Scientific Article

Postmastectomy Radiation Therapy Bolus Associated Complications in Patients Who Underwent 2-stage Breast Reconstruction

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Abstract

Purpose: This study aimed to evaluate the association of bolus and 2-stage breast reconstruction complications, and whether the dosimetric advantage translates into improvements in local control.

Methods and Materials: We retrospectively analyzed data from 2008 to 2019 of women who underwent a mastectomy and a planned 2-stage breast reconstruction, followed by adjuvant radiation therapy. We reviewed all data from medical records and radiation plans regarding patient characteristics, diagnoses, surgeries, complications, pathology, staging, systemic therapy, radiation therapy, and outcomes, and compared complication rates according to bolus usage.

Results: A total of 288 women, age 25 to 71 years, were included in the study. Of these women, 6 were treated with daily bolus and 19 with alternate days bolus, totaling 25 of 288 patients (8.7%) in the bolus group. A total of 226 patients (78.5%) had the second stage performed. The median follow-up time was 61 months. The rates for 5-year overall survival and locoregional control were both 97%, and the metastasis-free rate was 83%. In the first stage, 6.25% of patients in the entire cohort had an infection and 4.2% had implant loss. Daily bolus significantly increased the risk of expander infection (hazard ratio [HR]: 10.3; 95% confidence interval [CI], 1.7-61.8) and loss (HR: 13.89; 95% CI, 2.24-85.98), but alternate-day bolus showed a nonsignificant increase for expander infection (HR: 1.14; 95% CI, 0.14-9.295) and loss (HR: 1.5; 95% CI, 0.19-12.87). Bolus was not associated with second-stage complications or local-regional failure. Local infection and implant loss were more frequent in the second than in the first stage (5.2% vs 10.2% and 4.2% vs 12.8%, respectively).

Conclusions: Skin bolus significantly increased first-stage breast reconstruction complications (infection and reconstruction failure). Despite the small sample size and the need for future studies, these findings need to be taken into consideration when planning treatment and reconstruction, and recommendations should be individualized.

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Introduction

Mastectomy still plays an important role in breast cancer management for some patients. Breast reconstruction rates have been increasing over the last decades, and have been shown to have a positive psychological impact without compromising oncologic outcomes. In this scenario, postmastectomy radiation therapy (PMRT) can be an important component of treatment, because PMRT reduces recurrence and breast cancer mortality for node-positive and triple-negative patients and can improve local control if multiple risk factors are present.

Two-stage breast reconstruction (also known as delayed-immediate reconstruction) was developed to minimize PMRT reconstruction complications, and is the most common strategy when an implant-based approach is chosen. However, optimal integration with radiation therapy (RT) is still not completely understood, and the influence of many radiation parameters still needs to be elucidated.

The use of bolus has not been prospectively evaluated in randomized controlled trials, but is usually recommended for patients with cutaneous involvement to ensure skin coverage. However, its usage varies widely across radiation oncologists, and has been shown to increase radiation-related toxicities and treatment interruptions without a proven benefit in local control rates. To date, data specifically regarding the association between the use of bolus in PMRT and 2-stage breast reconstruction complications are lacking. Therefore, we retrospectively evaluated the association of skin bolus in PMRT and reconstruction complications in patients with breast cancer who underwent 2-stage reconstruction at a cancer center. Secondarily, we evaluated whether a decrease in local recurrence could be observed, and investigated other possible factors associated with increased complication rates.

Methods and Materials

We retrospectively reviewed data from all women treated at our institution who underwent a mastectomy and planned 2-stage breast reconstruction, followed by adjuvant RT, and who had at least the first stage performed. Data was reviewed from the first appointment related to breast cancer to the last appointment registered with the hospital for patients treated at our institution from 2008 to 2019. A 2-stage reconstruction was defined as follows: In the first stage, immediate reconstruction was performed using a tissue expander; in the second stage, the expander was replaced by a permanent implant. Patients whose surgical treatment (mastectomy or revisions) or radiation treatment were performed at another institution and patients who had a reconstruction failure before the beginning of RT were excluded.

Data was collected and managed using REDCap electronic data capture tools hosted at AC Camargo Cancer Center. We evaluated patient baseline characteristics, diagnostic evaluations, tumor pathology, staging, surgical descriptions (mastectomy and revisions), RT treatments, systemic therapies, complications, and disease progression. Clinical and pathologic staging information were collected, and patients were grouped according to the American Joint Committee on Cancer TNM 8th edition prognostic stage groupings (clinical for patients who had neoadjuvant chemotherapy and pathologic for those who had upfront surgery). The pathologic classification was recorded using World Health Organization criteria. We recorded complication-related data separately for both situations: expander (placed immediately after mastectomy and before RT) and permanent implant (placed after RT). The following complications were recorded: flap necrosis, capsular contracture, and respective Baker classification, seroma, hematoma, infection, and reconstruction failure (implant loss or conversion to autologous reconstruction). We considered the complication date as the first mention in the records. Although we recorded the Baker classification whenever mentioned, only Baker III and IV were considered complications.

With regard to RT, we evaluated treatment modality, dose and fractionation, dates, use of bolus, and complications. Radiation treatment plans were reviewed to ensure that the expander was present during RT, and medical and surgical records were thoroughly reviewed for patients who had 2-dimensional treatment to ensure they met the selection criteria. Acute and late effects were recorded using the Common Terminology Criteria for Adverse Events, but only radiation dermatitis was systematically recorded and reported.

Length of follow up was defined as the interval between diagnosis and the last note from a provider directly involved in the patient’s breast cancer care. We also evaluated the follow up of each reconstruction stage to address the potential bias related to different follow ups for each stage. First-stage follow up was defined as the interval between mastectomy and expander replacement or reconstruction failure or death or loss of follow up (whichever occurred first). Second-stage follow up was defined as the interval between expander replacement and reconstruction failure or death or loss of follow up (whichever occurred first).
occurred first). Disease progression was considered according to the evaluation of the clinician responsible for the patient’s evaluation at the time.

Baseline patient characteristics were described using proportions for categorical variables, and median and range for continuous variables. Complication rates between patients who had a bolus and those who did not were compared using Pearson’s $\chi^2$ test for larger samples, using a continuity correction for $2 \times 2$ tables or a Fisher’s exact test whenever appropriate. A multivariate analysis for potential factors associated with complications was done using a logistic regression. Time-to-event data for both complications and disease progression were described using the Kaplan–Meier method, and possible differences were evaluated using a log-rank test. Optimal timing to perform the second stage was evaluated using scatter plots to illustrate results and receiver operating characteristic curves. Missing data were addressed using a complete case analysis. No adjustment for multiple testing was made. An analysis was done using SPSS, version 25. This study was approved by the hospital’s institutional review board.

Results

Data from a total of 288 patients was analyzed. The median follow up was 61 months, ranging from 18 to 115 months. The median first-stage follow up was 22.8 months (range, 3.5–97.9 months), and the median second-stage follow up was 31.87 months (range, 4 days–90.7 months). The mean age of patients was 46 years old (range, 25–71 years), and 33 patients (11.46%) had stage T4 disease (T4b: n = 32; T4d: n = 1). The baseline characteristics of the cohort are shown in Table 1.

Most patients (92%) were treated using 3-dimensional RT, and the others were treated either with inverse planning intensity modulated RT (2.1%) or 2-dimensional RT (4.5%). Fractionation choice depended on the physician’s criteria, with 93% of patients treated with conventional fractionations (median dose: 50 Gy) and 7% with hypofractionation (median dose: 42.56 Gy). The supravacular fossa (levels III and IV) was included in 64% of patients, and axillary levels I and II in 13%. In 8.7% of cases (n = 25), a 0.5 cm thickness bolus was used due to skin involvement, either daily (n = 6) or on alternating days (n = 19).

All 288 patients underwent a mastectomy and immediate reconstruction with an expander (first stage), followed by PMRT. After completing treatment, 78.5% of patients (n = 226) had the second stage performed (permanent implant placement). After placement of the permanent implant, 19% of patients had further revision surgeries. The total number of revisions per patient ranged from 0 to 3 (median: 0; average: 0.26). The 5-year overall rates for survival and locoregional control were both 97%, and 83% for metastasis-free survival.

Complications overview

With regard to complications, 27.7% of patients had some complications during the first stage and 31.4% during the second stage. Despite similar overall complication rates, the profile differed according to stage (Table 2). Capsular contracture was more common after the first stage, but infection/flap necrosis and reconstruction failure were more common after the second stage. Seroma and hematoma rates were not systematically registered, and thus are not reported herein. Having a complication during the first stage of reconstruction was not associated with complications during the second stage, either when evaluating general or specific complications.

Timing

The mean time between mastectomy (first stage) and RT was 141 days (range, 15–319 days). The median time was 96 days (range, 15–319 days) in patients who had a first-stage complication and 158 days (range, 41–286 days) in those who did not have first-stage complications, and this difference was statistically significant ($P = .032$). The mean time between the first and second stage of the reconstruction was 20 months (range, 8–73 months).

Scatter plots and receiver operating characteristic curves did not show a clear cutoff for complications when evaluating time between the first-stage surgery and the beginning of PMRT, last chemotherapy, and second-stage surgery, and PMRT conclusion and second-stage surgery. Times from the beginning of RT to the first record of a complication related to the expander, and time from second-stage surgery to the first record of a complication related to the permanent is shown in Table 3.

Bolus

During the first stage of reconstruction, the use of bolus showed a trend toward an association with expander infection ($P = .059$) and an association with expander loss ($P = .023$). Daily bolus significantly increased the risk of expander infection (hazard ratio [HR]: 10.3; 95% confidence interval [CI], 1.7–61.8) and loss (HR: 13.89; 95% CI, 2.24–85.98), but alternate-day bolus showed a nonsignificant increase in expander infection (HR: 1.14; 95% CI, 0.14–9.295) and loss (HR: 1.5; 95% CI, 0.19–12.87; Table 4; Figs. 1 and 2). No significant association was observed between the use of skin bolus and complications during the second stage of reconstruction. Bolus was associated with radiation dermatitis ($P = .000$). There was also no association between the use of skin bolus and local-regional failure ($P = 1.00$).
### Table 1  Baseline characteristics

|                              | No bolus | Daily bolus | Alternate days bolus | p-value |
|------------------------------|----------|-------------|----------------------|---------|
|                              | median   | range       | median               | range   | p-value  |
| Age (years)                  | 46       | 25-71       | 49                   | 26-68   | p = 0.140 |
|                              | n        | percentage  | n                    | percentage |
| Smoking                      |          |             |                      |         |
| Smoker/ History of smoking   | 39       | 16.8%       | 3                    | 50%     | p = 0.053 |
| Never smoked                 | 193      | 83.2%       | 3                    | 50%     | p = 0.053 |
| Histology                    |          |             |                      |         |
| Invasive Carcinoma NST       | 181      | 70.2%       | 6                    | 100%    | p = 0.483 |
| Classic Lobular Carcinoma    | 37       | 14.3%       | 0                    | 0%      | 21.1%    |
| Pleomorphic Lobular Carcinoma| 12       | 4.7%        | 0                    | 0%      | 5.3%     |
| Invasive Micropapillary Carcinoma | 12  | 4.7%   | 0                    | 0%      | 5.3%     |
| Mixed Lobular Carcinoma      | 3        | 1.2%        | 0                    | 0%      | 5.3%     |
| Mucinous Carcinoma           | 3        | 1.2%        | 0                    | 0%      | 0%       |
| Metaplastic Carcinoma        | 2        | 0.8%        | 0                    | 0%      | 0%       |
| Other subtypes               | 8        | 2.9%        | 0                    | 0%      | 5.3%     |
| Estrogen receptor            |          |             |                      |         |
| Negative                     | 54       | 20.8%       | 1                    | 16.7%   | p = 0.830 |
| Positive                     | 205      | 79.2%       | 5                    | 83.3%   | 73.7%    |
| Progesterone receptor        |          |             |                      |         |
| Negative                     | 65       | 25.1%       | 2                    | 33.3%   | p = 0.458 |
| Positive                     | 194      | 74.9%       | 4                    | 66.7%   | 63.2%    |
| HER status                   |          |             |                      |         |
| Negative                     | 209      | 80.7%       | 4                    | 66.7%   | 78.9%    |
| Positive                     | 50       | 19.3%       | 2                    | 33.3%   | 21.1%    |
| Pathological Stage Group     |          |             |                      |         |
| Stage I                      | 105      | 42.2%       | 0                    | 0%      | 0%       |
| Stage II                     | 78       | 31.3%       | 0                    | 0%      | 0%       |
| Stage III/IV                 | 66       | 26.5%       | 6                    | 100%    | 100%     |
| Chemotherapy                 |          |             |                      |         |
| No                           | 9        | 3.5%        | 0                    | 0%      | 0%       |
| Yes                          | 250      | 96.5%       | 6                    | 100%    | 100%     |

### Table 2  Complications per reconstruction stage

|                             | First-stage complications | Second-stage complications | P value (Fisher exact test; 2-sided) |
|-----------------------------|---------------------------|----------------------------|--------------------------------------|
|                             | n | % | Overall | n | % | Overall |
| Overall                     | 80/288 | 27.7 | Overall | 71/226 | 31.4 | .381 |
| Infection/ flap necrosis    | 17/288 | 6.25 | Infection/ flap necrosis | 30/226 | 13.3 | .005 |
| Capsular contracture*       | 51/288 | 17.7 | Capsular contracture* | 11/226 | 4.9 | .000 |
| Reconstruction failure      | 12/288 | 4.2 | Reconstruction failure | 29/226 | 12.8 | .000 |

* Baker III and IV.
Table 3  Time to complication

| Time to complication | Minimum | Median | Maximum |
|----------------------|---------|--------|---------|
| First-stage complications (expander) |         |        |         |
| Time from beginning of RT to infection/flap necrosis | 9 d     | 73 d   | 19 mo   |
| Time from beginning of RT to capsular contraction | 44 d    | 7.6 mo | 56.4 mo |
| Time from beginning of RT to reconstruction failure | 35 d    | 3.4 mo | 19.4 mo |
| Second-stage complications (permanent implants) |         |        |         |
| Time from second-stage surgery to infection/flap necrosis | 11 d    | 49 d   | 39.8 mo |
| Time from second-stage surgery to capsular contraction | 4 d     | 34.4 mo| 90.7 mo |
| Time from second-stage surgery to reconstruction failure | 21 d    | 70 d   | 50.2 mo |

Abbreviations: RT = radiation therapy.

Table 4  Bolus complications

| Expander infection | Expander loss |
|--------------------|---------------|
| n/N (%) HR 95% CI  | n/N (%) HR 95% CI |
| No bolus           | 9/259 (3.5) 12/259 (4.6) |
| Daily bolus        | 2/6 (33) 10.3 1.7-61.8 2/6 (33) 13.89 2.24-85.98 |
| Alternate-day bolus| 1/19 (5.3) 1.14 0.14-9.295 1/19 (5.3) 1.5 0.19-12.87 |

Abbreviations: HR = hazard ratio.

Figure 1  Complication-free survival (first stage infection/necrosis) according to bolus usage.
Other factors

No significant associations were found between fractionation regime and complications \((P > .05)\) regardless of the reconstruction stage or complication type. In the multivariate analysis, grade 3 acute radiation dermatitis increased the risk of infection and reconstruction failure during the first stage \((HR: 16.934; 95\% \, CI, 3.909-73.349\) and \(HR: 10.6; 95\% \, CI, 2.37-47.48,\) respectively), but was not associated with second stage complications.

A higher number of revision surgeries was associated with the following second-stage complications: Infection \((P = .001)\), flap necrosis \((P = .002)\), and reconstruction failure \((P = .04)\). Other factors, such as molecular subtypes, systemic therapy (type and timing), insurance type, and smoking status, were not associated with complications (data not shown).

Discussion

Our results show that daily bolus significantly increased first-stage reconstruction failures and infections, but alternate-day bolus showed nonsignificant associations. Unsurprisingly, bolus was also associated with increased rates of radiation dermatitis. Local control rates were extremely high in both groups. The complication profile differed among reconstruction stages. During the first stage, the higher rates of capsular contraction could be explained by the irradiation of the expander. During the second stage, the higher rates of infection and implant loss could be the consequence of both previous surgery and RT, which can increase fibrosis and alter local blood supply.

Despite having a planned 2-stage reconstruction, approximately 20% of patients in our cohort did not go through all stages. Reasons for this included previous complications, disease progression, patient refusal to go through another surgery, or short follow up. Since the median follow-up times for the first and second stages were similar, we consider our complications estimations not biased toward one stage over the other. A longer interval between mastectomy and RT was associated with decreased complication rates, but no ideal cutoff could be found.

In a recent review, bolus was shown to increase complications without demonstrating benefit in local control.\(^{14}\) In fact, some studies even reported higher recurrence rates in the bolus group, probably due to
treatment interruptions and discontinuations. Similarly, a Delphi study and International Consensus Recommendations from the same group suggested that bolus should be limited to highly selected patients with breast cancer. In our cohort, local control rates were extremely high in all groups, which might be due to treatment advances and the fact that they were all managed at a specialized cancer center.

Our overall complication rates were within the range of previous reports. The association between complications and the need for revision surgeries was shown in a recent study from the Mastectomy Reconstruction Outcomes Consortium, and our revision surgery rate was similar to theirs. Daily bolus has already been shown to increase complications compared with alternate-day bolus, but there is concern this is due to decreased skin dose coverage that could impact local control. Despite only daily bolus showing a significant increase in complications, our results can not rule out that alternate-day bolus increases complications compared with no bolus. We used a 0.5-mm thickness bolus, as recommended by the European Society Radiation Oncology consensus.

Apart from the inherent limitations of a retrospective study, other important considerations need to be made. The sample in the bolus group was small, but considering the scarcity of data on this particular circumstance, reporting these findings is extremely important to increase awareness of this possible complication and stimulate further investigation. Our study was not powered to evaluate local control, but considering the current literature, we consider the chances of a false-negative result unlikely. There was only 1 case of local recurrence in a triple-positive pT1cN3 patient who did not have any indication of a bolus. Even though factors, such as smoking, are known to be associated with complications, we considered that limitations related to smoking status reports could have jeopardized our analysis of this factor. Bolus was recommended for all patients with skin involvement, but the final decision was at the physician’s discretion and considered patients’ preferences. Despite not being the institutional protocol, 1 T4d patient underwent reconstruction with a tissue expander. No hypofractionation was performed in the bolus group.

When evaluating complication dates, we considered the first mention in the medical records; therefore, this might not reflect the exact date of the complication onset. Similar to another study, we could not show a relationship between the timing of expander-implant exchange and complication rates in the overall cohort. Of note, in our study, this happened with at least an 8-month interval; therefore, drawing conclusions for shorter intervals is not possible. We did not evaluate whether timing influences the type of complication encountered. A multivariate analysis was not performed in most cases, because there usually was only 1 factor associated with each specific complication. There was no adjustment for multiple testing.

This study provides important information regarding complication patterns in 2-stage breast reconstruction, showing that they differ among the stages. In addition, this is the first report to provide specific information on the influence of bolus on reconstruction complications. These results cannot be seen as definitive, but add an important consideration for a scenario in which there is no strong evidence for bolus usage recommendations. The possibility of increasing reconstruction complications needs to be considered and ideally discussed with patients, and this issue needs to be explored further in future studies. Importantly, since this is a cohort of patients treated at a cancer center, these findings might not be generalizable to scarce resource settings where patients do not have access to all recommended diagnoses and treatment procedures. Still, our results probably reflect the population of patients treated at centers where standard treatment can be performed.

Conclusions

Our findings show that complication patterns are different across reconstruction stages and that the use of skin bolus significantly increases first-stage complications. Despite the small sample size, these findings should raise awareness and stimulate future research on this topic. Randomized controlled trials are still needed, but based on the currently available evidence, bolus in PMRT should be carefully evaluated and the final decision individualized for patients undergoing reconstruction.

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