather than the effects of adjuvant chemotherapy or radiation. Despite these limitations, this study reports on a high volume of NSMs performed at a single institution, with a detailed account of 30-day postoperative complications. In addition, our analysis was able to account for factors known to impact surgical complications, including the time interval between completing NACT and surgical intervention.

CONCLUSIONS

Overall, our single-institution experience demonstrates an oncologically and technically safe experience of performing NSM in patients completing NACT. Based on these data and discordance of the current literature, we continue to offer NSM at our institution for this subset of patients, while thoroughly counseling the risks and mitigating known risk factors. Due to improved, patient-centered outcomes of NSM, receipt of NACT should not be considered a contraindication.

REFERENCES

1. Headon HL, Kasem A, Mokbel K. The oncological safety of nipple-sparing mastectomy: a systematic review of the literature with a pooled analysis of 12,358 procedures. *Arch Plast Surg*. 2016;43(4):328.
2. Wei CH, et al. Psychosocial and sexual well-being following nipple-sparing mastectomy and reconstruction. *Breast J*. 2016;22(1):10–17.
3. Coopey SB, Tang R, Lei L, Freer PE, Kansal K, Colwell AS, et al. Increasing eligibility for nipple-sparing mastectomy. *Ann Surg Oncol* 2013;20(10):3218–3222.
4. Tousimis E, Haslinger M. Overview of indications for nipple sparing mastectomy. *Gland Surg*. 2018;7(3):288–300.
5. Agresti R, Sandri M, Gennaro M, Bianchi G, Maugeri I, Rampa M, et al. Evaluation of local oncologic safety in nipple–areola complex-sparing mastectomy after primary chemotherapy: a propensity score-matched study. *Clin Breast Cancer* 2017;17(3):219–231.
6. Burdge EC, Yuen J, Hardee M, Gadgil PV, Das C, Henry-Tillman R, et al. Nipple skin-sparing mastectomy is feasible for advanced disease. *Ann Surg Oncol*. 2013;20(10):3294–3302.
7. Jadeja P, Ha R, Rohde C, Ascherman J, Grant R, Chin C, et al. Expanding the criteria for nipple-sparing mastectomy in patients with poor prognostic features. *Clin Breast Cancer*. 2018;18(3):229–233.
8. Sanford RA, Lei X, Barcenas CH, Mittendorf EA, Caudle AS, Valero V, et al. Impact of time from completion of neoadjuvant chemotherapy to surgery on survival outcomes in breast cancer patients. *Ann Surg Oncol*. 2016;23(5):1515–1521.
9. Gerber B, Krause A, Dieterich M, Kundt G, Reimer T. The oncological safety of skin sparing mastectomy with conservation of the nipple-areola complex and autologous reconstruction: an extended follow-up study. *Ann Surg*. 2009;249(3):461–468.
10. Frey JD, Choi M, Karp NS. The effect of neoadjuvant chemotherapy compared to adjuvant chemotherapy in healing after nipple-sparing mastectomy. *Plast Reconst Surg*. 2017;139(1):10e–19e.
11. Santoro S, Loreti A, Cavaliere F, Costarelli L, La Pinta M, Manna E, et al. Neoadjuvant chemotherapy is not a contraindication for nipple sparing mastectomy. *Breast*. 2015;24(5):661–666.
12. JMP® version 13.1.0. Cary, NC: SAS Institute Inc.; 1989–2007.
13. Algaithy ZK, Petit JY, Lohsiriwat V, Maisonneuve P, Rey PC, Baros N, et al. Nipple sparing mastectomy: can we predict the

factors predisposing to necrosis? *Eur J Surgic Oncol*. 2012;38(2):125–129.
14. Komorowski AL, Zanini V, Regolo L, Carolei A, Wysocki WM, Costa A. Necrotic complications after nipple-and areola-sparing mastectomy. *World J Surg*. 2006;30(8):1410–1413.
15. Davies K, Allan L, Roblin P, Ross D, Farhadi J. Factors affecting post-operative complications following skin sparing mastectomy with immediate breast reconstruction. *Breast*. 2011;20(1):21–25.
16. Gould DJ, Hunt KK, Liu J, Kuerer HM, Crosby MA, Babiera G, et al. Impact of surgical techniques, biomaterials, and patient variables on rate of nipple necrosis after nipple-sparing mastectomy. *Plast Reconst Surg*. 2013;132(3):330e.
17. Oh E, Chim H, Soltanian HT. The effects of neoadjuvant and adjuvant chemotherapy on the surgical outcomes of breast reconstruction. *J Plast Reconst Aesthet Surg*. 2012;65(10):e267–e280.