

January 2013

Radiation Therapy And Expander-Implant Breast Reconstruction: Analysis Of Timing And Complications

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RADIATION THERAPY AND EXPANDER-IMPLANT BREAST
RECONSTRUCTION:
ANALYSIS OF TIMING AND COMPLICATIONS

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Rachel Brett Lentz

Yale University School of Medicine, Class of 2013

RADIATION THERAPY AND EXPANDER-IMPLANT BREAST RECONSTRUCTION: ANALYSIS OF TIMING AND COMPLICATIONS. Rachel B. Lentz, Reuben Ng, Susan A. Higgins, Michael M. Matthew, Stefano Fusi, and Stephanie L. Kwei. Section of Plastic Surgery, Department of Surgery, Yale University, School of Medicine, New Haven, CT.

The optimal timing of expander-implant exchange in the setting of post mastectomy radiation remains unclear with prior reports yielding inconsistent and variable results. The purpose of this study was to characterize complications associated with the sequencing of expander-implant breast reconstruction before or after radiation therapy and to compare the outcomes between early (< 4 months) and late (>4 months) expander-implant exchange in the subset of patients who received radiation prior to exchange.

The medical records of all patients receiving post-mastectomy radiation therapy in the setting of tissue expander-implant breast reconstruction between June 2004 – June 2011 at Yale-New Haven hospital were reviewed retrospectively. Patients were first classified as having undergone expander-implant exchange prior to the initiation of radiation or after the completion of radiation. Patients who underwent expander-implant exchange after radiation were then classified as having undergone exchange early (<4 months following radiation) or late (>4 months following radiation). All complications requiring additional surgery or hospitalization were recorded.

Fifty-five eligible patients were identified as having undergone 56 two-stage tissue expander-implant breast reconstructions. 22 reconstructions underwent exchange prior to radiation and 34 reconstructions underwent exchange following radiation. There was no significant difference in overall

complication rate (54.55% vs 47.06%, $p=0.785$) or reconstruction failure rate (13.64% vs 20.59%, $p=0.724$) between the two cohorts. 20 reconstructions underwent exchange <4 months following radiation and 14 underwent exchange >4 months following radiation. There was no significant difference in overall complication rate (40% vs 57.14%, $p=0.487$) or failure rate (25% vs 14.29%, $p=0.672$) between the two groups. Trends suggest a higher rate of infection in patients who underwent earlier exchange (30% vs 14.29%, $p=0.422$) and a higher rate of capsular contracture in patients who underwent later exchange (5% vs 21.43%, $p=0.283$), however statistical significance was not reached.

Our findings suggest that neither the sequencing nor timing of expander-implant exchange in the setting of radiation has an impact on overall complication or reconstruction failure rate. However, the timing of exchange may impact the type of complication encountered.

Acknowledgements

The work described herein was performed in the Section of Plastic Surgery, Department of Surgery, Yale University School of Medicine, New Haven, CT. It was conducted through the support of the NIH-CTSA fellowship.

The thesis author would like to acknowledge Stephanie Kwei, M.D., for her mentorship and guidance throughout this project. Additionally, the author would like to thank Susan Higgins, M.D., Michael Matthew, M.D., Nancy Kim, M.D., Stefano Fusi, M.D., and Reuben Ng for their assistance.

This research was presented at the Northeastern Society of Plastic Surgeons in Boston, Massachusetts, September 2012 and has been accepted for upcoming publication in *Annals of Plastic Surgery*.

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I. INTRODUCTION

Breast cancer remains the most commonly diagnosed cancer in women. Recent statistics indicate that 1 in every 8 American women will develop breast cancer at some point over the course of her lifetime(1). Over the past decade, there has been a marked rise in the number of women seeking breast reconstruction as part of their breast cancer treatment, with over 96,000 breast reconstruction operations performed in the United States in 2011 alone (2). During this same time period, the prevalence of adjuvant oncologic therapies, including chemo-and radiation therapies has increased as well. Ultimately, the management of breast cancer today requires a multidisciplinary approach, and it has become imperative to gain a better understanding of the impact of breast reconstruction on adjuvant treatments, and the impact that these treatments have on reconstruction outcomes.

Following the diagnosis of breast cancer, a patient may be referred to a medical oncologist for hormonal or chemotherapy, a breast surgeon for a lumpectomy or mastectomy, a radiation oncologist for radiation therapy, and a reconstructive surgeon to explore their reconstructive options. Care must be taken to appropriately coordinate all of these elements in order to optimize both oncologic treatment and reconstructive results. Figure 1 depicts a possible timeline of breast cancer management.

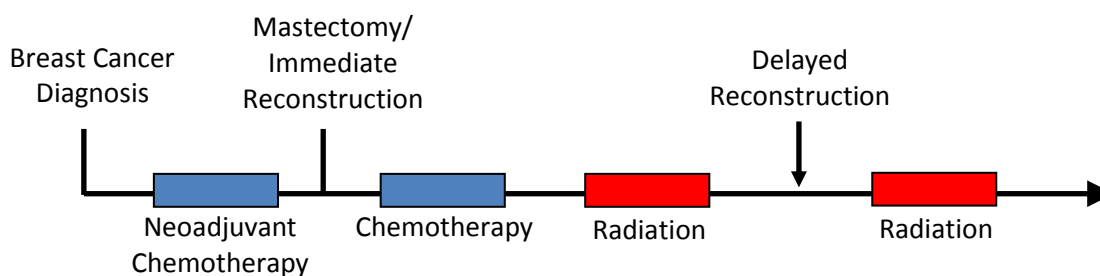


FIGURE 1. Breast Cancer Management Timeline

Several variables must be coordinated in the management of breast cancer patients. Neoadjuvant chemotherapy may be administered prior to mastectomy in order to shrink the primary tumor size. Reconstruction may be performed immediately at the time of mastectomy or in a delayed fashion, following the completion of adjuvant therapies. Radiation can be administered before or after reconstruction.

Post-mastectomy radiation therapy is becoming an increasingly common part of breast cancer treatment today; it has been shown to decrease the risk of locoregional recurrence and is associated with prolonged survival times (3).

Current absolute indications for radiation therapy include: presence of four or more positive lymph nodes, tumor size greater than 5cm, and positive margins following mastectomy (3-6). Factors associated with a higher risk of recurrence include: age at diagnosis < 40, histological grade 3 tumor, presence of lymphovascular invasion, <6 nodes removed during axillary dissection, significant nodal extracapsular spread, and presence of 1-3 positive nodes(7). Individuals with these characteristics are now being offered radiation at an increasing rate.

As a result, there has been a marked rise in the number of patients presenting for breast reconstruction who will also undergo radiation therapy as part of their

breast cancer treatment. Implant-based breast reconstruction in the setting of post-mastectomy radiation therapy remains a challenge. Radiation therapy engenders changes in mastectomy flap perfusion, which may result in infection, tissue necrosis, capsular contracture, implant extrusion, wound dehiscence, and complete reconstructive failures (8-11). The deleterious effect of radiation tends to be more pronounced with prosthetic reconstruction as compared to autologous reconstruction(12-14). However, autologous reconstruction is not always a viable option for patients. Autologous reconstruction necessitates an additional donor site and often requires a longer post-operative hospitalization and recovery period. Subsequently, implant based breast reconstruction remains the most popular option for immediate breast reconstruction today(15).

The majority of prosthetic reconstructions are performed as two stage tissue expander-implant reconstructions. Typically, the tissue expander is placed under the pectoralis major muscle, within the breast pocket at the time of mastectomy. Immediate placement of the tissue expander helps to preserve the integrity of the breast skin envelope and maintain the patient's natural inframammary fold. Periodic expansions of the tissue expanders occur over the course of weeks to months. Once the breast has reached an adequate volume and the soft tissue pocket has been appropriately expanded, the tissue expander is removed and exchanged for a permanent implant (figure 2).

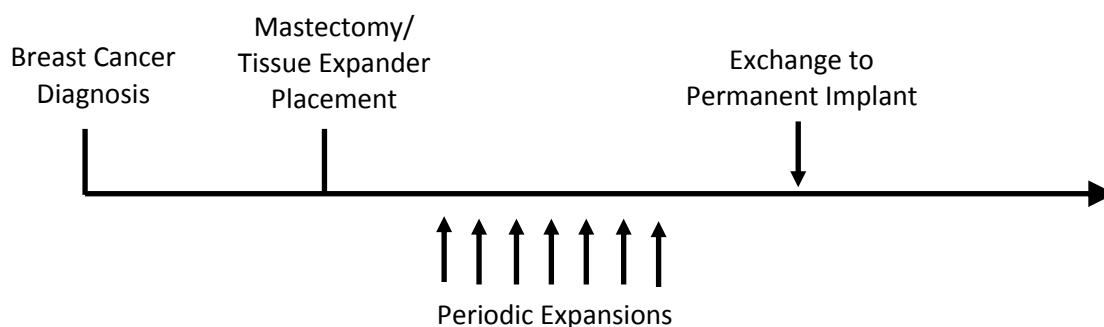


FIGURE 2. Tissue Expander-Implant Breast Reconstruction

Typically the tissue expander is placed at the time of mastectomy. Following period expansions, the tissue expander is replaced with a permanent implant.

The necessity of radiation therapy complicates the typical breast reconstruction timeline. Given the high risk of complications associated with radiation, many surgeons advocate delaying reconstruction until all adjuvant therapies have been completed (12, 16). In Kronowitz's 2007 review of immediate versus delayed reconstruction, he reports that if radiation is required, delayed reconstruction is usually the best course, however, if radiation is not required, immediate reconstruction should be performed (16). The benefits of immediate breast reconstruction are well documented in the plastic surgery literature. Patients who undergo immediate reconstruction have been shown to have improved psychosocial well-being and superior final aesthetics when compared to those who undergo delayed reconstructions (17, 18).

Unfortunately, the requirement of radiation therapy in patients who are clinically node negative is often unknown at the time of mastectomy. Final pathology

reports may not be available until days later. In patients undergoing tissue expander-implant reconstruction, by the time the necessity of radiation has been determined, the tissue expander has already been placed.

At this point, the plastic surgeon and radiation oncologist are faced with the question of how to optimally coordinate the timing of the rest of the reconstruction with radiation treatment. Is it better to complete the two-stage reconstruction and perform the exchange to permanent implant prior to radiation, thus irradiating the permanent implant, or to perform the exchange following completion of radiation, thus irradiating the tissue expander?

Although complications of implant based breast reconstruction in the setting of radiation are well described, little is known about the physiological and temporal effects of how radiation therapy influences the sequence of two-stage expander-implant reconstruction. Prior studies that have attempted to answer this question have yielded inconclusive and inconsistent results with some reporting exchange prior to radiation results in fewer complications(19), while others report no difference(20-22).

Additionally, from an oncologic perspective, we know there is a therapeutic benefit to administering radiation soon after mastectomy. A 2003 review examining the impact of delayed initiation of radiation found that the 5-year local recurrence rate was significantly higher in patients whose radiation was started

more than 8 weeks after surgery(23). Does performing expander-implant exchange prior to radiation contribute towards a delay in initiation of radiation therapy? To date, no previous study has investigated this question.

Lastly, for patients who undergo exchange following the completion of radiation, there is limited data that describes the optimal time to wait following completion of radiation before proceeding with exchange to permanent implants. Most surgeons recommend waiting between 3 – 6 months following the completion of radiation before proceeding with exchange to permanent implant. However, these time frames are largely subjective and not evidence based.

Statement of Purpose

Purpose

The purpose of this study was to investigate and characterize the impact of timing of expander-implant exchange and post-mastectomy radiation therapy on breast reconstruction outcomes.

Specific Aims

The specific aims of this study were:

1. to characterize the complications associated with the sequencing of expander-implant exchange before or after post-mastectomy radiation therapy¹,
2. to determine the impact of sequencing of expander-implant exchange on delivery of radiation therapy, and
3. to compare the outcomes between early (< 4 months) and late (>4 months) expander-implant exchange in the subset of patients who received post-mastectomy radiation therapy prior to expander-implant exchange.

¹ To clarify, if the expander-implant exchange occurs prior to radiation, then the permanent implant is getting irradiated. If the expander-implant exchange occurs after radiation, then the tissue expander is getting radiated. Another way to interpret the first aim of our study is: to characterize the complications associated with radiating a permanent implant versus radiating a tissue expander.

Hypotheses

The null hypotheses were:

1. sequencing of expander-implant exchange before or after post-mastectomy radiation does not have an impact on complications,
2. sequencing of expander-implant exchange does not impact the delivery of radiation therapy, and
3. there is no difference between the outcomes of patients who undergo early or late expander-implant exchange.

As alternative hypotheses, the investigators posited that:

1. the sequencing of expander-implant exchange would impact the complications seen in reconstruction patients,
2. the sequencing of expander-implant exchange would impact the timing to radiation therapy administration, and
3. there would be a difference in outcomes in patients who undergo early versus late expander-implant exchange following radiation.

II. METHODS

Under the auspices of the Yale University School of Medicine's Human Investigation Committee, we identified all patients who underwent tissue expander-implant breast reconstruction at Yale New Haven Hospital and received post-mastectomy radiation therapy as part of their breast cancer treatment between June 2004 – June 2011.

A de-identified database was then created and maintained by the thesis author for the purposes of this study. An extensive retrospective review of patient medical records was performed in order to screen for possible study inclusion and collect demographic, therapeutic, and operative data for subsequent analysis.

In total, seventy-three patients were identified as having undergone immediate tissue expander placement at the time of mastectomy followed by radiation therapy at Yale New Haven Hospital. Thirteen of those patients were excluded because they chose to undergo autologous reconstruction instead of exchanging their expanders for permanent implants following radiation therapy. An additional five patients were excluded because their tissue expanders were permanently removed prior to implant exchange, thus they did not complete the two-stage expander-implant reconstruction. For patients who underwent bilateral breast

reconstruction and received post-mastectomy radiation to both breasts, each breast was recorded as an independent data point.

After exclusions, a total of fifty-five eligible patients were identified with fifty-six breasts that underwent completed tissue expander-implant reconstruction and received post-mastectomy radiation therapy.

Sequencing of Expander-Implant Exchange and Radiation

In order to address the first aim of this study, the impact of the sequencing of expander-implant exchange on reconstructive outcomes, we divided our sample into two cohorts: breasts that underwent expander-implant exchange prior to the initiation of radiation therapy and breasts that underwent expander-implant exchange after the completion of radiation therapy (figure 3). The primary outcomes of interest were complications requiring additional, unplanned operations and hospitalizations.

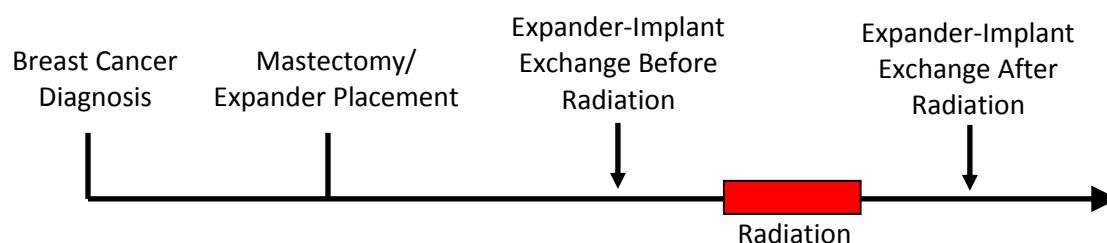


FIGURE 3. Sequencing of Expander-Implant Exchange and Radiation

The sample of eligible breasts was divided into two cohorts: those that underwent expander-implant exchange before radiation (irradiating the permanent implant)

and those that underwent expander-implant exchange after radiation (irradiating the tissue expander).

Impact of Sequencing on Delivery of Radiation Therapy

For the second aim of this study, the impact of sequencing of expander-implant exchange on delivery of radiation therapy, we excluded all patients who received neoadjuvant chemotherapy, as its administration may impact the timing of post-mastectomy adjuvant therapies. In the remaining patients, the number of days from mastectomy/tissue expander placement to the initiation of radiation therapy was recorded for comparison. The primary outcome of interest for this aim was the number of days to initiation of radiation.

Timing of Expander-Exchange Following Radiation

For the third aim of this study, comparing the outcomes between early and late expander-implant exchange following radiation completion, we only included breasts that underwent expander-implant exchange after the completion of radiation therapy. Breasts were then classified as having undergone exchange early, less than 4 months after radiation, or late, more than 4 months after radiation (figure 4). The time point of 4 months was chosen because it provided groups of relatively equal size and characteristics for comparison. The primary

outcomes of interest for this aim were complications requiring additional, unplanned operations and hospitalizations.

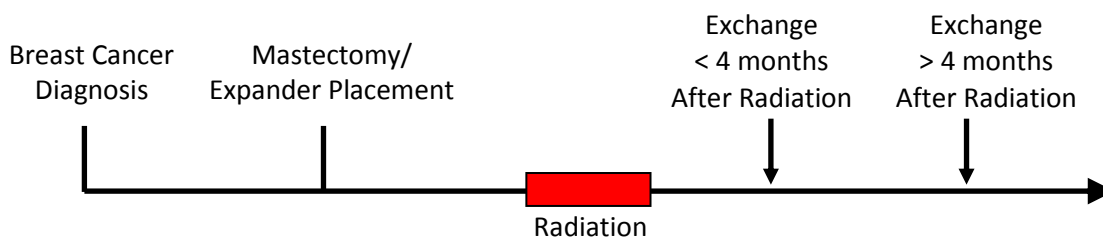


FIGURE 4. Timing of Expander-Implant Exchange After Radiation

The sample of eligible breasts that underwent expander-implant exchange after radiation (irradiated tissue expanders) was divided into two cohorts: those that underwent early exchange to permanent implant (within 4 months of completion of radiation therapy) and those that underwent late exchange to permanent implant (greater than 4 months after completion of radiation therapy)

All complications requiring additional surgery or hospitalization were recorded.

Complications included: cellulitis/prosthesis infection, wound dehiscence/implant extrusion, seroma, hematoma, capsular contracture and suspected implant leak.

For the purposes of this study, we defined reconstruction failure as removal of the permanent implant following initial successful expander-implant exchange.

Length of follow up was defined as the interval between date of mastectomy/expander placement and date of last provider note.

Statistical Analysis

Independent t-tests were performed to determine whether any significant differences existed between the groups being compared. Additional statistical analysis was performed using multivariate regression analysis, student's t test and Fischer exact test where appropriate. Statistical significance was determined where $p < 0.05$. Analysis was performed using IBM SPSS Statistics v20.0 software.

Contributions to Methods

The thesis author performed all aspects of this project including: thorough review of the literature, preparation and submission of HIC documents, data collection, database maintenance, and statistical analysis. In addition, I prepared an abstract with data from this project that was accepted for an oral presentation at the Northeastern Society of Plastic Surgeons in Boston, Massachusetts in September 2012. I also prepared a manuscript of this study that has been accepted for publication in an upcoming issue of *Annals of Plastic Surgery*.

III. RESULTS

Sequencing of Expander-Implant Exchange and Radiation

From June 2004 – June 2011, a total of 56 two-stage tissue expander-implant breast reconstruction surgeries were performed (by six different surgeons) that also underwent radiation as part of their breast cancer treatment. Of these, 22 completed exchange for permanent implant prior to initiation of radiation (irradiated their permanent implants) and 34 underwent exchange to permanent implant following completion of radiation (irradiated their tissue expanders).

Patient characteristics can be found in Table A.

TABLE A: Patient Characteristics

	Exchange Before Radiation (n = 22)	Exchange After Radiation (n = 34)	<i>p</i>
Age, mean (y)	48.1	44.8	0.25
BMI, mean (kg/m ²)	24.3	25.4	0.53
Race (n, %)			0.28
White	16 (72.7)	30 (88.2)	
Black	4 (18.2)	2 (5.9)	
Hispanic	2 (9.1)	1 (2.9)	
Other		1 (2.9)	
Smoking Status (n, %)			0.13
None	11 (50.0)	21 (61.8)	
Former	6 (27.3)	12 (35.3)	
Current	4 (18.2)	1 (2.9)	
Comorbidities (n, %)			
Diabetes	1 (4.6)	1 (2.9)	0.75
Hypertension	3 (13.6)	4 (11.8)	0.84
Follow Up Time, mean(mos)	46.0	27.3	0.00*

* Denotes statistical significance

There was no statistical difference between two groups' demographic data; the cohorts were similar with respect to age at mastectomy, BMI, race, smoking status, and comorbidities. The group that completed exchange following radiation had a significantly shorter follow up time.

TABLE B: Oncologic and Treatment Characteristics

	Exchange Before Radiation (n = 22)	Exchange After Radiation (n = 34)	p
Histology (n, %)			0.29
Infiltrating Ductal (IDC)	13 (59.1)	26 (76.5)	
Infiltrating Lobular (ILC)	4 (18.2)	3 (8.8)	
IDC with lobular features	2 (9.1)	4 (11.8)	
IDC with tubular features	1 (4.6)	0 (0.0)	
Mucinous carcinoma	0 (0.0)	1 (2.9)	
Adenosquamous	1 (4.6)	0 (0.0)	
Pathologic Stage (n, %)			0.41
0	0 (0.0)	3 (8.8)	
1	1 (4.6)	1 (2.9)	
2A	6 (27.3)	9 (26.5)	
2B	11 (50.0)	11 (32.4)	
3A	4 (18.2)	7 (20.6)	
3B	0 (0.0)	3 (8.8)	
Neoadjuvant Chemotherapy (n, %)	8 (36.4)	17 (50)	0.32
Adjuvant Chemotherapy (n, %)	17 (77.3)	25 (73.5)	0.75
Chest Wall XRT (n, %)	22 (100.0)	34 (100.0)	1
Supraclavicular XRT (n, %)	19 (86.3)	29 (85.3)	0.80
Axilla XRT (n, %)	1 (4.6)	7 (20.6)	0.10
Internal Mammary XRT (n, %)	0 (0.0)	3 (8.8)	0.15
Scar Boost XRT (n, %)	0 (0.0)	1 (2.9)	0.42
Mastectomy (n, %)			0.09
Simple	11 (50.0)	10 (29.4)	
Modified Radical	10 (45.5)	24 (70.6)	
Unknown	1 (4.6)	0 (0.0)	
Skin Sparing (n, %)	3 (13.6)	5 (14.7)	0.91
Nipple Sparing (n, %)	1 (4.6)	8 (23.5)	0.06
Implant Type – silicone (n, %)	9 (40.9)	28 (82.4)	0.00*
ADM (n, %)	9 (40.9)	27 (79.4)	0.01*

* Denotes statistical significance

ADM = acellular dermal matrix

Oncologic and treatment characteristics of the two groups can be found above, in Table B. The groups were similar in their oncologic characteristics including tumor histology and cancer staging. Additionally, the two groups were similar in the adjuvant therapies received. Of note, the group that completed exchange following radiation had significantly higher use of both acellular dermal matrix (ADM)² and silicone implants during the reconstruction process.

The overall complication and reconstructive failure rates can be found in figure 3. There was no significant difference between the two groups with respect to overall complication rate (54.5% vs 47.1%, $p = 0.58$). The group that underwent exchange after radiation experienced a higher reconstructive failure rate of 20.6% versus the 13.6% rate of reconstructive failure in the group that underwent exchange before radiation; however, this difference was not statistically significant.

² Acellular dermal matrix (ADM) is a soft tissue lattice that is becoming more prevalent in prosthetic based breast reconstruction. It is frequently employed as a sling or coverage reinforcement, providing the tissue expander or implant with additional support within the breast envelope.

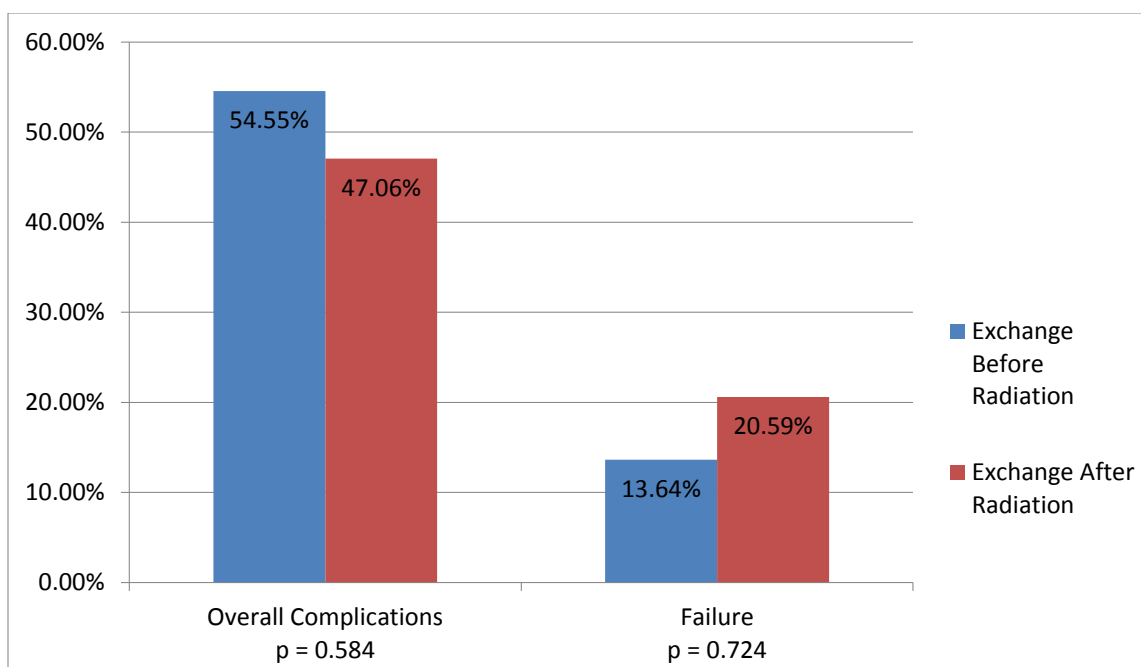


FIGURE 3: Overall Complication and Failure Rates

There was no statistically significant difference between the two groups with respect to overall complication or reconstructive failure rate.

The complications requiring additional, unplanned surgery or hospitalization that occurred in both groups included: infection, wound dehiscence/implant extrusion, seroma, hematoma, capsular contracture, and suspected implant leak. The specific break down of complications in each group can be found in Table C.

While there was no statistically significant difference between the two groups with respect to infection, wound dehiscence, seroma or hematoma, the group that underwent exchange prior to radiation, thus irradiating their permanent implant, experienced a significantly higher incidence of capsular contracture (40.9% vs 11.8%, $p < 0.05$) than the group that underwent exchange before radiation.

TABLE C: Complications Necessitating Surgery/Hospitalization

	Exchange Before Radiation (n = 22)		Exchange After Radiation (n = 34)		p
	n	%	n	%	
Infection	4	18.2	8	23.5	0.75
Wound Dehiscence/Extrusion	1	4.5	5	14.7	0.39
Seroma	0	0	1	2.9	1
Hematoma	0	0	2	5.9	0.51
Capsular Contracture	9	40.9	4	11.8	0.02*
Suspected Implant Leak	1	4.5	0	0	0.39

* Denotes statistical significance

The group that underwent exchange before radiation (irradiating the permanent implant) experienced significantly more operative capsular contracture complications (40.9% vs 11.8%, $p = 0.02$) than the group that underwent exchange after radiation (irradiating the tissue expander).

The results of a multivariate logistic regression analysis to explore predictors of experiencing complications can be seen in Table D. Of note, the sequencing of exchange with relation to radiation did not increase the odds of developing a complication (OR = 0.998, $p = 0.998$). The only variable associated with an overall increased risk of experiencing a complication was current smoking activity (OR = 14.866, $p = 0.046$).

TABLE D. Predictors of Complication Among All Patients

Variables	Odds Ratio	95% CI	P
Age	1.009	0.95-1.07	0.774
BMI	1.053	0.95-1.17	0.338
Current Smoker	14.866	1.04-211.64	0.046*
Silicone Implant	4.670	0.88-24.70	0.070
Neoadjuvant Chemotherapy	0.194	0.05-0.74	0.016*
Sequence of Expander-Implant Exchange	0.998	0.21-4.83	0.998

* Denotes statistical significance

Impact of Sequencing on Initiation of Radiation Administration

In order to address our second aim, the impact of sequencing of expander-implant exchange on delivery of radiation, we excluded all patients from our sample that received neoadjuvant chemotherapy. This left 14 patients who underwent exchange prior to radiation and 17 patients who underwent exchange following radiation. Both groups underwent adjuvant chemotherapy following mastectomy/tissue expander placement and prior to the initiation of radiation therapy. In the group that experienced exchange after radiation, the initiation of radiation therapy occurred an average of 188.0 days following mastectomy, while the group that underwent exchange prior to radiation therapy experienced an average of 220.4 days from mastectomy to initiation of radiation therapy, representing a statistically significant difference. (Table E).

Table E. Impact of Sequencing on Delivery of Radiation

	Exchange Before Radiation (n = 14)	Exchange After Radiation (n = 17)	<i>p</i>
Time to Radiation start, mean (days)	220.4	188.0	0.034*
*Denotes statistical significance			

Timing of Expander-Implant Exchange Following Radiation

To address the impact of timing of exchange following radiation, we only examined the patients who underwent exchange to permanent implant following radiation completion. Of those 34 patients, 20 underwent exchange to permanent implant within 4 months (early) of completing radiation therapy and 14 underwent

exchange to permanent implant greater than 4 months (late) following the completion of radiation therapy. The average time between radiation completion and exchange to permanent implant was 2.75 ± 0.76 months for the early group and 7.25 ± 2.81 months for the late group. Table F compares the patient and treatment characteristics. The groups were similar in demographics, comorbidities, and treatment characteristics.

TABLE F: Patient and Treatment Characteristics Across Early and Late Exchange Groups

	Early Exchange (n = 20)	Late Exchange (n = 14)	p
Age, mean (y)	47.1	41.6	0.13
BMI, mean (kg/m ²)	26.0	24.5	0.55
Race (n, %)			0.68
White	17 (85.0)	13 (92.9)	
Black	1 (5.0)	1 (7.1)	
Hispanic	1 (5.0)	0 (0)	
Other	1 (5.0)	0 (0)	
Smoking Status (n, %)			0.31
None	14 (70.0)	7 (50.0)	
Former	6 (30.0)	6 (42.9)	
Current	0 (0)	1 (7.1)	
Comorbidities (n, %)			
Diabetes	1 (5.0)	0 (0)	1
Hypertension	3 (15.0)	1 (7.1)	0.63
Follow Up Time, mean(mos)	26.5	28.5	0.68
Time from PMRT to exchange, mean(mos)	2.83	7.35	0.00*
Neoadjuvant Chemotherapy (n, %)	10 (50.0)	7 (50.0)	1
Adjuvant Chemotherapy (n, %)	13 (65.0)	12 (85.7)	0.25
Implant Type – Silicone (n, %)	18 (90.0)	10 (71.4)	0.20
Alloderm (n, %)	16 (80.0)	11 (78.6)	1

*Denotes statistical significance

In comparing the complications between early and late exchange, the group that underwent early exchange had a 40% overall complication rate, whereas the group that underwent late exchange had a 57.1% complication rate. This did not represent a statistically significant difference. When looked at overall reconstructive failure rate, the group that underwent early exchange had a 25% failure rate while the group that underwent exchange late had a 14.3% failure rate. Again, these differences were not found to be statistically significant.

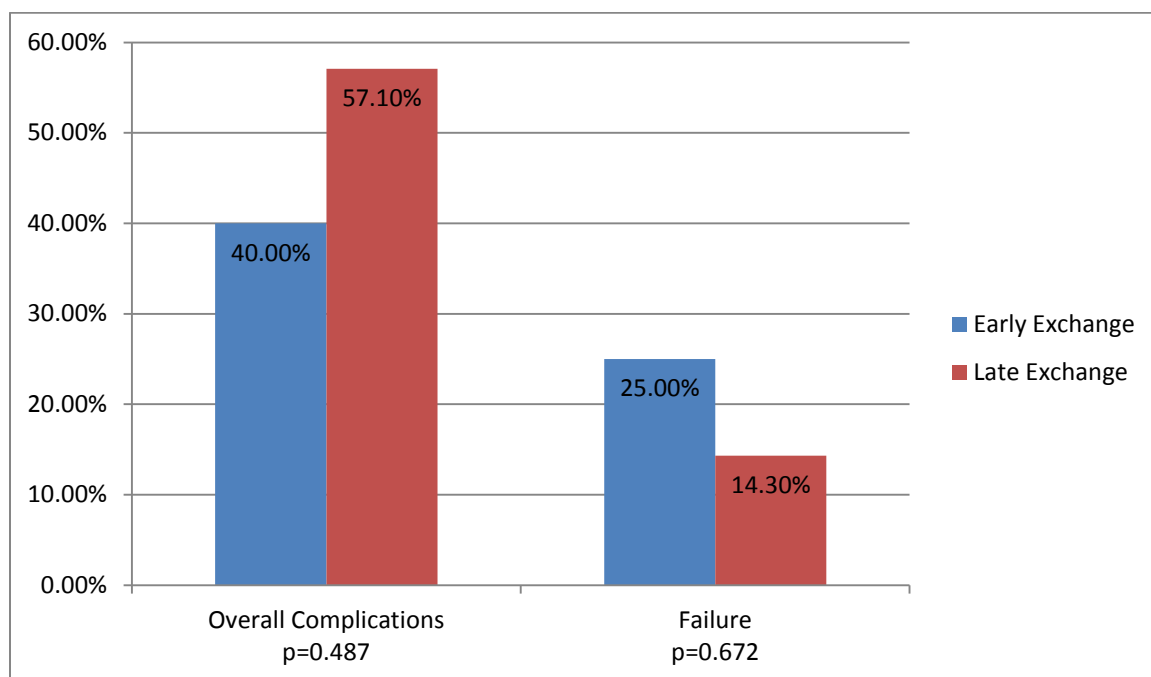


FIGURE 4: Comparison of Overall Complication and Failure Rates Between Early and Late Expander-Implant Exchange

There was no statistically significant difference in overall complication (40% vs 57.14%, $p = 0.487$) or reconstructive failure rate (25% vs 14.29%, $p = 0.672$).

TABLE G: Complications Necessitating Surgery/Hospitalization Across Early and Late Expander-Implant Exchange Groups

	Early Exchange (n = 20)		Late Exchange (n = 14)		p
	n	%	n	%	
Infection	6	30.0	2	14.3	0.42
Wound Dehiscence/Extrusion	3	15.0	2	14.3	1
Seroma	1	5.0	0	0	1
Hematoma	0	0	2	14.3	0.16
Capsular Contracture	1	5.0	3	21.4	0.28

*Denotes statistical significance

Analysis of specific complications using Fischer's exact test can be seen in Table G. When looking at the specific complications, there was no statistically significant difference between the groups with respect to rate of infection, wound dehiscence/extrusion, seroma, hematoma, or capsular contracture. Further exploring the data trends, it is interesting to note that the group that underwent exchange early experienced an infection rate of 30%, more than double the 14.3% infection rate seen in the group that underwent exchange late. Whereas, the group that underwent exchange late had a 21.4% rate of capsular contracture, four times the 5.0% rate of capsular contracture seen in the group that underwent exchange early. Given the small numbers of the sample, neither of these trends reached statistical significance.

IV. DISCUSSION

As the indications for adjuvant post-mastectomy therapy increase, we can anticipate seeing an increase in the number of patients presenting for breast reconstruction who will also undergo radiotherapy as part of their treatment. While many have championed the use of autologous reconstruction to minimize the high complication and reconstructive failure rates associated with irradiating implants, implant-based reconstructions remain the most common form of immediate breast reconstruction. Despite the increasing prevalence of this issue, there remains a lack of consensus regarding the optimal timing and coordination of radiation into the prosthetic reconstructive timeline. The purpose of this study was to evaluate the relationship between expander-implant exchange and timing of radiation administration, and how this relationship ultimately impacts reconstruction complications in the context of two-stage tissue expander-implant breast reconstruction.

Sequencing of Expander-Implant Exchange and Radiation

Our study represents one of the largest reported series investigating the impact of sequencing of expander-implant exchange with relation to radiation therapy. This report demonstrates that there is no statistically significant difference in overall complication or reconstructive failure rates if the exchange to permanent implant is performed before or after radiation, thus we were unable to reject our

initial null hypothesis. However, we did find that sequencing may impact the type of complication experienced, as our results indicated that patients who underwent exchange prior to radiation, thus irradiating their permanent implants, experienced a higher incidence of capsular contracture necessitating additional operative interventions.

The higher incidence of capsular contracture could possibly be explained by the fact that during most expander-implant exchange operations, a capsulotomy or capsulectomy is performed. A capsulotomy is a procedure in which the capsule (scar tissue that surrounds the tissue expander or implant) is surgically released. In a capsulectomy, the entire capsule is surgically removed. All patients who undergo prosthetic reconstruction develop some form of a capsule; it is the result of the body's normal physiologic immune response when presented with a foreign body. The capsule itself can be beneficial in supporting the expander or implant, helping to preserve breast shape and maintain breast projection. However, capsular contracture is a pathologic process that occurs when excess scar tissue develops, resulting in a physically painful, firm, and aesthetically displeasing breast. Radiation significantly increases the risk of developing capsular contracture. For patients that underwent exchange to permanent implant after radiation, any pathologic capsular formation that occurred surrounding the tissue expander could have been addressed at the time of the exchange to permanent implant, circumventing the need for an additional, unplanned operation. In the patients who underwent exchange prior to radiation,

thus irradiating their permanent implant, the only way to address any radiation-induced capsule formation was through an additional, unplanned capsulotomy or capsulectomy procedure.

Previous single center studies that have attempted to investigate the impact of sequencing of expander-implant exchange related to radiation have yielded variable and inconsistent results. The majority of these studies have been retrospective in nature and limited by a small number of patients. Furthermore, most single center studies have been limited by their own institutional protocols regarding sequencing, resulting in the publication of outcomes related to irradiating tissue expanders or outcomes related to irradiating permanent implants, with very few studies directly comparing the two.

Ascherman et al. explored the outcomes of patients who underwent two-stage expander-implant breast reconstruction, comparing groups that underwent neoadjuvant radiotherapy prior to mastectomy and groups that underwent radiotherapy during the tissue expander stage to patients who did not receive any radiotherapy at all. There was no analysis of patients who underwent radiation therapy to a permanent implant. Their finding of a 40.7% overall complication rate included both neoadjuvant radiation and adjuvant radiation groups. Based on this, they concluded that there is an overall increase in complications associated with radiation and prosthetic breast reconstruction. However, their analysis did not provide additional information regarding the

optimal timing of radiotherapy(11). Lin et al. found comparable 43.8% and 41.2% complication rates in patients who underwent neoadjuvant radiotherapy and adjuvant radiotherapy prior to exchange, respectively(24).

Cordeiro and McCarthy's analysis of tissue expander-implant outcomes included 29 patients who received neoadjuvant radiotherapy and 62 patients who were irradiated after expander-implant exchange. Their findings included a statistically significant increase in capsular contracture in patients who were irradiated after exchange as compared to patients who received neoadjuvant radiation (50.1% vs 20%)(25). Our findings of increased incidence of capsular contracture in patients who undergo exchange prior to radiation are consistent with this prior report.

Nava et al. conducted the largest retrospective study investigating the sequencing of exchange, consisting of 109 patients who underwent exchange prior to radiation therapy and 50 patients who underwent exchange following radiation therapy. Their results showed a statistically significant difference in complication and failure rate between the two groups with a 6.4% failure rate for exchange prior to radiation and 40% failure rate for exchange following radiation, contrary to our results which suggested that there is no difference in overall complication or failure rate with respect to radiotherapy sequencing(19). Of note, our study only included patients who had completed both stages of tissue expander-implant reconstruction, whereas the Nava study included patients who

had their reconstructions fail during the tissue expander stage and patients who opted for autologous reconstruction instead of an implant following tissue expansion. If we had included the patients who experienced failure during the tissue expander stage and patients who chose to undergo autologous reconstruction following undergoing radiation to their tissue expanders, we also would have seen a much higher complication and failure rate in the group that underwent exchange to permanent implants after radiation completion.

Of note, when we performed our multivariate regression analysis, examining the variables that could be predictors of increased complications, sequencing of the expander-exchange was not associated with worse outcomes. The only variable that was associated with worse outcomes was smoking. This finding is consistent with the literature. In Petersen et al.'s 2012 retrospective study of 208 prosthetic breast reconstruction patients found smoking to be the most significant risk factor for infection and post-operative complications(26).

The limitations of this report include the retrospective nature of the study. With retrospective reviews of this nature, we are limited in the amount and variability of information provided in the medical record. While our numbers reflect one of the largest series to investigate this question, there remained areas where statistical significance was not achieved. Performing a power analysis based on our results indicated that in order to observe the 7% difference in failure rate with 80% power, we would need an n of 390 patients in each group. No previous

single institution study that has explored this subject has reached this sample size, suggesting that a multi-institutional study may be the best way to answer this question in the future.

Additionally, we only included patients who had completed two-stage expander-implant reconstruction. By excluding both patients who experienced failure or permanent removal of their tissue expander without undergoing implant reconstruction and patients who opted to undergo flap reconstruction following tissue expander radiation, it is possible that we minimized the actual complication rate experienced in the irradiated tissue expander group.

The mastectomies and breast reconstruction operations were performed by a number of different surgeons. Reconstructive surgeon preference has a significant impact on the time course of when operations occur with two-stage expander-implant breast reconstructions. However, our total sample size was too small to control for the impact of surgeon bias.

Impact of Sequencing on Initiation of Radiation Administration

From an oncologic viewpoint, radiation oncologists would prefer to initiate radiation therapy as soon as possible following mastectomy. The results of our study indicated a statistically significant delay of 32 days in the initiation of post-mastectomy radiation therapy administration when the exchange procedure

occurs prior to radiation start. The clinical significance of this delay is not currently known. Prior studies examining the impact of immediate breast reconstruction on oncologic outcomes have indicated acceptable disease control(27). This is the first study to examine the impact of sequencing of implant exchange on initiation of adjuvant radiation.

Logically, it makes sense that there would be a delay when performing the exchange prior to radiation administration. Typically, radiation oncologists will not proceed with radiation administration until a patient is well healed post-operatively. Furthermore, if there are any signs of infection or wound complications following the operation, this could further delay the start of radiation administration as it would add additional days or even weeks until the skin is satisfactorily healed enough to begin radiation therapy.

Timing of Expander-Implant Exchange Following Radiation

The duration of time to wait following radiation completion before proceeding with expander-implant exchange remains a question of clinical judgment for most surgeons. For patients who will not receive radiation, the literature is supportive of proceeding with exchange to permanent implants as early as 1 month following the completion of expansion (28, 29). Understandably, the addition of radiation complicates this timeline, and current recommendations range from

waiting anywhere from 3-6 months following radiation completion before proceeding with additional reconstructive operations (28, 30, 31).

While our results suggest that there is no difference in overall complication or failure rates between groups who underwent exchange <4 months and >4 months following radiation therapy, there does appear to be a trend in the types of complications, with respect to the time of exchange. Patients who underwent exchange earlier had a higher incidence of cellulitis, whereas patients who underwent exchange later had a higher incidence of capsular contracture.

The pathophysiology of radiotherapy's effects on skin and soft tissue may explain these differences in complication type. The acute changes related to radiation occur within the first 70 days following radiation administration. They include erythema, skin reactions, and moist desquamation. All of which may leave the skin more susceptible to infection and possible cellulitis. The later effects of radiation are related to dermal injury and include tissue atrophy, subcutaneous fibrosis and necrosis, which may contribute toward the higher rates of capsular contracture seen in patients who underwent exchange later.(32)

Most recently, in 2012, Peled et al., were the first to explore this question of timing of exchange following radiation in the literature, comparing the failure rates of 88 patients who underwent expander-implant exchange less than 6 months after completion of post-mastectomy radiation therapy to 39 patients who

underwent exchange at least 6 months following post-mastectomy radiation therapy. Contrary to our findings, their results indicated a statistically significant increase in failure of 22.4% vs 7.7%, $p = 0.036$, in the group undergoing exchange earlier. Additionally, when they further subdivided the time interval of exchange following radiation, they found the highest rate of failure, 28.6%, in the group that underwent exchange less than 3 months following radiation completion as compared to the 17.9% failure rate in the group that underwent exchange between 3 to 6 months following radiation completion.(31) Our findings also indicated a higher failure rate in the group that underwent reconstruction earlier (25% vs 14.29%), however these results did not reflect a significant difference. It is possible that as our numbers increase, this difference may become more pronounced, and we would be able to draw similar conclusions. Additionally, implant exchange occurred sooner following radiation completion at our institution with a mean time between radiation and exchange to permanent implant of 2.75 months and 7.25 months in our study, while their study had a mean time between radiation completion and exchange of 3.4 months and 8.6 months.

The small sample size of our study limited the power of our generated results, and we were unable to reach significance when we were comparing specific complications between groups. In order to obtain a better understanding regarding the impact of timing of exchange following radiation completion on outcomes, it would be necessary to perform a larger study with an greater

number of patients in each group. Performing a power calculation based on these results indicated that in order to see the 12% difference in failure rate with 80% power, we would need an n of 176 patients in each group. Again, this would be another question that may be better served by performing a multi-institutional study, where we're able to analyze outcomes from a greater pool.

As mentioned previously, the fact that our study contained the results of six surgeons, as opposed to solely examining the outcomes of a single surgeon introduced some degree of surgeon bias into this study. The decision on when to proceed with expander-implant exchange following radiation is largely at the surgeon's discretion, and many have well developed preferences of which they follow. Our sample size was too small to control for this factor.

CONCLUSION

Our findings suggest that neither the sequencing nor the timing of expander-implant exchange in the setting of post-mastectomy radiation therapy has an impact on overall complication or reconstruction failure rate. The timing of exchange, however, may have an influence on the types of complications experienced by patients. Performing implant exchange prior to radiation, and thus radiating a permanent implant, results in a higher incidence of capsular contracture, necessitating additional surgical revisions.

The sequencing of expander-implant exchange does impact the start time of radiation therapy administration. Performing the exchange prior to radiation can result in a delay of initiation of adjuvant therapy.

Additionally, while there was no difference in overall complication or reconstructive failure rates with respect to timing of exchange following completion of radiation, there may be an association with different types of complications depending on the timing of exchange. Performing exchange to permanent implant earlier following the completion of radiation therapy may result in increased risk of infectious related complications, whereas performing exchange later following the completion of radiation therapy may result in an increased risk of fibrotic related complications.

Ultimately, the management of breast cancer today requires the collaboration of a team of doctors from varying specialties in order to optimize both oncologic outcomes and reconstructive results. All patients who are presenting with newly diagnosed breast cancer should be provided with information regarding the various treatment modalities and all available reconstruction options. Patients should also be made aware of the impact that adjuvant therapies can have on reconstructive outcomes.

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