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Neoadjuvant therapy and breast cancer surgery: a closer look at postoperative complications

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KEYWORDS: Neoadjuvant; Breast cancer surgery; Postoperative complications

Abstract

BACKGROUND: Neoadjuvant therapy is important in the treatment of advanced breast cancer.
METHODS: Postoperative complications in neoadjuvant patients were analyzed.
RESULTS: One hundred forty patients underwent 148 breast cancer surgeries after neoadjuvant therapy: 28% breast-conserving therapy procedures, 36% mastectomies, 28% mastectomies with immediate reconstruction, and 8% mastectomies with delayed reconstruction. Forty-seven patients (34%) suffered 59 complications: 18% of those undergoing breast-conserving therapy, 30% of those undergoing mastectomy, 44% of those undergoing mastectomy with delayed reconstruction. and 67% of those undergoing mastectomy with delayed reconstruction. Major complications occurred in 18% of patients. Skin loss occurred in 6% of patients. One patient had partial nipple necrosis. Three patients suffered implant loss. One patient had deep inferior epigastric artery perforator flap loss. Eleven hematomas and 5 infectious complications required reoperation.

CONCLUSIONS: Surgery after neoadjuvant therapy is safe, but careful counseling is warranted given that 18% of patients experienced major complications. Complications rates are higher with reconstruction, but feared complications of skin, nipple, implant, or flap loss were infrequent.

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Neoadjuvant therapy plays an important role in treating advanced breast cancer. Initially indicated for inoperable tumors or inflammatory breast cancer, the indication for neoadjuvant therapy has been expanded to include operable tumors. Multiple studies have shown no difference in overall or disease-free survival between patients undergoing neoadjuvant or adjuvant therapy. However, fewer studies have focused on the adverse surgical outcomes associated with neoadjuvant therapy, especially with respect to breast reconstruction. The most common complication associated with breast surgery has been reported to be wound infection. Given that cytotoxic chemotherapy is known to cause neutropenia, it has been hypothesized that neoadjuvant chemotherapy may lead to increased infectious complications. However, a recent American College of Surgeons National Surgical Quality Improvement Program study showed no association between neoadjuvant chemotherapy and postoperative wound complications. Oh et al provided an up-to-date, concise review of the plastic surgery literature with respect to the effects of neoadjuvant and adjuvant therapy.
chemotherapy on the outcomes of breast reconstruction, citing studies that show no increase in postoperative complications with the use of adjuvant or neoadjuvant therapy. The caveats of this review were that most studies were small, underpowered, and not designed to directly analyze the relationship between neoadjuvant therapy and postoperative complications. The purpose of this study was to determine the rates of all postoperative complications in patients treated with neoadjuvant therapy with respect to the type of breast surgery performed (breast-conserving therapy [BCT] vs mastectomy vs mastectomy with reconstruction) and to the timing of reconstruction (immediate vs delayed).

Methods

A prospective breast cancer database at a single institution was reviewed, identifying all patients aged >18 years who were treated with neoadjuvant therapy before breast cancer surgery from January 2000 through May 2012. At our institution, neoadjuvant therapy is recommended for all patients with inflammatory breast cancer and all patients with inoperable breast cancer and is considered in patients who present with large primary tumors (T2 disease or greater). All patients received preoperative antibiotics. For those patients who underwent reconstruction and had drains in place, postoperative antibiotics were continued until the drains were removed. All patients also received venous thrombosis prophylaxis. All patients received thromboembolism deterrent hose and sequential compressive devices, while patients who underwent inpatient procedures also received preoperative and postoperative subcutaneous heparin. All patients were stratified into groups on the basis of type of surgical procedure: BCT; mastectomy; mastectomy with immediate reconstruction (Mast+IRecon), defined as reconstruction taking place at the time of the breast cancer surgery; and mastectomy with delayed reconstruction (Mast+DRecon), defined as reconstruction taking place after the index breast cancer surgery. Further subgroups for patients who underwent reconstruction were created on the basis of mastectomy type: skin-sparing mastectomy (SSM), nipple-sparing mastectomy (NSM), modified radical mastectomy, and total mastectomy. Postoperative complications included seromas, hematomas, wound infections, tissue expander or implant rupture or loss, skin necrosis, nipple loss, and flap loss. A major complication was defined as any complication requiring unplanned repeat surgical intervention. Complication rates were calculated with respect to the number of patients who experienced a complication. Institutional review board approval was obtained.

Results

Of the 2,643 patients with breast cancer over the 12.5-year study period, 140 (5%) underwent 148 breast cancer surgeries after completing neoadjuvant therapy. All patients were female, and the average age was 55 years (range, 24 to 90 years). The majority of patients (86%) were Caucasian, with the remaining as follows: 6% Hispanic, 4% African American, 3% Native American, and 1% Asian. Ninety patients (64%) were postmenopausal. The majority of patients (114 (81%)) underwent neoadjuvant chemotherapy, 12 (9%) had only neoadjuvant hormonal therapy, 10 (7%) had combinations of neoadjuvant biologic and chemotherapy, 3 (2%) had combinations of neoadjuvant hormonal and chemotherapy, and 1 (1%) had only neoadjuvant radiation therapy. Thirty-nine patients (28%) underwent 41 BCT procedures, 50 (36%) underwent 53 mastectomies, 39 (28%) underwent 42 Mast+IRecon procedures, and 12 (8%) underwent 12 Mast+DRecon procedures. Of the 101 patients who underwent mastectomies, 34 (34%) underwent contralateral prophylactic mastectomies.

Types of reconstruction included 30 tissue expander/implants, 16 deep inferior epigastric artery perforator (DIEP) flaps, 4 transverse rectus abdominis myocutaneous (TRAM) flaps, and 4 other flaps, including 1 superficial inferior epigastric artery, 1 superior gluteal artery perforator, and 2 latissimus dorsi flaps. One tissue expander/implant patient was ultimately converted to a DIEP flap because of complications and therefore was counted as a tissue expander/implant patient. Of the 42 Mast+IRecon procedures, 3 (7%) were total mastectomies, 7 (17%) were modified radical mastectomies, 22 (52%) were SSM procedures, and 10 (24%) were attempted NSM procedures, with 1 patient requiring conversion to SSM (counted as SSM in Table 1).

Forty-seven patients (34%) suffered 59 complications, including 7 of 39 (18%) of those who underwent BCT, 15 of 50 (30%) of those who underwent mastectomy, 17 of 39 (44%) of those who underwent Mast+IRecon, and 8 of 12 (67%) of those who underwent Mast+DRecon (Table 1). Major complications, defined as those requiring repeat surgical intervention, occurred in 25 of 140 patients (18%): 5 of 50 mastectomy patients (10%), 15 of 39 Mast+IRecon patients (38%), and 5 of 12 Mast+DRecon patients (42%). There were no major complications in BCT patients. Skin loss requiring operative debridement occurred in 8 of 140 patients (6%): 1 of 50 mastectomy patients (2%), 4 of 39 Mast+IRecon patients (10%), and 3 of 12 Mast+DRecon patients (25%). One of the 9 NSM patients (11%) had partial nipple necrosis requiring operative debridement. Three of the 20 skin-sparing Mast+IRecon patients (15%) suffered implant loss after 2 infections and 1 rupture. Two of the 16 DIEP flap patients (13%) required early operative revision because of venous congestion, both of which occurred after skin-sparing Mast+IRecon. One of the 16 DIEP flap patients (6%) had flap loss after Mast+DRecon secondary to a postoperative hematoma and venous thromboses. There were 11 hematomas (8%) and 1 infected seroma that required reoperation. There were 11 infectious complications (8%), 5 of which were major:
1 in a mastectomy patient and the other 4 in patients who underwent skin-sparing Mast+DRecon. Other minor complications included 9 seromas managed conservatively, 8 seromas requiring aspiration, 6 hematomas managed conservatively, and 6 wound infections treated with antibiotics. Lymphedema occurred in 14% of patients.

Overall, 103 of 140 patients (74%) underwent postoperative radiation therapy, including 30 BCT patients, 38 mastectomy patients without reconstruction, 25 Mast+IRrecon patients, and 10 Mast+DRecon patients. Thirty-seven of the 47 patients (79%) who experienced complications were treated with adjuvant radiation. The 1 patient who received neoadjuvant radiation therapy did not experience a complication. Three of the 12 patients (25%) who received only neoadjuvant hormonal therapy experienced complications: 1 major infection, 1 infection treated with antibiotics, and 1 seroma managed conservatively.

**Comments**

Breast cancer surgery, although generally well tolerated, is not without its complications. A 2007 study determined wound infection to be the most common complication after breast cancer surgery and found an incidence of 4.3% in mastectomy patients versus 1.97% in BCT patients, while other studies have cited a range of 3% to 19% for wound infection. Our overall infectious complication rate was 8%, and all patients received preoperative antibiotics. Seroma, epidermolysis, and hematoma can also complicate breast cancer procedures, with reported rates of 29% for seroma in mastectomy versus 18% in BCT and 18% for epidermolysis in mastectomy versus 0% in BCT and overall rates of hematoma in breast cancer surgery ranging from 2% to 10%. In our series, the rates of seroma and hematoma were 11.6% each, and 2% of mastectomy patients without reconstruction had epidermolysis.

The addition of reconstruction to the breast cancer procedure creates the potential for more postoperative complications. Breast reconstruction can be achieved through a variety of procedures, each with its own set of medical and cosmetic complications. The risks associated with tissue expander and implant reconstruction include infection, malposition, deflation, implant exposure or extrusion, and seroma and hematoma formation, with long-term risks further including capsular contracture and wrinkling of the implant. The use of postoperative radiation therapy often exacerbates implant-related complications, with some sources citing reconstruction failure in 24% to 37% versus 8% in patients not treated with radiation, capsular contraction in 32.5%, and an overall complication rate of 53% to 68% versus 31% in patients not treated with radiation. The majority of our patients who had complications, regardless of reconstruction or timing, underwent postoperative radiation therapy. The above studies, and our present study, highlight the important relationship between postoperative radiation and the risk for postoperative complications; the risk for postoperative radiation therapy should not be underestimated. Interestingly, our 1 patient who received neoadjuvant radiation, who later underwent mastectomy without reconstruction, did not experience a postoperative complication.

The alternative to implant-based reconstruction is an autologous pedicled or free perforator tissue flap. In 1 study, a pedicled, compared to a free, TRAM flap was associated with a 12% versus 18% risk for infection, a 4% versus 4.5% to 9% risk for hematoma or seroma, a 16% versus 15% risk for partial flap loss, a 1% versus 1.5% risk for total flap loss, and an 8% versus 12% long-term risk for abdominal wall laxity or hernia, while another study showed total flap loss for free TRAM flaps as low as .18%. Only 1 of our 4 TRAM flap patients experienced a complication, but it was a major complication: wound breakdown requiring operative debridement. Compared with pedicled TRAM flaps, DIEP flaps initially were thought to have a higher risk for total flap loss, but more recent studies have shown no difference in flap failure rates, with a rate of 3.1% for DIEP flaps. Another study showed lower rates of flap loss at 2.5% for partial flap loss and .5% for total flap loss. Other DIEP

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**Table 1** Number and percentage of patients with complications by type of procedure performed

<table>
<thead>
<tr>
<th>Variable</th>
<th>BCT</th>
<th>Mastectomy</th>
<th>SSM+IR</th>
<th>NSM+IR</th>
<th>MRM+IR</th>
<th>TM+IR</th>
<th>Mast+DRecon</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedures</td>
<td>41</td>
<td>53</td>
<td>23</td>
<td>9</td>
<td>7</td>
<td>3</td>
<td>12</td>
<td>148</td>
</tr>
<tr>
<td>Patients</td>
<td>39</td>
<td>50</td>
<td>20</td>
<td>9</td>
<td>7</td>
<td>3</td>
<td>12</td>
<td>140</td>
</tr>
<tr>
<td>Any complication</td>
<td>7 (18%)</td>
<td>15 (30%)</td>
<td>10 (50%)</td>
<td>5 (56%)</td>
<td>2 (29%)</td>
<td>—</td>
<td>8 (67%)</td>
<td>47 (34%)</td>
</tr>
<tr>
<td>Major complication</td>
<td>—</td>
<td>5 (10%)</td>
<td>10 (50%)</td>
<td>3 (33%)</td>
<td>2 (29%)</td>
<td>—</td>
<td>5 (42%)</td>
<td>25 (18%)</td>
</tr>
<tr>
<td>Skin loss</td>
<td>—</td>
<td>1 (2%)</td>
<td>3 (15%)</td>
<td>—</td>
<td>1 (14%)</td>
<td>—</td>
<td>3 (25%)</td>
<td>8 (6%)</td>
</tr>
<tr>
<td>Nipple loss (partial)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1 (11%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Flap loss</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1 (8%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Implant loss</td>
<td>—</td>
<td>—</td>
<td>3 (15%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Major infection</td>
<td>—</td>
<td>1 (2%)</td>
<td>4 (20%)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5 (4%)</td>
</tr>
</tbody>
</table>

BCT = breast-conserving therapy; IR = immediate reconstruction; Mast+DRecon = mastectomy plus delayed reconstruction; MRM = modified radical mastectomy; NSM = nipple-sparing mastectomy; SSM = skin-sparing mastectomy; TM = total mastectomy.
complications include a 12.5% rate of hematoma or seroma and a 12.5% rate of infection. Only 1 of our 16 DIEP flap patients failed, but 2 required early reoperation for salvage. Superficial inferior epigastric artery flaps are associated with a 2% to 2.9% risk for flap loss and a 17.4% risk for venous thrombosis. Superior or inferior gluteal artery perforator flaps can have sciotic nerve complications and high rates of flap loss at 6.5% for inferior gluteal artery perforator flaps. Latissimus dorsi flaps often have complications at the donor site, namely seroma, with rates reported as high as 56%. Our 1 patient with a superior gluteal artery perforator flap required operative debridement for wound breakdown, but our 1 patient with a superficial inferior epigastric artery flap and 2 with latissimus dorsi flaps did not have any complications.

Special consideration must also be given to the added risks of SSM and NSM, mainly skin and nipple necrosis. Skin necrosis in SSM, however, was reported at 10.7% versus 11.2% in non-SSM. Skin loss requiring operative debridement occurred in 8 of our 140 patients (6%), only 3 of whom were SSM patients and none of whom underwent NSM. The rates of nipple necrosis are generally reported in the 2% to 13% range. Skin and nipple necrosis are thought to be related to the type of skin incision, surgical dissection, flap length, and breast size, all factors that are unlikely to be influenced by neoadjuvant chemotherapy. Partial nipple necrosis requiring operative debridement occurred in 1 of our 9 NSM patients (11%).

Despite all of the literature on breast cancer surgery and reconstruction complications, the impact of neoadjuvant therapy on such outcomes has been less well studied. The 2012 National Surgical Quality Improvement Program study looked at a large number of patients and found no association between neoadjuvant chemotherapy and postoperative wound complications at a rate of 3.4% in those treated with neoadjuvant therapy versus 3.1% for those who were not; however, there was a trend toward an increase in operative wound complications at a rate of 6.5% for inferior gluteal artery perforator flaps. Latissimus dorsi flaps often have complications at the donor site, namely seroma, with rates reported as high as 56%. Our 1 patient with a superior gluteal artery perforator flap required operative debridement for wound breakdown, but our 1 patient with a superficial inferior epigastric artery flap and 2 with latissimus dorsi flaps did not have any complications.

One study cited complication rates in neoadjuvant patients of 1.9% for wound infection, 9.3% for seroma formation, and 14.8% for skin flap necrosis. The majority of the currently sparse neoadjuvant literature relates to breast reconstruction outcomes. Tissue expander and implant use has been cautioned against in neoadjuvant patients on the basis of a 32% tissue expander loss, mostly due to infection and extrusion. Our rate of tissue expander/implant loss was 3 of 30 patients (10%): 2 infections and 1 rupture. A high complication rate (55%) has been noted after neoadjuvant therapy in patients undergoing reconstruction with a pedicled TRAM or free TRAM flap. Our complication rate for TRAM reconstruction was 1 of 4 patients (25%). One small study reported rates of 7.4% total and 14.8% partial DIEP flap loss after neoadjuvant therapy. Our rate of total DIEP flap loss was 1 of 16 patients (6%). Our complication rate of 44% for neoadjuvant patients who underwent immediate reconstruction is higher than prior data from our prospectively maintained breast cancer database, which demonstrated a 30% postoperative complication rate for patients who underwent immediate breast reconstruction.

The main limitation of our study was the small, heterogeneous sample size. Neoadjuvant therapy is 1 of many factors that may contribute to the development of a postoperative complication. Age, comorbidities, body mass index, tobacco use, and radiation therapy, for example, must be taken into consideration. A larger sample size with multivariate analysis could help better define the relationship between the above factors and postoperative complications.

Conclusions

Surgery after neoadjuvant therapy is safe, but careful counseling is warranted given that 18% of patients experienced major complications. Complication rates were higher in those patients undergoing reconstruction, but feared complications of skin, nipple, implant, and flap loss were infrequent.

References


Discussion

Anees Chagpar, M.D. (New Haven, CT): I have the privilege of discussing this paper. To begin with, I’d like to congratulate the authors on presenting their work examining postoperative complication rates after neoadjuvant therapy. Often times I think such data are not reported simply because none of us like to admit that we have any complications. So I am glad to see that the folks at Mayo Arizona have the integrity to present these data which will help us to better present the risks of surgery after systemic therapy to our breast cancer patients. I do have several questions for the authors. First, you point out that the overall rate of complications was 34%, ranging from 18% for breast conserving surgery to 67% for those who had a mastectomy with delayed reconstruction. In your last slide or next to last slide, you had pointed out that your data aligned with the literature and historically other studies have not found a difference between those who had neoadjuvant therapy and those who did not. What were the rates of complications in patients not treated with neoadjuvant therapy at your institution? This would help us to put these data into better context. Second, you note that 74% of the patients in your cohort underwent radiation therapy postoperatively and you correctly mentioned this often is also associated with a higher complication rate. But it makes it difficult to sort out what proportion of the complication rate you found in your population was attributed to the neoadjuvant systemic therapy and what proportion was attributable to postoperative radiation therapy. Did you do a factor analysis or a multivariate model or some way to give us a sense of the respective rates of each of these? And finally, while it is good to be able to tell our patients about what complication rates they can expect, it is even better if we can determine how to lower these. Did you look at potential techniques that may influence complication rates, for example closing cavities or using drains to prevent seromas, using hemostatic agents to prevent...
hematomas or perhaps varying antibiotic regimens preoperatively to prevent infection or heparin for venous congestion to prevent the complication that you showed us. I realize that the sample size may limit the inferences that you may be able to make, but I would be remiss if I at least didn’t ask.

I thank the authors once again for a fine presentation and for the Congress the opportunity to discuss it.

Erin M. Garvey, M.D. (Phoenix, AZ): Thank you. I’ll begin with your first question. You asked about the rates of complications and non-neoadjuvant patients at our institution. We are currently in the process of comparing this current data to our large cohort of 2,600 patients to specifically stratify non-neoadjuvant and neoadjuvant. However, prior studies that we have done at our institution, specifically in a skin-sparing mastectomy cohort, had the following results. Thirty percent of our skin-sparing mastectomy patients had no complications, 35% had a minor complication, and 35% had a major complication. So that is not a perfect 1-to-1 comparison, but that gives us something to reflect back on with our non-neoadjuvant patients at Mayo. I do agree with you that there would be more value in being able to perform that multivariant analysis in the full cohort and that is our ongoing process that we are working with right now, at which point I think we will have the data to run a meaningful multivariant analysis in order to be able to evaluate multiple factors, especially radiation as a potential contributor to the increased risk of complications. With that said, once we do have that full cohort of data, I think that may point to certain techniques or certain things that we can focus on as surgeons to hopefully prevent complications. As the general surgeon, I think our focus, especially when doing skin or nipple sparing needs to be on meticulous flap creation not compromising the blood flow in order to attempt to prevent the skin necrosis or even infections. In terms of what our plastic surgeons do at this time, they do routinely use drains and we have a standardized protocol for antibiosis. But perhaps once we have our full analysis, we will be able to better address things and alter our techniques accordingly.

Dr Chagpar: Did you look at smokers versus non-smokers or diabetics versus nondiabetics, patient related factors that may influence your complication rate?

Dr Garvey: I think that will be incredibly important in the next step that we have; just the few demographic pieces of data I shared with you is what we mainly looked at for this small cohort, but diabetics and smokers will certainly be evaluated.