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The effect of wound complications following mastectomy with immediate reconstruction on breast cancer recurrence

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ABSTRACT

Introduction: The aim of this study was to determine whether complications following mastectomy with immediate breast reconstruction (IBR) were associated with breast cancer recurrence.
Methods: A retrospective review was performed of women diagnosed with stage I-III breast cancer who underwent mastectomy with IBR between 2005 and 2010. Patient demographics, tumor data, surgical wound complications, treatment details and timing were recorded and analyzed.
Results: We identified 458 women with a median follow up time of 7.6 years. A total of 22% of patients experienced IBR complications. There was a delay in initiation of adjuvant therapy in patients who had a complication (52 vs 41 days, $p < 0.001$). There was no significant difference in recurrences between groups with and without complications ($p = 0.65$).
Conclusions: In breast cancer patients who undergo mastectomy with IBR, wound complications delayed initiation of adjuvant systemic therapy, but were not associated with an increased risk of cancer recurrence.

Introduction

Rates of reconstruction following mastectomy for breast cancer have increased over recent years with approximately 40% of patients receiving immediate breast reconstruction (IBR).[1] Performing IBR at the time of mastectomy for breast cancer treatment offers patients psychological benefit and has been shown to be oncologically safe.[2] However, IBR can be associated with increased risks of wound complications compared to mastectomy alone, with studies reporting up to 49% incidence of post-operative reconstruction related complications.[3] Factors associated with increased post-surgical complications include patient characteristics such as age, diabetes, elevated body mass index (BMI) and smoking, as well as reconstruction type (implant versus autologous reconstruction).[1] The oncologic significance of decreasing surgical wound complications in cancer patients is important because complications can risk postponement in the time to initiation of adjuvant chemotherapy or radiation. Literature has suggested that delay in receipt of adjuvant treatment beyond 4–6 weeks after breast surgery is associated with increased risk of cancer recurrence and decreased survival.[4] Specifically, these studies have shown that patients who initiate chemotherapy arbitrarily ≤30 days, 31–60 days and >60 days after surgery have a difference in cancer survival outcomes.[4] Recently, studies have suggested that the actual incidence of an IBR wound complication itself may be associated with an increased risk of breast cancer recurrence, proposing that inflammatory immune components may play a role.[5,6] These important risk factors and survival implications for breast cancer patients who receive IBR and develop post-operative complications have recently gained attention, but have not yet been well studied.

The aim of our study was to identify patient and tumor risk factors that are associated with IBR complications following mastectomy and determine the relationship between complications, time to adjuvant treatment (AT) and breast cancer recurrence.

Methods

A retrospective review was performed to identify women with stage I-III breast cancer treated at our institution between 2005 and 2010 who received mastectomy with IBR and had a minimum of 5 years of follow up. Data points collected included patient age, diabetes, BMI, smoking status, tumor biology, stage, surgical

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reconstruction type, as well as neoadjuvant and adjuvant therapies given. Time to AT was defined as date of first surgery to initiation of first adjuvant therapy, either chemotherapy or radiation therapy. All 60 day post-operative wound complications were documented. Complications were described as seroma requiring drainage, hematoma requiring evacuation, infection requiring intravenous antibiotics, delayed wound healing or dehiscence, hospital readmission, flap necrosis requiring debridement, and autologous flap or implant loss. A single patient could have more than one complication documented. Breast cancer specific recurrence and overall survival were documented.

Complication status and recurrences were compared for demographics, tumor characteristics and survival using Chi-square, Fisher's exact and two sample t-tests. Logistic regression univariate (UA) and multivariant (MVA) models were used to assess the association between complication status, recurrence and potential predictive factors. Kaplan-Meier estimates were calculated in each time to event analyses. Cox proportional hazard models were applied to assess the effect of BMI and smoking on different event outcomes. All tests were two-tailed and performed at a significance level of 0.05. Institutional Board Review approval was obtained for this study.

Results

A total of 458 patients were identified with the median age of 49 years old (range 26–85) and median follow up time of 7.54 years (range 5.47–12.08). Patient demographics, tumor characteristics and treatment data are shown in Table 1. For surgical treatment, 72% of patients had unilateral mastectomy, and 28% had bilateral mastectomy performed. Overall, 64% of our patients received chemotherapy, 50% adjuvant chemotherapy and 14% neoadjuvant chemotherapy. Subsequently, 22% of patients received post-mastectomy radiation.

Complications

A total of 136 complications were recorded in 100 patients (22%). These included 31 seromas requiring aspiration (7%), 11 hematomas requiring evacuation (2%), 31 infections necessitating intravenous antibiotics (7%), 22 delayed wound healing (5%), 27 skin flap necrosis requiring surgical debridement (6%), and 14 implant or tissue flap loss (3%). Of the 100 patients who developed post-operative complications, 50 patients experienced hospital readmission, 45 required minor in-office procedures, and 55 required return to the operative room for surgical intervention.

On univariate analysis (UA) (Table 1), increasing BMI ($p = 0.001$), was associated with increased complications. When evaluated with multivariate analysis (MVA) (Table 2), increasing BMI continued to show a statistically significant association with post-operative complications. Specifically, the odds of developing a post-op complication in patients with BMI in range of 30–35 was 2.9 time more likely compared to patients with BMI less than 25 ($p < 0.001$) and 3.5 times more likely in patients with BMI >35 compared to patients with BMI <25 ($p = 0.002$). Increasing Tumor (T) stage was associated with increasing complications on UA ($p = 0.034$), however the number of patients with T3 or T4 tumors was small and the association with surgical complications was not statically significant on MVA. Reconstruction type was associated with increased complications on UA ($p = 0.036$) with 20% of tissue expander/implant IBR experiencing complications versus 30% of autologous IBR, but this was not found to be significant on MVA. Patient age, diabetes, smoking history, tumor receptor status, chemotherapy timing (neoadjuvant versus adjuvant), and extent of axillary surgery were not associated with increased complications.

Recurrence

There were a total of 42 (9.2%) recurrences overall in the study group, 9 patients experienced a local recurrence, 9 patients had a regional recurrence and 24 patients had a metastatic recurrence. Table 1 demonstrates that UA for recurrence identified smoking, tumor histology, T stage, nodal stage, cancer stage and tumor grade as statistically significant factors for recurrence. On MVA however (Table 2), only nodal stage (N2) was found to have a statistically significant association with recurrence (OR 18.67, CI 2.34–211.65, $p = 0.01$). Patient demographics, BMI, smoking status, tumor receptor status and reconstruction type were not found to be statistically associated with recurrence.

When evaluating breast cancer recurrence between patients who experienced a post-operative IBR wound complication (12%) versus those who did not have a complication (8.4%), there was no statistically significant association identified on either UA ($p = 0.52$) or MVA (OR 1.51, CI 0.64–3.36, $p = 0.325$). Fig. 1 shows that the time to breast cancer recurrence for patients with complications versus without complications was not statistically different ($p = 0.12$). During the study period, 3% of patients died from their breast cancer, which included 6 patients with complications and 10 with no complications. Due to these small numbers, no association could be made between complications and breast cancer survival.

Time to treatment

A total of 272 patients (59%) received AT which included 227 women receiving adjuvant chemotherapy and 45 receiving radiation as first AT after surgery. Median time from surgery to AT was 43 days (rage 33–57). Women having any post-operative IBR complication were found to have a statistically significant delay in the initiation of AT with a median delay of 11 days (41 days no complication (range 32–54) versus 52 days with complication (rage 38–70), $p < 0.001$). However, the patients with a IBR complication who experienced a breast cancer recurrence did not have a significant delay to receiving AT compared to those who did not have a complication (42 days no complication (range 33–52) versus 43 days with complication (range 33–57), $p = 0.65$).

Discussion

The risk for breast cancer recurrence is complex and multifactorial. Breast cancer stage at diagnosis and tumor biology are two factors the clinician uses to aid treatment decisions aimed to improve patient survival. Our study suggests that lymph node involvement >4 lymph nodes is the most significant predictor for breast cancer recurrence. Although tumor stage at diagnosis and tumor biology are factors which are not modifiable, studies have shown that chemotherapy given neoadjuvantly to triple negative and HER2 amplified breast cancer biological subtypes, can downstage the axilla in up to 65% of these patients.[7,8] Receipt of neoadjuvant chemotherapy (NAC) followed by mastectomy with IBR has been shown to be a safe option.[9] While there may be concern for increased complications in patients who receive NAC followed by IBR, in our study, 14% of patients received NAC with no increase in post-operative wound complications or recurrence compared to those who had surgery first.

Identifying modifiable risk factors associated with cancer treatment may improve patient operative outcomes and decrease risk for recurrence. Our study had a 22% over-all inclusive complication rate, which is consistent with other published reports.[3] Diabetes and smoking were not associated with increased complications in our study, but are known risks for wound

Table 1
Patient, Tumor and treatment characteristics and univariate analyses for surgical wound complications and cancer recurrence.

	All Patients		Surgical Complications			Recurrence		
	N = 458	%	No	Yes	p	No	Yes	p
			N = 322	N = 136		N = 416	N = 42	
Age at Diagnosis	50.2		49.9	51.2	0.28	50.2	50.4	0.88
Diabetic	38	8%	25 (66%)	13 (34%)	0.085	33 (87%)	5 (13%)	0.40
Smoker	62	14%	47 (76%)	15 (24%)	0.75	51 (82%)	11 (18%)	**0.043**
BMI					**0.001**			0.69
<25	204	45%	174 (85%)	30 (15%)		183 (90%)	20 (10%)	
25-30	125	27%	100 (80%)	25 (20%)		114 (91%)	11 (9%)	
BMI 30–35	89	19%	59 (66%)	30 (36%)		81 (91%)	8 (9%)	
BMI >35	40	9%	25 (63%)	15 (37%)		34 (85%)	6 (15%)	
Tumor Histology					0.76			**0.023**
Invasive Ductal	321	70%	254 (79%)	67 (21%)		298 (93%)	23 (7%)	
Invasive Lobular	49	11%	38 (78%)	11 (22%)		41 (84%)	8 (16%)	
Mixed	68	15%	50 (74%)	18 (26%)		57 (84%)	11 (16%)	
Other	20	4%	16 (80%)	4 (20%)		17 (85%)	3 (15%)	
T Stage					**0.034**			**0.024**
1	272	59%	208 (76%)	64 (24%)		255 (94%)	17 (6%)	
2	151	33%	127 (84%)	24 (16%)		131 (87%)	20 (13%)	
3	27	6%	19 (70%)	8 (30%)		22 (81%)	5 (19%)	
4	8	2%	4 (50%)	4 (50%)		8 (100%)	0 (0%)	
Nodal Stage					0.98			**0.001**
0	297	65%	231 (78%)	66 (22%)		276 (93%)	21 (7%)	
1	122	27%	95 (78%)	27 (22%)		112 (92%)	10 (8%)	
2	32	7%	26 (81%)	6 (19%)		23 (72%)	9 (28%)	
3	7	2%	6 (86%)	1 (14%)		5 (71%)	2 (29%)	
Stage					0.75			**0.047**
I	208	45%	160 (77%)	48 (23%)		195 (94%)	13 (6%)	
II	189	41%	151 (80%)	38 (20%)		170 (90%)	19 (10%)	
III	61	13%	47 (77%)	14 (23%)		51 (84%)	10 (16%)	
Tumor Grade					0.33			**0.036**
1	82	18%	59 (72%)	23 (28%)		76 (93%)	6 (7%)	
2	194	42%	155 (80%)	39 (20%)		168 (87%)	26 (13%)	
3	163	36%	127 (78%)	36 (22%)		155 (95%)	8 (5%)	
unknown	19	4%	17 (89%)	2 (11%)		17 (89%)	2 (11%)	
Tumor Biology								
ER positive	350	76%	269 (77%)	81 (23%)	0.22	315 (90%)	35 (10%)	0.99
ER negative	106	37%	88 (83%)	18 (17%)		96 (91%)	10 (9%)	
HER 2 positive	87	19%	74 (85%)	13 (15%)	0.16	78 (90%)	9 (10%)	0.99
Reconstruction type					**0.036**			0.60
Tissue Expander/Implant	362	79%	291 (80%)	71 (20%)		327 (90%)	35 (10%)	
Autologous	96	21%	67 (70%)	29 (30%)		89 (93%)	7 (7%)	
Lymph Node Surgery					0.69			0.065
None	3	<1%	3 (100%)	0 (0%)		3 (100%)	0 (0%)	
SLNB	274	60%	217 (79%)	57 (21%)		254 (93%)	20 (7%)	
ALND	181	39%	138 (76%)	43 (24%)		156 (86%)	25 (14%)	
Chemotherapy	292	64%	232 (79%)	60 (21%)	0.44	260 (89%)	32 (11%)	0.36
Neoadjuvant Chemotherapy	65	14%	53 (82%)	12 (28%)		60 (92%)	5 (8%)	
Adjuvant chemotherapy	227	50%	179 (79%)	48 (21%)		200 (88%)	27 (12%)	
Radiation	103	22%	82 (80%)	21 (20%)	0.79	88 (85%)	15 (15%)	0.10
Complications								0.52
Yes	100	22%	–	–	–	88 (88%)	12 (12%)	
No	358	78%	–	–	–	328 (92%)	30 (8%)	
Time from Surgery to Adjuvant treatment – Median Days (range)	272	43 days (33; 57)	41 days (32; 54)	52 days (38; 70)	**0.001**	42 days (33; 52)	43 days (33; 57)	0.665

Table 2
Maultivariant analysis.

Variable	Odds Ratio	95% Confidence Interval	P value
	Complications = yes		
Body Mass Index (BMI)			
<25	1.00		
25.1–30.1	1.32	0.72–2.40	.359
30.1–35	2.90	1.59–5.31	<.001
>35	3.46	1.56–7.56	.002
Tumor (T) Stage			
1	1.00		
2	0.54	0.31–0.91	.025
3	1.21	0.46–2.93	.682
4	2.97	0.65–13.48	.146
Reconstruction Type			
Tissue Expander/Implant	1.0		
Autologus Reconstruction	1.60	0.93–2.71	.085
	Recurrence = Yes		
Histology			
Invasive Ductal Cancer	1.00		
Invasive Lobular Cancer	1.87	0.64–5.08	.231
Mixed IDC/ILC	1.57	0.60–3.80	.334
Other	3.63	0.74–13.41	.072
Smoking			
No	1.00		
Yes	1.57	0.63–3.61	.307
T Stage			
1	1.00		
2	2.59	0.93–7.53	.072
3	3.44	0.66–16.96	.131
4	0.00	NA	.988
N Stage			
0	1.00		
1	1.46	0.51–4.15	.475
2	18.67	2.34–211.65	.010
3	13.89	0.75–293.44	.077
Stage			
I	1.00		
II	0.77	0.21–2.75	.687
III	0.15	0.01–1.63	.142
Grade			
1	1.00		
2	2.44	0.93–7.37	.088
3	0.73	0.21–2.63	.617
Unknown	2.30	0.30–11.95	.352
Reconstruction Type			
Tissue Expander/Implant	1.0		
Autologus Reconstruction	1.54	0.66–3.41	.295
Complication			
No	1.00		
Yes	1.51	0.64–3.36	.325

complications. This difference may be because the numbers of diabetic or smoking patients were too low in our study to show an association. At our institution we preferentially defer IBR in smokers due to the known increased risks of complications. Therefore, 14% of patients in our cohort were smokers compared to other studies which showed an association with smoking and complications, where 34.9% of their reconstruction patients were active smokers.[5] Analysis of our data showed that obesity is a statistically significant predictor for developing complications after mastectomy with IBR. Overall, 55% of our patients had a BMI greater than 25, and the incidence of wound complications in our study was shown to significantly increase with each increasing degree of obesity. This is consistent with other studies demonstrating the strong relationship between obesity and post-operative wound complications.[1] Despite the increased complications, obesity was not associated with increased risk of cancer recurrence.

When evaluating the type of IBR performed, autologous reconstruction did have a higher 60 day complication rate compared to implant based reconstruction. However, when all factors were controlled for on MVA, the type of reconstruction performed ultimately did not affect the complication or recurrence rate in our study.

Surgical trauma itself is hypothesized to have an influence on cancer recurrence. The use of IBR, hypothetically increases the amount of surgical trauma, but prior studies have found no difference in recurrence rates or overall survival with the use of IBR compared to mastectomy alone.[3,10] Interestingly, recent studies have suggested that post-operative wound complications may have an association with increased risk for cancer recurrence in multiple types of cancer.[5,6] The various hypotheses propose that the inflammatory response of surgery creates an environment that supports tumor growth due to release of growth factors including interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-a) and vascular endothelial growth factor (VEGF). If complications are superimposed on this, it may magnify the inflammatory response which could lead to an increase in recurrence rate. In 2016, Beecher et al. reported a statistically significant association between wound complications and increased breast cancer recurrence.[6] Our study population and results are similar to their study in many regards such as wound complications, (22% versus 23.1%), however our incidence of infections (7% versus 19%) were lower, recurrences (9.2% versus 19.2%) were lower and our conclusions demonstrating an association with wound complications and recurrence is opposing. In our study we had a lower percentage of smokers than their group and their patient BMI was not reported; factors which could account for differences in reported infection rates. They also did not report time from surgery to AT, so it is unclear whether there was any association between IBR wound complications and a subsequent delay in time to AT.

Time to treatment in cancer is a rising heterogeneous topic, with multiple factors and definitions of what constitutes the true encompassing definition of the time frame for “time to treatment”. Some studies focus on time from biopsy to first treatment, time to completion of all treatment or, as we chose in this study, time from surgery to AT. A systematic review evaluating time to AT in mastectomy patients receiving IBR versus no reconstruction showed that IBR is safe, with patients in both groups receiving AT within the 12 week time-frame of initial diagnosis.[11] In our study, 59% of patients required AT after their mastectomy and IBR, with a median of 43 days between surgery and AT. Those who experienced complications did experience a significant delay in AT by a median of 11 days, but this was not associated with an increase in breast cancer recurrence. A possible explanation for no difference in recurrence despite the delay in AT may be that despite complications and delay, most patients were still treated within the 30–60 day proposed safety window (41 versus 52 days). Studies have suggested that delay in adjuvant chemotherapy for breast cancer more than 60 days was associated with worse outcomes, especially for stage II or III tumors with estrogen receptor negative and HER2 amplified subtypes[4] However, other studies using the National Cancer Database to evaluate Stage I and II triple negative tumors and treatment times did not show an increase in recurrence for prolonged treatment times, with the threshold being all treatment completed at <18 months.[12]

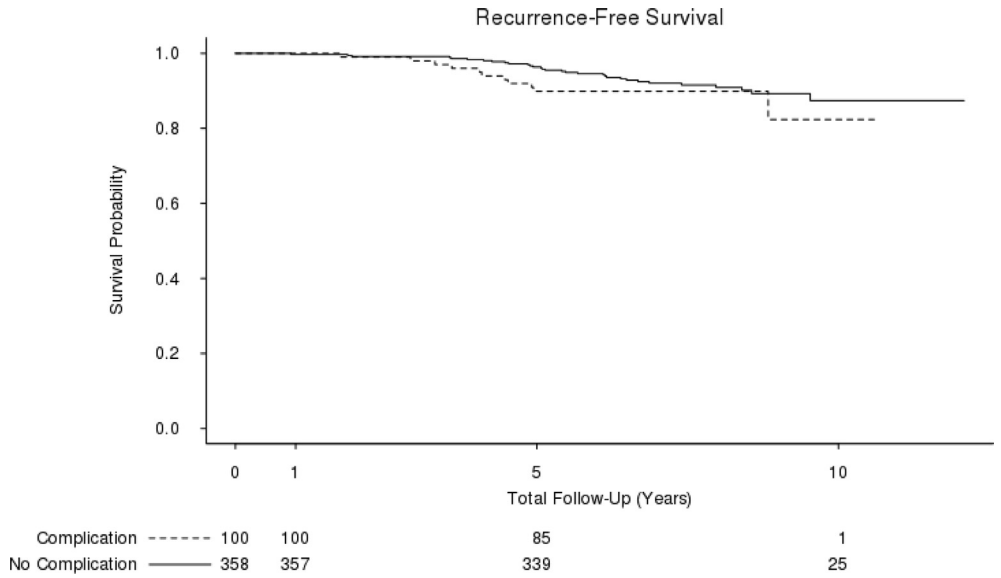

Fig. 1. Kaplan-Meier Graph shows the time to recurrence for patients with complications was not statistically different from patients without complications ($p = 0.12$).

In our treatment population, 65 of patients received NAC and 19% of this cohort experienced a post-operative complication, with no increase in recurrence compared to the remainder of the group. It could be hypothesized, that patients who received NAC had the more aggressive tumors, larger tumor size or nodal burden and receiving chemotherapy as the first treatment was beneficial in removing the post-operative complications from the equation of risk of recurrence for delay in receiving adjuvant systemic therapy.

Our study is limited by being retrospective and having small numbers of advanced stage cancers (low numbers of larger T stage, advanced N stage and over all Stage III cancers) who had IBR performed. IBR was most likely only offered as a delayed procedure in this higher-risk patient population. Given that 86% of patients were stage I or II, there were accordingly also a low number of recurrences and deaths. This limits our ability to make definitive statements on the relationship between post-operative complications following mastectomy with IBR and breast cancer survival. However, with over 458 patients and over 7.5 years of follow up, we find no significant association between IBR complications and breast cancer recurrence is this cohort. We contribute additional data supporting obesity as a risk factor for post-operative complications following mastectomy with IBR. This risk for complications increases with the degree of obesity. The option of delayed reconstruction following definitive treatment of the cancer and subsequent intentional weight loss is an option that could be offered to the morbidly obese patients due to the complication risks.

When counseling women on having mastectomy with IBR, it is important to take these patient factors into consideration. Patients need to be aware that their medical conditions and lifestyle behaviors can affect their final cancer treatment outcome and delay their treatment time. Our data does not show an association between surgical complications and increased risk in recurrence, but this differs from other studies. More studies are needed to better delineate if this association is real or, as our study suggests, related to tumor factors. Our study confirms that the increasing degree of lymph node involvement is the strongest predictor of increased risk of recurrence, more than complications or delayed time to treatment.

Summary

Wound complications following mastectomy with immediate breast reconstruction (IBR) were associated with increased time to adjuvant therapy but did not increase breast cancer recurrence.

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