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THE IMPACT OF CHEMOTHERAPY AND RADIATION ON THE REMODELING OF ACELLULAR DERMAL MATRICES IN STAGED, PROSTHETIC BREAST RECONSTRUCTION

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Abstract

Background—An acellular dermal matrix (ADM) used in prosthetic breast reconstruction will typically incorporate, in time, with the overlying mastectomy skin flap. This remodeling process may be adversely impacted in patients that require chemotherapy and radiation therapies that influence neovascularization and cellular proliferation.

Methods—Multiple biopsies of the submuscular capsule and ADM were procured from 86 women (N=94 breasts) undergoing exchange of a tissue expander for a breast implant. These were divided by biopsy location : submuscular capsule (control) as well as superiorly, centrally and inferiorly along the ADM. Specimens were assessed grossly for incorporation and semi-quantitatively for cellular infiltration, cell type, fibrous encapsulation, scaffold degradation, extracellular matrix deposition, neovascularization, mean composite remodeling score, as well as Type I and III collagen area and ratio. Five oncologic treatment groups were compared : no

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adjuvant therapy (untreated), neoadjuvant chemotherapy $\pm$ radiation ; and chemotherapy $\pm$ radiation.

Results—ADM and submuscular capsule biopsies were procured 45 to 1805 days after ADM insertion and demonstrated a significant reduction in Type I collagen over time. Chemotherapy adversely impacted fibrous encapsulation relative to the untreated group ($p=0.03$). Chemotherapy with or without radiation adversely impacted Type I collagen area ($p=0.02$), cellular infiltration ($p<0.01$), extracellular matrix deposition ($p<0.04$), and neovascularization ($p<0.01$). Radiation exacerbated the adverse impact of chemotherapy for gross incorporation as well as several remodeling parameters. Neoadjuvant chemotherapy also caused a reduction in Type I ($p=0.01$) and III collagen ($p=0.05$), extracellular matrix deposition ($p=0.03$), and scaffold degradation ($p=0.02$).

Conclusions—Chemotherapy and radiation therapy limit ADM remodeling.

INTRODUCTION

Acellular dermal matrices (ADMs) are used as an adjunct to prosthetic-based breast reconstruction^{1–4}. Perceived advantages including expedited tissue expansion, less pain, and improved lower pole fullness are countered by reports of increased seromas⁵, necrosis⁶, infection^{5, 6}, explantation^{6, 7}, and complications⁸. While the impact of ADMs on complications^{7, 9}, consistent aesthetic outcomes¹⁰, and cost^{11–15} is debated, there is little doubt that the successful biologic incorporation and vascularization of this material is important for optimizing outcomes¹⁶.

The impact of radiation on breast reconstruction overall has been studied in several clinical studies demonstrating a deleterious, but somewhat variable effect^{17–21}. Recently reviewed²², the specific performance of an ADM in a radiated field undergoing prosthetic breast reconstruction demonstrated higher complication rates relative to non-irradiated cohorts^{23–25}. In another study, irradiated patients undergoing prosthetic reconstruction supplemented with an ADM had fewer reconstructive failures requiring autologous tissue relative to historical controls that were radiated but not supplemented with an ADM⁴.

One can hypothesize that body mass index²⁶, radiation²⁷, smoking²⁶, and other factors known to impact mastectomy skin flap perfusion^{26–28} will also influence ADM incorporation²⁹. The mechanisms of action of several chemotherapeutic agents used to treat breast cancer work to limit DNA replication³⁰, cellular proliferation³¹, repair³⁰, migration^{32, 33}, and neovascularization^{32, 34}. All of these properties could attenuate ADM remodeling and incorporation. Moreover, corticosteroids given as an adjunct to chemotherapy to optimize tolerance of cytotoxic chemotherapy are also known to impact cellular proliferation and migration^{35–39}.

Delaying chemotherapy to facilitate a more robust incorporation of an ADM following immediate reconstruction, however, may be of concern⁴⁰. Fortunately, immediate reconstruction does not⁴¹, or only modestly delays adjuvant chemotherapy⁴². Neither neoadjuvant^{26, 43}, nor adjuvant chemotherapy was shown to increase complications with breast reconstruction in several^{26, 44}, but not all studies⁴⁵. Still, the specific impact of

adjuvant or neoadjuvant chemotherapy on the incorporation of an ADM in the context of prosthetic breast reconstruction has yet to be reported. Herein we report on the histological remodeling of an ADM in humans undergoing staged prosthetic breast reconstruction and the potential impact of neoadjuvant or postoperative chemotherapy, as well as radiation therapy.

MATERIALS & METHODS

Patient Selection

Women (N=86) undergoing staged unilateral or bilateral prosthetic breast reconstructions aided by an ADM between August 2007 and April 2013 were considered (N=94 breasts). This study meets the ethical guidelines for human research conduct and is approved by the Human Research Protection Office (HRPO) at the Washington University School of Medicine (Institutional Review Board # 201101959) and is also registered with clinicaltrials.gov (identification # NCT01060046). Written consent was obtained from every patient participant and demographic and clinical information including preoperative Baker Grade were obtained by chart review.

Specimen Collection

During implant exchange, specimens measuring 1 cm² were procured from the superior, central, and/or inferior aspects of the implanted biologic scaffold, and from the submuscular capsule (Fig. 1). Tissue procurement was avoided when the patient declined participation, was infected, or when the soft tissue envelope was so thin that biopsy was concerning for developing a wound or contour deformity. ADM incorporation was graded by the surgeon as “fully”, “mostly”, “minimally” or “not at all” and then immediately preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned at 5 µm, and stained.

Remodeling Characteristics

H&E stained slides were evaluated for six remodeling characteristics : cellular infiltration, cell types, host extracellular matrix (ECM) deposition, scaffold degradation, fibrous encapsulation, and neovascularization. A single slide of each specimen was evaluated under light microscopy at 100× magnification by a pathologist using a previously-reported semi-quantitative scoring system^{46,47, 48}. Specimens from the submuscular capsule of each patient served as an internal control for the ADM specimens. Scores ranged from 0 to 3, with higher scores representing more favorable remodeling characteristics. A mean composite remodeling score was calculated from the six component remodeling scores.

Collagen Distribution

Sirius Red/Fast Green (SR/FG) stained slides were prepared and evaluated as previously reported^{48, 49}. Sirius Red stains collagen fibers that are differentiated with red (Type I) to green (Type III) birefringence while Fast Green optimizes this effect and stains non-collagenous proteins. Biopsies from ADM and submuscular controls were photographed under cross-polarized light using an Axioskop 40® microscope (Carl Zeiss®, Thornwood, NY) equipped with a Zeiss Axiocam® at 400× magnification (n=10 photographs per

specimen). Axiovision 4.7® (Zeiss®) software was utilized to quantify both the areas (μm^2) stained red (Type I) and green (Type III) on each slide and their ratio calculated.

Statistical Analysis

Data was stored in Research Electronic Data Capture® (REDCap®). For approximately normal distributions (skewness < 5 and kurtosis < 5), summary statistics were reported as mean with standard deviation, student's t-test was used to compare two groups, and one-way analysis of variance (ANOVA) was used for multiple groups. For non-normal distributions (skewness > 5 and kurtosis > 5), summary statistics were reported as median with interquartile range (IQR), Wilcoxon rank-sum was used to compare two groups, and Kruskal-Wallis was used for multiple groups. To assess collagen deposition versus time, simple linear regression was performed using all ADM biopsies. Spearman's correlation was used to test for a linear relationship since our time variable was not normally distributed. All tests required two-sided = 0.05 to indicate statistical significance. All analyses were performed with either STATA v12.0 (College Station, TX) or Prism 6.0 for Mac OSX (GraphPad, La Jolla, CA).

RESULTS

Patient Characteristics

Patients undergoing immediate placement of a tissue expander and ADM were grouped as i) untreated [(-)C(-)R], ii) neoadjuvant chemotherapy alone [NC(-)R], iii) neoadjuvant chemotherapy with postoperative radiation [NC(+)R], iv) postoperative chemotherapy [(+)C(-)R], or v) postoperative chemotherapy and radiation [(+)C(+)R]. There were no statistically significant differences between groups with respect to age, BMI, race, diabetes, or smoking (Table 1). All patients receiving adjuvant therapy and the majority that did not require adjuvant therapy had breast cancer, while the remainder were prophylactic. Every enrolled patient was implanted with Alloderm Regenerative Tissue Matrix (Alloderm RTM; LifeCell Corporation, Branchburg, New Jersey). The majority of patients received a textured, shaped Allergan (Irvine, CA) tissue expander ($p < 0.01$), and the others a textured, shaped Mentor (Santa Barbara, CA) device. Baker grade was significantly higher in patients who received radiation therapy ($p < 0.05$) compared to those who did not (Fig. 2).

Duration of Implantation and ADM Remodeling

When characterized by the duration of ADM implantation, there were three broad groups (Supplemental Table 1) (See table which displays a global comparison of duration of implantation and Type I and III collagen in ADMs across treatment types.). Patients that did not require adjuvant breast cancer therapy (159 days), and those that required neoadjuvant

“SUPPLEMENTAL FIGURE & TABLE LEGENDS

Supplemental Figure 1. Representative histologic images after H&E staining. A) Composite score of “3”. B) Composite score of “2”. C) Composite score of “1”.

Supplemental Figure 2. Representative histologic images after Sirius Red and Fast Green staining of Type I and III collagen under polarized light at 400× magnification.

Supplemental Table 1. Global comparison of duration of implantation and Type I and III collagen in ADMs across treatment types.

Supplemental Table 2. Submuscular capsule histology between treatment groups.

Supplemental Table 3. Impact of adjuvant breast cancer therapy on ADM remodeling.

Supplemental Table 4. Impact of biopsy site on ADM remodeling in patients treated with Chemotherapy Alone (+)C(-)R

chemotherapy alone (168 days) were defined by the shortest median interval between mesh implantation and biopsy ($p<0.01$). The second group included patients that received neoadjuvant chemotherapy with radiation, as well as those that received chemotherapy alone as both had a median time of 208 days from implantation to ADM biopsy. The remaining patients received chemotherapy and radiation with a mean interval from ADM implantation to biopsy of 505 days.

Next, we sought to determine how duration of ADM implantation affected collagen remodeling. Collagen remodeling data from every treatment group and ADM biopsy site was plotted against time from implantation to biopsy (Fig. 3). At earlier time points (<500 days), there were highly variable quantities of type I and III collagen. Over time there were significantly lower concentrations of Type I collagen (Slope = -3.29 , p -value = 0.02), and a trend towards less Type III collagen (Slope = -1.37 , p -value = 0.12) particularly in patients treated with chemotherapy and radiation (Fig. 4) with no significant impact on the Type I:III collagen ratio (Slope = 0 , p -value = 0.74). Neither collagen content nor ratio had a statistically significant correlation with Baker Grade (Figs. 2–4).

Remodeling Characteristics and Collagen Distribution

Histologic scoring of the submuscular capsule did not vary significantly between treatment groups (Supplemental Table 2) (See table which displays submuscular capsule histology between treatment groups.). Grossly, the majority of ADMs were “fully” or “mostly” incorporated. Only (+)C(+)R patients had a significant ($p<0.05$) proportion of ADMs that were completely unincorporated (Fig 2), as corroborated by histologic evaluation (Table 2, Figs 4 & 5, Supplemental Figs 1 & 2) (See SDC1 which displays representative histologic images after H&E staining.). (See SDC 2 which displays representative histologic images after Sirius Red and Fast Green staining of Type I and III collagen under polarized light at $400\times$ magnification.). Patients treated with chemotherapy had significantly lower fibrous encapsulation scores ($p=0.03$) than untreated controls, while a reduction in ECM deposition in patients treated with chemotherapy also approached statistical significance ($p=0.08$). These differences occurred even though the time from mesh implantation to biopsy was significantly longer ($p<0.01$) in chemotherapy patients. Patients treated with chemotherapy with or without radiation were noted to have less Type I collagen ($p=0.02$), significantly less cellular infiltration ($p<0.01$), ECM deposition ($p<0.04$), neovascularization ($p<0.01$), and a lower mean composite remodeling score ($p<0.01$) than the untreated cohort. Patients treated with chemotherapy and radiation had significantly less cellular infiltration ($p=0.01$), ECM deposition ($p=0.04$), fibrous encapsulation ($p<0.01$), and neovascularization ($p<0.01$) compared to chemotherapy only. The chemotherapy and radiation group demonstrated less Type I collagen ($p=0.04$), and lower cell type ($p<0.01$), ECM deposition ($p<0.01$), fibrous encapsulation ($p<0.01$), and neovascularization ($p<0.01$) than untreated controls.

Neoadjuvant chemotherapy was associated with less Type I ($p=0.01$) and III collagen ($p=0.05$), ECM deposition ($p=0.03$), and scaffold degradation ($p=0.02$) relative to untreated patients (Table 3). Chemotherapy had a greater impact on ADM remodeling than neoadjuvant chemotherapy with radiation including less Type I collagen deposition ($p<0.01$)

and a significantly lower cell type score ($p<0.01$) (Supplemental Table 3) (See table which displays the impact of adjuvant breast cancer therapy on ADM remodeling.).

Biopsy Location and ADM Remodeling

A global comparison (Table 4) across ADM biopsy sites suggested that significant differences were present for the following remodeling scores: cellular infiltration ($p=0.03$), ECM deposition ($p=0.02$), scaffold degradation ($p=0.03$), neovascularization ($p=0.03$), mean composite score ($p=0.03$), and Type III collagen ($p=0.05$). Central biopsies also demonstrated lower scores for fibrous encapsulation ($p=0.02$), neovascularization ($p=0.03$), and mean composite score ($p=0.03$) in patients treated with chemotherapy alone (Supplemental Table 4) (See table which displays the impact of biopsy site on ADM remodeling in patients treated with Chemotherapy Alone (+)C;(-)R.).

DISCUSSION

Tissue remodeling of an ADM is dependent upon cellular infiltration, neovascularization, and the deposition of collagen and other ECM components. Remodeling is adversely impacted by cross-linking which limits cellular penetration into the scaffold⁵⁰, and by fibrous encapsulation and scar formation due to an inflammatory response^{47, 48, 51–53}.

Our understanding of ADM remodeling in prosthetic breast reconstruction is derived from clinical experience^{54, 55}, translational animal models^{53, 56–58}, and extrapolation from the hernia literature^{48, 59}. Remodeling of an ADM sandwiched between well-vascularized surfaces^{60–62} is expected to be more robust than around a prosthesis. When implanted subcutaneously an ADM incorporates within 14 weeks in rats^{61, 62}, and in rabbits a 21 sq cm ADM sheet interposed between viscera and a cutaneous flap revascularizes within 30 days⁶⁰, with evidence of early infiltration at 3 days in a human to rabbit xenograft⁵⁸. Conversely, rolled human ADM grafts with less vascularized surface contact have incomplete vascular penetrance at 4 weeks⁶³. In rats, a human ADM encircling a vascular pedicle that is otherwise isolated from its recipient bed has some revascularization by 7 days and early evidence of lymphatic reconstitution at 14 days⁶⁴. In rats treated with radiation⁶⁵, and non-human primates⁵⁶, ADMs prevent pseudoepithelial hyperplasia and capsular contracture for at least 10 weeks and may limit the periprosthetic inflammatory response in humans⁶⁶. This study differs from these valuable contributions since it specifically evaluates histologic remodeling of ADMs in breast cancer patients subjected to common therapies to time points as long as 1805 days (Fig 3) post-implantation.

Chemotherapy adversely impacted fibrous encapsulation and ECM deposition in this study. Fibrous encapsulation is mediated in part by an increase in the proportion of M1 macrophages that promote scar formation, versus M2 macrophages that facilitate ADM remodeling^{51, 52, 67} but also suppress natural killer and T-cells^{68–72}. In fact, several chemotherapeutic regimens used in breast cancer therapy including cyclophosphamide⁷³, doxorubicin⁷⁴, and paclitaxel disrupt the pro-tumor properties of M2 macrophages⁷⁵. By contrast, an increased concentration of M2 macrophages hinders the chemotherapeutic response in both a murine breast cancer model⁷⁶, and clinically⁷⁷. Consistent with other institutions⁴², our patients started chemotherapy within 8 weeks of reconstruction, during

active ADM remodeling. A paradoxical relationship between M2 macrophages, ADM remodeling, and chemotherapy deserves further targeted investigation^{51, 52, 68–72, 74, 75, 78–81}.

The impact of chemotherapy on ADM remodeling could have several etiologies. Anthracyclines are potent inhibitors of hypoxia-inducible factor 1 (HIF-1)-mediated gene transcription, and downstream vascular endothelial growth factor (VEGF) and stromal-derived factor 1^{82, 83}. Taxanes prevent angiogenesis by downregulating VEGF and angiopoietin-1 expression in tumor cells, and increasing the secretion of thrombospondin-1^{84, 85}. We observed a trend towards reduced neovascularization in patients treated with neoadjuvant chemotherapy relative to untreated controls ($p=0.07$; Table 3) with a comparable duration of ADM implantation (Supplemental Table 1).

Radiotherapy further attenuated ADM remodeling. Patients treated with radiation and chemotherapy versus chemotherapy alone had significantly less cellular infiltration, ECM deposition, neovascularization and more fibrous encapsulation (Table 2). During the acute phase of wound healing, radiation therapy has a variable effect on VEGF^{86–88}, and causes an overexpression of proinflammatory cytokines like TGF- β , TNF- α , and interferon- γ , leading to scar formation that can hinder remodeling^{87, 88}. Nitric oxide release, which induces collagen deposition, is impaired by radiation^{89, 90}. Matrix metalloproteinase-1 (MMP-1), a collagenase that contributes to ECM breakdown during normal tissue remodeling⁹¹, is inhibited by radiation therapy^{92, 93}. The dysregulation of matrix metalloproteinases are considered at least one mechanism by which radiation causes the disorderly deposition of collagen by fibroblasts, further hindering remodeling^{94, 95}. While our findings are consistent with the wound healing literature, the impact of radiation therapy on neovascularization is complex, as some evidence shows that radiation both promotes and hinders angiogenesis⁹⁶.

Collagen remodeling was also significantly impacted by chemotherapy and radiation. Alloderm, studied here, contains elastin, laminin, and collagen types I, III, IV and VII that remain after pretreatment with a freeze-drying process^{53, 63, 97, 98}. Collagen content is likely to vary significantly between pieces of Alloderm due to variations between donors, area of procurement, and thickness. Accordingly, we noted a highly variable distribution of collagen types I and III in specimens procured earlier rather than later (Fig 3). Type I collagen, prominent in remodeled scar tissue, dropped significantly over time relative to Type III collagen, produced by immature fibroblasts. Patients treated with chemotherapy and radiation had significantly less Type I collagen than untreated controls, an effect conceivably attributable to continued resorption of the ADM over time (Table 2). However, patients that received neoadjuvant chemotherapy without radiation also had significantly less type I and III collagen relative to untreated controls whose ADM was implanted for an equivalent duration (Table 3) suggesting neoadjuvant chemotherapy impacted collagen remodeling. Several chemotherapeutic agents are known to inhibit collagen synthesis^{99–105}. In particular, cyclophosphamide inhibits the hydroxylation of proline in collagen¹⁰⁵, anthracyclines like doxorubicin may inhibit a metalloprotease-mediated component of collagen synthesis¹⁰⁰, while 5-fluorouracil specifically blocks type I collagen synthesis by affecting c-Jun kinase activity¹⁰⁴. Corticosteroids, administered at the time of

chemotherapy^{39, 106}, also limit collagen synthesis^{107–109}. Capsular contracture, which was significantly higher in radiated patients, did not demonstrate a statistically significant correlation with collagen type, distribution or proportion in our study. Capsular contracture is characterized by little change in the Type I to III collagen ratio¹¹⁰, despite elevated collagen concentration^{110, 111} organized into thick, cable-like bundles¹¹². Baker grade and other measures of breast compliance^{113–116}, however, are less specific measures of capsular contracture in breast reconstruction¹¹⁷. Radiation induced skin fibrosis, a reduced skin envelope surface area following mastectomy, and the fill volume of the tissues expander will also impact breast compliance underscoring the contributions of these other parameters to Baker Grade beyond the histologic characteristics of the periprosthetic capsule.

Consistent with our hypothesis that ADM procured from a central location would be the slowest to remodel, global comparison showed an overall impact of biopsy site on ADM remodeling (Table 4). Centrally-located biopsies had significantly more fibrous encapsulation and less neovascularization in patients treated with chemotherapy (Supplemental Table 4). Superior and inferior biopsies were closer to the vascularized pectoralis and chest wall while the only vascularized tissue approximating the central biopsy was the mastectomy flap.

The clinical relevance of our findings, which show that radiation and chemotherapy influence ADM remodeling should be interpreted with caution. What characterizes complete ADM remodeling in breast reconstruction is not well defined. Recellularization and revascularization by host tissue are considered favorable for ADM incorporation, prevent seroma, and reduce the foreign body burden of the implanted scaffold. On the other hand, ADMs possess some unique properties suggesting that remodeling is incomplete, but still clinically favorable. Namely, the absence of migrating myofibroblasts or myocytes from adjacent muscular tissue that possess alpha-smooth muscle actin that would otherwise trigger capsular contracture⁵⁶. The ADMs evaluated in patients treated with chemotherapy and radiation demonstrated the poorest remodeling both grossly (Fig 2) and histologically, but it was sufficient to proceed with the next steps of reconstruction suggesting that it was not the only predictor of a successful outcome. Not only is a clear definition of complete ADM remodeling lacking, but it may not necessarily directly relate to favorable clinical outcomes.

We acknowledge several limitations with this study, and the need for further investigation. Numerous variables characterizing our patient population, chemotherapeutic regimens, mastectomy flap characteristics, and sheets of ADM used contributed to the heterogeneity of our study population and mandate more detailed analyses with a larger sample size. Our study population was retrospectively identified at the time of pending implant exchange, and subject to some selection bias. Biopsies were not performed in instances where a potential risk of impaired vascularity or contour deformity was perceived, nor were they performed in failures due to infection or necrosis. Resorbed or failed ADMs may have had poorer remodeling scores and impacted our results.

CONCLUSIONS

This study demonstrates that chemotherapy and radiation impact Type I and III collagen distribution as well as cellular remodeling of an ADM in the context of human breast reconstruction with a tissue expander. The clinical relevance and differential impact of these treatments requires further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Schematic representation of biopsy site locations. The capsular biopsy was taken from the subpectoral periprosthetic capsule while the superior, central, and inferior biopsies were taken as full-thickness ADM biopsies at the paramedian region of the breast.

Figure 2.

Summary of Baker Grade and gross ADM integration (“fully”, “mostly”, “minimally”, and “none”) by treatment group. *Baker grade was statistically significantly higher in patients treated with radiation (groups NC(+)R and (+C)(+)R) versus those who were not ($p < 0.05$).

** Gross evaluation revealed that patients treated with chemotherapy and radiation ((+)C(+)R) were significantly more likely to have a completely unincorporated ADM ($p < 0.05$).

Figure 3.

Linear regression analysis of Type I, Type III, and the Type I:III collagen ratio over time using aggregate data from all treatment types (45 to 1805 days) and all ADM biopsy specimens. Type I collagen area, in particular dropped over time ($p=0.02$).

Figure 4.

Total Type I and III collagen area and ratio over time. Data shown was obtained from central ADM biopsies harvested at time points ranging from 115 to 979 days post-implantation. Each value was generated from the mean pooled value of ten randomly assessed high-powered fields per biopsy. Radiation, and then chemotherapy demonstrate the greatest impact on Type I:III collagen ratio over time. Linear regressions were generated using 95% confidence intervals and Prism 6.0 software for Mac OS X.

Figure 5.

Total Type I and III collagen area and ratio per biopsy site. Data is shown as a mean for a particular biopsy site and treatment group independent of duration of implantation at the time of procurement.

Table 1

Summary statistics by treatment group.

	Treatment Type					P-Value
	(-)C(-)R (n = 42)	NC(-)R (n = 13)	NC(+)R (n = 8)	(+)C(-)R (n = 16)	(+)C(+)R (n = 15)	
Age (Years)	50.3 (39.6–61.0)	42.9 (35.2, 50.6)	47.0 (41.4, 53.6)	48.3 (35.5, 61.1)	50.0 (43.5, 56.6)	0.19
Duration of Mesh Implantation (Range in Days)	100–979	45 – 1805	176–476	161–552	322–658	<0.01
BMI	28.1	28.8	27.9	29.6	29.0	0.91
Mesh Type	Alloderm® 100%	Alloderm® 100%	Alloderm® 100%	Alloderm® 100%	Alloderm® 100%	-
Expander Type	Mentor 3/42 Allergan 39/42	Mentor 3/13 Allergan 10/13	Mentor 6/8 Allergan 28	Mentor 1/16 Allergan 15/16	Mentor 0/15 Allergan 15/15	<0.01
Race	Caucasian 38/42 African-American 4/42 Latin American 0/42 Asian 0/42 Pacific Islander 0/42 Native American 0/42 Other 0/42 Unknown 0/42	Caucasian 13/13 African-American 0/13 Latin American 0/13 Asian 0/13 Pacific Islander 0/13 Native American 0/13 Other 0/13 Unknown 0/13	Caucasian 8/8 African-American 0/8 Latin American 0/8 Asian 0/8 Pacific Islander 0/8 Native American 0/8 Other 0/8 Unknown 0/8	Caucasian 14/16 African-American 1/16 Latin American 0/16 Asian 0/16 Pacific Islander 0/16 Native American 0/16 Other 1/16 Unknown 0/16	Caucasian 12/15 African-American 2/15 Latin American 1/15 Asian 0/15 Pacific Islander 0/15 Native American 0/15 Other 0/15 Unknown 0/15	0.36
Diabetes	No 39/42 Yes 3/42	No 13/13 Yes 0/13	No 8/8 Yes 0/8	No 15/16 Yes 1/16	No 14/15 Yes 1/15	0.82
Breast Cancer	No 8/42 Yes 34/42	No 0/13 Yes 13/13	No 0/8 Yes 8/8	No 0/16 Yes 16/16	No 0/15 Yes 15/15	0.03
Smoking	No 27/15 Yes 15/42	No 9/13 Yes 4/13	No 5/8 Yes 3/8	No 11/16 Yes 5/16	No 8/15 Yes 7/15	0.90
Gender	Female 42/42	Female 13/13	Female 8/8	Female 16/16	Female 15/15	-

Table 2
Impact of Adjuvant Chemotherapy and Radiation on ADM Remodeling Scores and Collagen Deposition

	(-)C(-)R	(+)C(-)R	(+)C(+)R	(+)C(±)R	P-Value (-)C(-)R vs. (+)C(-)R	P-Value (-)C(-)R vs. (+)C(+)R	P-Value (-)C(-)R vs. (+)C(±)R	P-Value (+)C(-)R vs. (+)C(+)R
Time	159 (128–184)	208 (177–233)	505 (344–571)	280 (196–498)	< 0.01	< 0.01	< 0.01	< 0.01
Collagen I	7977 (3763–10614)	6646 (1310–9672)	5813 (325–10502)	6458 (383–9805)	0.08	0.04	0.02	0.62
Collagen III	2117 (1274–4404)	2463 (1386–4042)	1531 (300–7014)	2415 (357–4996)	0.88	0.32	0.52	0.76
Ratio	1.92 (1.06–5.99)	2.32 (1.21–5.04)	1.73 (1.00–3.24)	2.17 (1.03–4.28)	0.77	0.60	0.51	0.45
Cell Type	2.34	2.25	2.4	2.32	0.27	< 0.01	0.72	0.16
Cellular Infiltration	2.92	2.87	2.63	2.76	0.25	0.75	< 0.01	0.01
ECM Deposition	2.86	2.75	2.47	2.62	0.08	< 0.01	< 0.01	0.04
Scaffold Degradation	2.56	2.49	1.92	2.24	0.49	0.08	< 0.01	0.07
Fibrous Encapsulation	3	2.96	2.93	2.95	0.03	< 0.01	0.08	< 0.01
Neovascularization	2.78	2.72	2.30	2.53	0.43	< 0.01	< 0.01	< 0.01
Mean Composite	2.74	2.67	2.44	2.57	0.13	< 0.01	< 0.01	< 0.01

Table 3

Impact of Neoadjuvant Chemotherapy and Radiation on ADM Remodeling Scores and Collagen Deposition

	(-)C(-)R	NC(-)R	NC(-)R & NC(+)R Pooled	P-Value (-)C(-)R vs. NC(-)R
Time	159 (128–184)	168 (147–370)	206 (149–370)	0.03
Collagen I	7977 (3763–10614)	6633 (1276–8445)	7536 (3309–9723)	0.01
Collagen III	2117 (1274–4404)	1481 (680–3419)	2027 (793–5316)	0.05
Ratio	1.92 (1.06–5.99)	2.80 (1.16–10.14)	2.33 (1.21–7.00)	0.74
Cell Type	2.34	2.44	2.53	0.29
Cellular Infiltration	2.92	3	2.93	0.08
ECM Deposition	2.84	3	2.82	0.03
Scaffold Degradation	2.56	2.88	2.63	0.02
Fibrous Encapsulation	3	3	3	n/a
Neovascularization	2.78	2.92	2.75	0.07
Mean Composite	2.74	2.87	2.78	0.03

Table 4

Global comparison as a function of biopsy site

	Superior	Inferior	Central	P- Value
Time	203 (159–368)	203 (159–368)	203 (159–387)	0.90 [¥]
Cell Type	2.48	2.44	2.44	0.71 [¶]
Cellular Infiltration	2.78	2.93	2.78	0.03 [¶]
ECM Deposition	2.67	2.84	2.58	0.02 [¶]
Scaffold Degradation	2.35	2.53	2.19	0.03 [¶]
Fibrous Encapsulation	3	2.96	2.97	0.54 [¶]
Neovascularization	2.49	2.75	2.57	0.03 [¶]
Mean Composite	2.61	2.74	2.59	0.03 [¶]
Collagen I	8082 (1074–10790)	7459 (1260–10034)	7933 (3572–11140)	0.42 [¥]
Collagen III	1676 (927–4499)	2279 (1026–4176)	3744 (1310–7221)	0.05 [¥]
Ratio	2.63 (1.33–6.93)	2.58 (1.36–6.38)	1.85 (0.93–1.66)	0.13 [¥]

[¥]Kruskal-Wallis equality-of-populations rank test[¶]One-way analysis of variance test