Post-mastectomy radiotherapy bolus associated complications in patients who underwent two-stage breast reconstruction

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breast reconstruction

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Declaration of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ABSTRACT:

Background and purpose: To evaluate the association of bolus and two-stage breast reconstruction complications, and if the dosimetric advantage translates into improvements in local control.

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

Results: 288 women were included, ages 25 to 71. Of these, 6 were treated using daily bolus and 19 using alternate days bolus, totalizing 25 out 288 (8.7%) patients in the bolus group. Two hundred and twenty-six patients (78.5%) had the second stage performed. Median follow-up was 61 months. The rates for five-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 infection and 4.2% implant loss. Daily bolus significantly increased the risk of expander infection (HR 10.3 [CI 95% 1.7 - 61.8]) and loss (HR 13.89 [CI 95% 2.24 - 85.98]), while alternate days bolus showed a nonsignificant increase for expander infection (HR 1.14 [CI 95% 0.14 - 9.295]) and loss (HR 1.5 [CI 95% 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% versus 10.2% and 4.2% versus 12.8%, respectively).

Conclusion: 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.

Key-words: Radiotherapy; Mastectomy; Radiotherapy, Adjuvant; Breast Neoplasms; Mammaplasty; Breast Implants; Rehabilitation

INTRODUCTION

Mastectomy still plays an important role in breast cancer management for some patients. Breast reconstruction rates have been increasing over the last decades[1], since it has been shown to have a positive psychological impact[2] without compromising oncological outcomes[3]. In this scenario, post-mastectomy radiotherapy (PMRT) can be an important component of treatment, because it reduces recurrence and breast cancer mortality for node positive[4] and triple-negative [5] patients, and can improve local control if multiple risk factors are present [6 7].

Two-stage breast reconstruction (also known as delayed-immediate reconstruction) was developed aiming to minimize PMRT reconstruction complications[8] and it is the most common strategy when an implant-based approach is chosen[8]. However, the optimal integration with radiotherapy is still not completely understood and the influence of many radiation parameters still needs to be elucidated[8].

The use of bolus has not been prospectively evaluated in randomized controlled trials but it is usually recommended for patients with cutaneous involvement to ensure skin coverage [9 10]. However, its usage varies widely across radiation oncologists[11] and it has been shown to increase radiation-related toxicities[12] and treatment interruptions[13] without a proven benefit in local control rates[14]. To date, data specifically regarding the association between the use of bolus in PMRT and two-stage breast reconstruction complications are lacking[14].

Therefore, we retrospectively evaluated the association of skin bolus in PMRT and reconstruction complications in breast cancer patients who underwent two-stage reconstruction in a Cancer Center. Secondarily, we evaluated if a decrease in local recurrence could be observed, and we also investigated other possible factors associated with increased complication rates.

METHODS

We retrospectively reviewed the data from all the women treated in our institution who underwent a mastectomy and a planned two-stage breast reconstruction followed by adjuvant radiotherapy, and who had at

least [redacted] ast appointment registered in the hospital for patients treated at our institution from 2008 to 2019. A two-stage reconstruction was defined as follows: in the first stage, immediate reconstruction was performed using a tissue expander; in the second stage, the expander would be replaced by a permanent implant. Patients whose surgical treatment (mastectomy or revisions), or radiation treatment were performed in another institution, and patients who had a reconstruction failure before the beginning of radiotherapy were excluded.

Data were collected and managed using REDCap [15 16] electronic data capture tools hosted at "Anonymized for Review". We evaluated the patient's baseline characteristics, diagnostic evaluations, tumor pathology, staging, surgical descriptions (mastectomy and revisions), radiotherapy treatments, systemic therapies, complications, and disease progression. Clinical and pathological staging information were collected and patients were grouped according to the AJCC TNM 8th edition prognostic stage groupings[17] (clinical for those who had neoadjuvant chemotherapy and pathological for those who had upfront surgery). The pathological classification was recorded using World Health Organization criteria[18]. We recorded complications-related data separately for both situations: the expander (placed immediately after mastectomy and before radiotherapy) and the permanent implant (placed after radiotherapy). The following complications were recorded: flap necrosis, capsular contracture, and respective Baker classification[19], seroma, hematoma, infection, and reconstruction failure (implant loss or conversion to autologous reconstruction). We considered the complication date as the first mention on the records. Although we recorded Baker classification whenever it was mentioned, only Baker III and IV were considered as complications.

Regarding radiotherapy, 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 radiotherapy and for those who had 2D treatment, medical and surgical records were thoroughly reviewed to ensure that they met the selection criteria. Acute and late effects were recorded using the CTCAE criteria[20], but only radiation dermatitis was systematically recorded and thus reported in this text.

The l tly 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 happened first). Second-stage follow-up was defined as the interval between expander replacement and reconstruction failure or death or loss of follow-up (whichever happened 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-square test for larger samples, using continuity correction for 2x2 tables or Fisher's exact test whenever appropriate. Multivariate analysis for potential factors associated with complications was done using logistic regression. Time-to-event data for both complications and disease progression was 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 ROC curves. Missing data were addressed using complete case analysis. No adjustment for multiple testing was made. Analysis was done using SPSS version 25'. This study was approved by the hospital's review board.

RESULTS

A total of 288 patients were analyzed. The median follow-up was 61 months, ranging from 18 to 115 months. The median first-stage follow-up was 22.8 months (3.5-97.9 months) and the median second-stage follow-up was 31.87 months (4 days - 90.7 months). The mean age of patients was 46 years old, ranging from 25 to 71 years, and 33 patients (11.46%) were stage T4 (32 were T4b and 1 was T4d). The baseline characteristics of the cohort are in table 1.

Most patients (92%) were treated using 3DRT, the others were treated either with inverse planning IMRT (2.1%) or 2DRT (4.5%). Fractionation choice depended on the physician's criteria, 93% of patients were treated with conventional fractionations (median dose: 50 Gy) and 7% with hypofractionation (median dose: 42.56

Gy). II in 13%. In 8.7% of cases (25 patients), a 0.5 cm thickness bolus was used due to skin involvement, either daily (6/25) or on alternating days (19/25).

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

Complications overview

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

Timing

The mean time between mastectomy (first-stage) and radiotherapy was 141 days (range 15 to 319). In those who had a first-stage complication the median time was 96 days (15-319) and in those who did not have first-stage complications was 158 days (41 - 286), and this difference was statistically significant ($p = 0.032$). The mean time between the first and the second stage of the reconstruction was 20 months, ranging from 8 months to 73 months.

Scatt

first-stage surgery and beginning of PMRT, last chemotherapy and second-stage surgery, and PMRT conclusion and second-stage surgery. Times from the beginning of radiotherapy 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 in table 3.

Bolus

In the first stage of reconstruction, the use of bolus showed a trend towards an association with expander infection (p = 0.059), and an association with expander loss (p = 0.023). Daily bolus significantly increased the risk of expander infection (HR 10.3 [CI 95% 1.7 - 61.8] and loss (HR 13.89 [CI 95% 2.24 - 85.98]), while alternate days bolus showed a non-significant increase in expander infection (HR 1.14 [CI 95% 0.14 - 9.295]) and loss (HR 1.5 [CI 95% 0.19 - 12.87]), (see table 4 and figures 1 and 2). No significant association was observed between the use of skin bolus and complications in the second stage of reconstruction. Bolus was associated with radiation dermatitis (p = 0.000). There was also no association between the use of skin bolus and local-regional failure (p = 1.00).

Other factors

No significant associations were found between fractionation regime and complications (p > 0.05), regardless of the reconstruction stage or complication type.

In multivariate analysis, grade three acute radiation dermatitis increased the risk of infection and reconstruction failure in the first stage (HR 16.934 [CI 95% 3.909 - 73.349] and HR 10,6 [CI 95% 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 = 0.001); flap necrosis (p = 0.002) and reconstruction failure (p = 0.04).

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 increases first-stage reconstruction failures and infections, while alternate day bolus showed non-significant 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. In the first stage, the higher rates of capsular contraction could be explained by the irradiation of the expander. In the second stage, the higher rates of infection and implant loss could be the consequence of both previous surgery and radiotherapy, which can increase fibrosis and alter the local blood supply.

Despite having a planned two-stage reconstruction, approximately 20% of patients in our cohort did not go through all the stages. Reasons for this included previous complications, disease progression, the patient's 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 that our complications estimations are not biased towards one stage over the other. A longer interval between mastectomy and radiotherapy was associated with decreased complication rates, but no ideal cut-off 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[14]. Similarly, a Delphi study and International Consensus Recommendations from the same group[10] suggested that bolus should be limited to highly selected breast cancer patients. In our cohort, local control rates were extremely high in all groups, and this might be due to treatment advances and the fact that they were all managed in a specialized cancer center.

Our overall complications rates are within the range of previous reports[21 22] . 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 [23].

Daily bolus has already been shown to increase complications compared to alternating day bolus[10], but there is a concern that this is due to a 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 alternating days bolus increases complications compared to no bolus. We used a 0.5 mm thickness bolus as recommended by the ESTRO consensus[10].

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 one case of local recurrence in a triple positive pT1cpN3 patient who did not have any indication of a bolus. Even though factors such as smoking are known to be associated with complications[24], we consider 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, one T4d patient underwent reconstruction with a tissue expander. No hypofractionation was performed in the bolus group.

When evaluating complication dates, we considered the first time it was mentioned on the medical records and therefore this might not reflect the exact date of the complication onset. Similar to another study[25], we could not show a relationship between the timing of expander-implant exchange and complication rates in the overall cohort. It is important to highlight that in our study this happened with at least an 8-month interval and therefore it is not possible to draw conclusions for shorter intervals. We did not evaluate if timing influences the type of complication encountered. Multivariate analysis was not performed in most cases because usually there was only one factor associated with each specific complication. There was no adjustment for multiple testing.

This [illegible], showing that they differ among the stages. In addition to that, it is the first report to provide specific information on the influence of bolus on reconstruction complications. These results cannot be seen as definitive, but they 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 in 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 in centers where standard treatment can be performed.

CONCLUSION

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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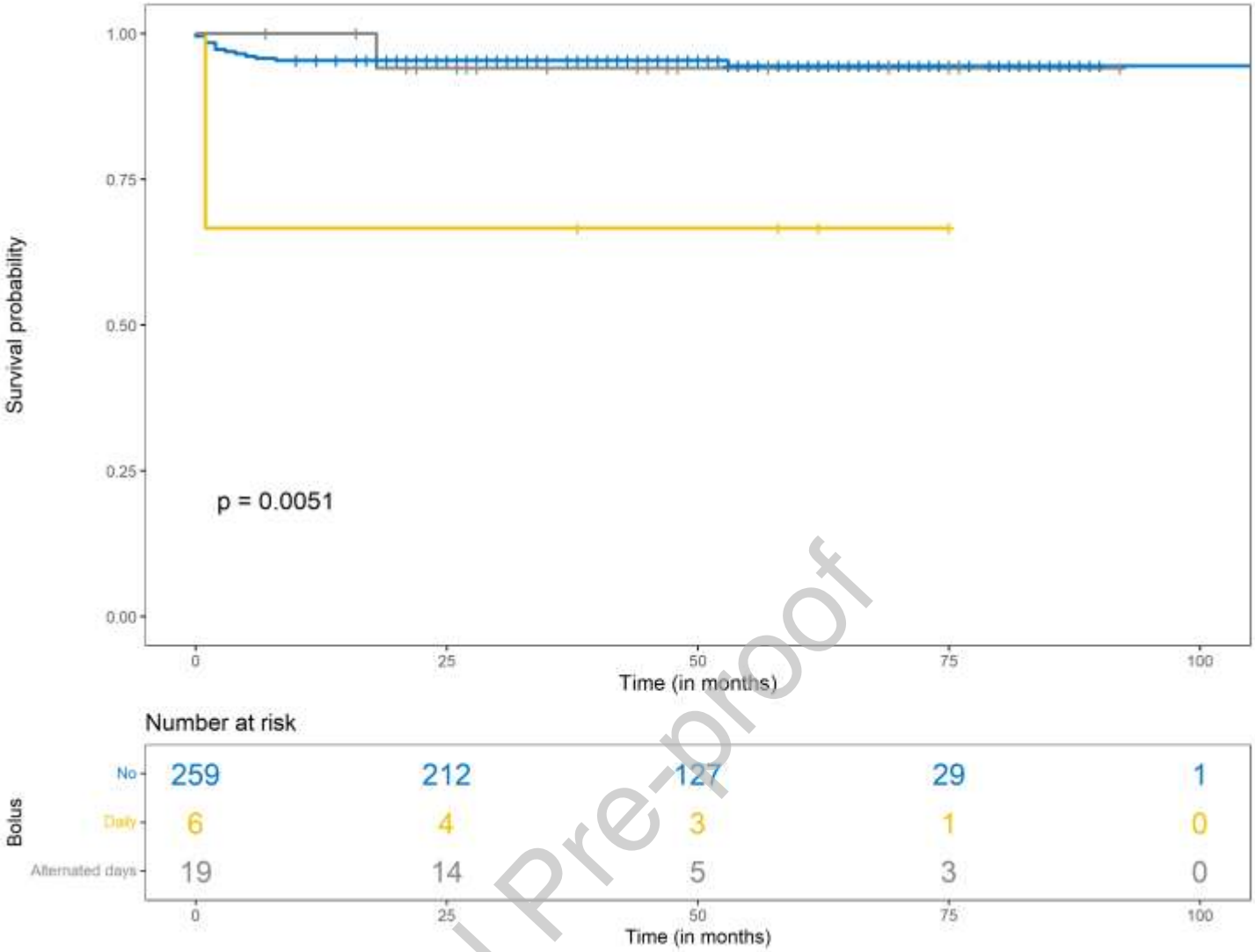
FIGURES AND TABLES

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



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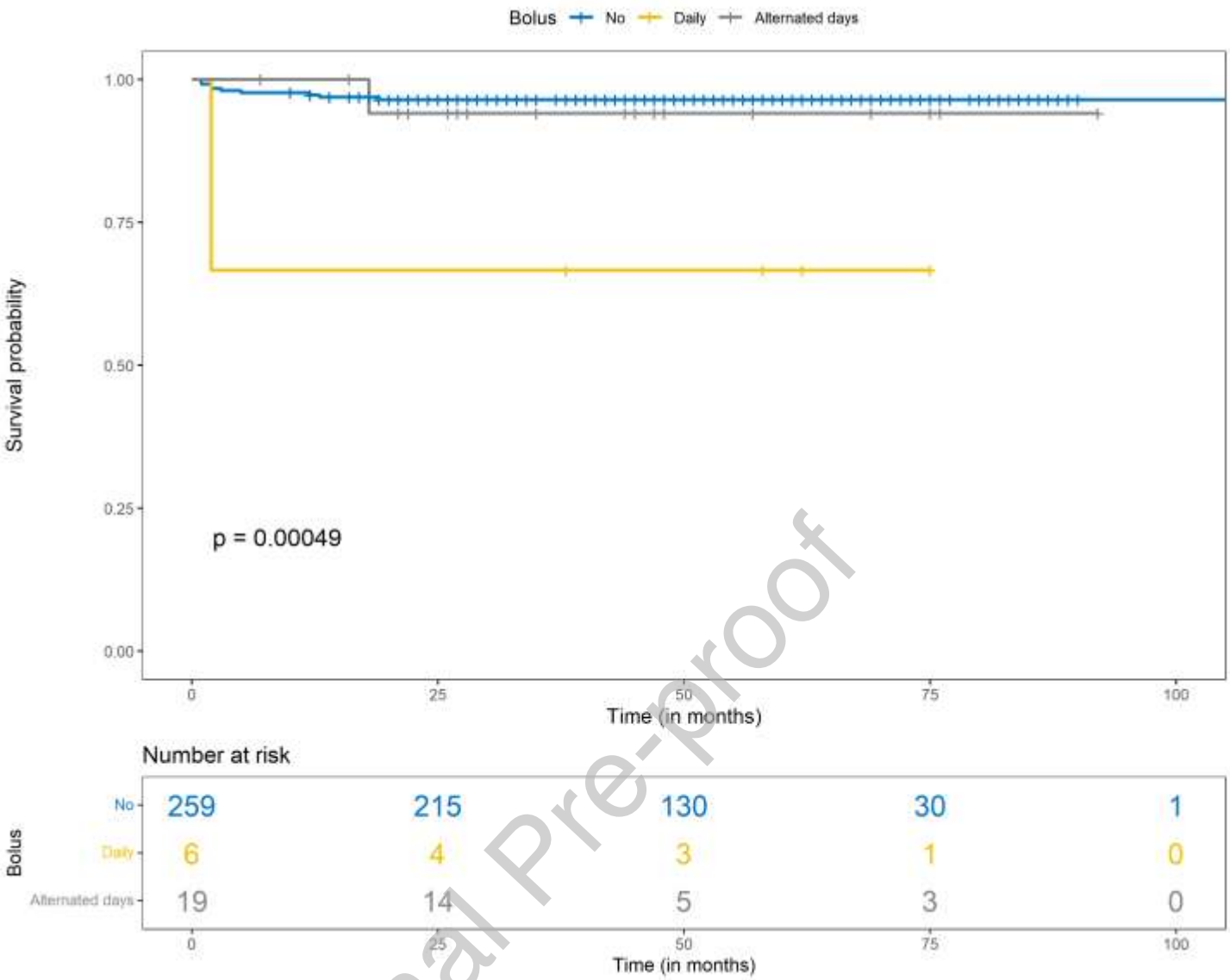

	No bolus		Daily bolus		Alternate days bolus		
	median	range	median	range	median	range	
Age (years)	46	25-71	49	26-68	41	26-58	p = 0.140
Smoking							
Smoker/ History of smoking	39	16.8%	3	50%	4	26.7%	p = 0.053
Never smoked	193	83.2%	3	50%	11	73.3%	
Histology							p = 0.483
Invasive Carcinoma NST	181	70.2%	6	100%	10	52.6%	
Classic Lobular Carcinoma	37	14.3%	0	0	4	21.1%	
Pleomorphic Lobular Carcinoma	12	4.7%	0	0	1	5.3%	
Invasive Micropapillary Carcinoma	12	4.7%	0	0	1	5.3%	
Mixed Lobular Carcinoma	3	1.2%	0	0	1	5.3%	
Mucinous Carcinoma	3	1.2%	0	0	0	0	
Metaplastic Carcinoma	2	0.8%	0	0	1	5.3%	
Other subtypes	8	2.9%	0	0	1	5.3%	
Estrogen receptor							
Negative	54	20.8%	1	16.7%	5	26.3%	p = 0.830
Positive	205	79.2%	5	83.3%	14	73.7%	
Progesterone receptor							
Negative	65	25.1%	2	33.3%	7	36.8%	p = 0.458
Positive	194	74.9%	4	66.7%	12	63.2%	
HER status							
Negative	209	80.7%	4	66.7%	15	78.9%	p = 0.518
Positive	50	19.3%	2	33.3%	4	21.1%	
Pathological Stage Group							p = 0.000
Stage I	105	42.2%	0	0%	0	0	
Stage II	78	31.3%	0	0	0	0	
Stage III/IV	66	26.5%	6	100%	19	100%	
Stage IV total							

No	9	3.5%	0	0	0	0	p = 1.000
Yes	250	96.5%	6	100%	19	100%	

Table 2 - Complications per reconstruction stage

FIRST STAGE COMPLICATIONS			SECOND STAGE COMPLICATIONS			
	n	%		n	%	Fisher exact (two-sided)
Overall	80/288	27.7%	Overall	71/226	31.4%	p = 0.381
Infection/ Flap necrosis	17/288	6.25%	Infection/ Flap necrosis	30/226	13.3%	p = 0.005
Capsular contracture*	51/288	17.7%	Capsular contracture*	11/226	4.9%	p = 0.000
Reconstruction failure	12/288	4.2%	Reconstruction failure	29/226	12.8%	p = 0.000
* Baker III and IV						

Table 3 - Time to complication

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

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 days bolus	1/19 (5.3%)	1.14	0.14 - 9.295	1/19 (5.3%)	1.5	0.19 - 12.87