Outcomes of Acellular Dermal Matrix for Immediate Tissue Expander Reconstruction with Radiotherapy: A Retrospective Cohort Study

Elizabeth S. Craig, MD; Mark W. Clemens, MD; John C. Koshy, MD; James Wren, BS; Zhang Hong, PhD; Charles Butler, MD; Patrick Garvey, MD; Jesse Selber, MD; and Steven Kronowitz, MD

Abstract

Background: Despite increasing literature support for the use of acellular dermal matrix (ADM) in expander-based breast reconstruction, the effect of ADM on clinical outcomes in the presence of post-mastectomy radiation therapy (PMRT) has not been well described.

Objectives: To analyze the impact ADM plays on clinical outcomes on immediate tissue expander (ITE) reconstruction undergoing PMRT.

Methods: We retrospectively reviewed patients who underwent ITE breast reconstruction from 2004 to 2014 at MD Anderson Cancer Center. Patients were categorized into four cohorts: ADM, ADM with PMRT, non-ADM, and non-ADM with PMRT. Outcomes and complications were compared among cohorts.

Results: Over 10 years, 957 patients underwent ITE reconstruction (683 non-ADM, 113 non-ADM with PMRT, 486 ADM, and 88 ADM with PMRT) with 1370 reconstructions. Overall complication rates for the ADM and non-ADM cohorts were 39.0% and 16.7%, respectively ($P < 0.001$). Within both cohorts, mastectomy skin flap necrosis (MSFN) was the most common complication, followed by infection. ADM use was associated with a significantly higher rate of infections and seromas in both radiated and non-radiated groups; however, when comparing radiated cohorts, the incidence of explantation was significantly lower with the use of ADM.

Conclusions: The decision to use ADM for expander-based breast reconstruction should be performed with caution, given higher overall rates of complications, including infections and seromas. There may, however, be a role for ADM in cases requiring PMRT, as the overall incidence of implant failure is lower than non-ADM cases.

Level of Evidence: 3

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aesthetic advantages have been tempered by the controversial data regarding seroma, infection, and other complication rates.\textsuperscript{10,12-15}

The beneficial impact that PMRT has on decreasing loco-regional recurrence in breast cancer patients has been well documented.\textsuperscript{16} In 2004, Kronowitz et al introduced the concept of "delayed-immediate" and "delayed-delayed" breast reconstruction, in an effort to preserve the breast footprint and skin envelope in cases in which the risk of PMRT is unknown.\textsuperscript{5} However, this has posed a growing challenge to reconstructive surgeons, as the literature is replete with evidence illustrating the deleterious effects of PMRT on expander/implant-based reconstruction, with complication rates as high as 58.8\%\textsuperscript{12,16,19}. In addition, the literature has highlighted the light proportion of patients in this population with unacceptable aesthetic results leading to expander/implant removal.\textsuperscript{19-21} While most reconstructive surgeons prefer autologous tissue reconstruction to expander/implant-based reconstruction in patients at risk for PMRT, it is not always feasible.

As indications for PMRT continue to grow, understanding the outcomes of ADM in a radiated field becomes critical. The purpose of our study was to examine the impact of ADM with PMRT on clinical outcomes in ITE by performing a retrospective cohort study, which included ADM/non-ADM and PMRT/non-PMRT cohorts.

METHODS

We retrospectively reviewed a prospectively maintained database of consecutive patients who underwent ITE breast reconstruction from June 2004 to December 2014 at The University of Texas MD Anderson Cancer Center. Patients were categorized into 4 cohorts: ADM, ADM with PMRT, non-ADM, and non-ADM with PMRT. Demographic information, comorbidities, perioperative data, operative data, and complications were collected for comparison. The primary outcomes evaluated were seroma (clinically appreciable fluid collection requiring drainage), infection (cellulitis requiring antibiotic treatment), delayed wound healing (incision opening greater than 5 mm), and MSFN (including sloughing, desquamation, and full-thickness loss requiring bedside or operative debridement). The timing of complications was evaluated by comparing both ADM and non-ADM groups, as well as PMRT and non-PMRT groups. Patients were excluded from the study if they received pre-mastectomy radiation therapy, or did not reach the endpoint of explantation or implant exchange and were lost to follow-up. This study was approved and carried out under the guidelines of the Institutional Review Board of MD Anderson Cancer Center.

Statistical Analysis

A univariate analysis was utilized to examine the associations between outcomes and patient characteristic. Patient characteristics that were found to have both associations and $P$ values less than or equal to 0.25 in the univariate analysis, were then included as independent variables in the multivariate generalized estimation model (GEE). The final multivariate model was determined using a backward-selection algorithm. Multivariate GEE was used to assess the impact of various confounders on patient outcomes. The analyses were performed in SAS 9.2 (SAS Institute, Inc., Cary, NC). The timing of occurrence of complications among the cohorts was compared using a 2-sided Wilcoxon rank sum test, with a $P$ value less than 0.05 considered significant.

In order to rule out temporal bias, outcomes between the first and last 5 years of the study were compared, and the rates of overall complications were found to be equivalent. In addition, plastic surgeons and breast surgeons were grouped by the number of cases performed and included in the multivariate analysis to evaluate surgeon technique or experience as potential confounders; however, these were also not found to be significant.

Surgical Techniques

Tissue expanders were placed in the subpectoral pocket. Reconstructions without ADM involved either partial or total muscle coverage with standard elevation of the serratus anterior and/or rectus fascia. Reconstructions utilizing ADM were performed by securing a sheet of ADM to the inferior border of the pectoralis muscle once it had been released from the chest wall as a pectoralis muscle extension. Intraoperative tissue expansion was performed to tissue tolerance. Drains were placed according to surgeon preference. On average, the length of drains was 10 days (range 7-22 days). Removal of drains was at the discretion of the attending physician and therefore was not standardized across all physicians. In general, drains were removed when output was less than 30 mL for 2 consecutive days.
Perioperative antibiotics were administered and, in general, continued postoperatively until all drains were removed.

**RESULTS**

One-thousand-three-hundred-seventy-six breast reconstructions in 957 patients with ITE (574 reconstructions performed with ADM, and 796 without ADM) met our inclusion criteria (Table 1). The type of ADM used was divided, as 24.7% of surgeons utilized SurgiMend (TEI Biosciences, Boston, MA) and 75.3% utilized Alloderm (LifeCell Corporation, Bridgewater, NJ). The type of mesh used in ADM reconstructions was analyzed against primary outcomes and found to have no influence. Fifteen percent of the entire cohort received PMRT, 27% received neoadjuvant chemotherapy, and 28% received adjuvant chemotherapy. The majority of mastectomies (90.4%) utilized a skin-sparing technique; 6% were nipple sparing. The average follow-up was 210 days (range, 146-304).

Demographics were comparable among all groups (Table 2), with the following exceptions. Patients in the ADM without PMRT cohort were older and had a higher incidence of diabetes than patients in the other cohorts (P = 0.002 and P < 0.001, respectively). Invasive disease and axillary dissections were statistically more prevalent in the cohorts who underwent PMRT than in those who did not. Nipple-sparing mastectomies were statistically more prevalent within the ADM without PMRT cohort (8.8%, P < 0.0008). Reconstructions completed with ADM had higher initial TE fill volumes than did those in the non-ADM groups, despite having similar preoperative bra volumes (258 cc versus 152 cc, respectively, P < 0.001).
Overall complication rate refers to all measured outcomes with the exception of explantation, which we considered a “reconstructive failure” and, therefore, reported separately. The incidence of complications (MSFN, infection, hematoma/seroma, dehiscence, and explantation) was reviewed within the cohorts and overall population (Table 3 and Figure 1). When analyzing the cohorts, data for 6 breasts had to be excluded from the radiated-ADM cohort due to incomplete radiation treatment data.

MSFN was the most common type of complication (Table 3). Higher preoperative bra volume, nipple-sparing mastectomy, PMRT, and the use of ADM were independent risk factors for necrosis. Active smoking was surprisingly not found to be an independent risk factor, but this was
increased the chance of seroma by threefold (seroma formation (along with higher bra volume), and of ADM was found to be an independent risk factor for patients with ADM but without PMRT at 10.9%. The use of ADM was associated with an increased risk of infection compared with no ADM [odds ratio (OR) = 1.93, P = 0.01]. Among the patients who did not receive PMRT, the use of ADM increased the chance of having an infection 2 and a half times (OR = 2.48, P = 0.002). For patients reconstructed without ADM, the effect of PMRT alone increased their chance of infection 3 and a half times (Table 4). In contrast, PMRT appeared to have no significant impact on infection rate in patients reconstructed with ADM (P = 0.60).

Only 33% of the patients who developed infections had a history of seroma; conversely, 9% had infections prior to being diagnosed with a seroma, but the majority of infections appeared to occur de novo. Seven percent of the patients, overall, developed seromas. Patients reconstructed with ADM who received PMRT had the highest incidence of seroma, at 13.6%, followed by the cohort of patients with ADM but without PMRT at 10.9%. The use of ADM was found to be an independent risk factor for seroma formation (along with higher bra volume), and increased the chance of seroma by threefold (P < 0.0001). Smoking, PMRT, and initial expander fill volume were not contributing factors for incidence of seroma.

Explosion occurred in 119 patients or 8.6% of the cohort overall. Age, BMI, PMRT, bra volume, intraoperative TE fill volume, nipple-sparing mastectomy, axillary dissection, and invasive disease were significant risk factors for explantation in the univariate analysis. Neither ADM nor PMRT were found to be independent risk factors for explantation overall. However, for patients who underwent PMRT, ADM was associated with fewer explantations and lower odds of explantation when compared with non-ADM patients (OR = 0.38, P = 0.04). In fact, the highest rate of explantation occurred in the non-ADM with PMRT cohort (20.4%, P = 0.0012). Within the non-ADM group, PMRT increased the odds of explantation threefold (OR = 3.19, P = 0.002).

The main reason for explantation overall was infection (both overall and among cohorts), which occurred in 46% of the explantations, followed by mastectomy skin necrosis, which occurred in 30.9%. Reasons for explantation other than complications comprised only 15% of all explantations and included pain, unsatisfactory aesthetic outcome, TE rupture, and need for/interference with further treatment (Table 4).

Multivariate analysis was performed to evaluate the role of preoperative variables in contributing to complications, and identified older age, higher bra volume, smoking, PMRT, and the use of ADM as independent risk factors for overall complication rate (Table 5). Notably, neither the use of either neoadjuvant or adjuvant chemotherapy, nor initial fill was associated with increased overall complication or explantation rates. While controlling for these factors and others, including preoperative bra volume, type of mastectomy, BMI, and smoking status, we were able to note several relationships among ADM, radiation, and the occurrence of complications (Table 6).

The timing of these complications occurring did not differ significantly between the ADM/non-ADM and PMRT/non-PMRT groups. The only differences that were identified were that nonirradiated TEs were explanted much later than non-irradiated TEs (median 111.5 days vs 56.0 days; P value 0.02) and the timing of seromas (15.0 vs 29.0 days, P value 0.001); mastectomy skin flap necrosis (15.0 vs 10.0 days, P value 0.01) was different between the ADM and non-ADM groups, although these differences are not clinically significant. There was no difference in radiated groups in terms of the timing of infection, seroma, or necrosis, or differences between the ADM groups in terms of timing of explantation or seroma occurrence.

**DISCUSSION**

While the literature is replete with data regarding the risks and benefits of ADM in ITE reconstructions, we performed the largest retrospective cohort study specifically aimed at assessing the impact of ADM in the setting of PMRT. As expected, the overall complication rate, as well as the incidence of infection and seroma, appeared to be higher in patients undergoing ITE with ADM; however, there were
fewer expander failures in the PMRT who utilized ADM. In fact, the use of ADM appeared to play a protective role in preventing re-operation and explantation in patients undergoing PMRT (Figure 2).

The overall complication rate of 26% in our study is slightly higher than that reported in the literature; however, this is likely due to the significantly larger sample of irradiated patients, a known risk factor for negative outcomes.22,23 Similar to previous reports, we found a higher complication rate in the ADM cohort than in the non-ADM cohort. In addition to age, BMI, PMRT, and smoking, risk factors previously reported in the literature, bra volume was found to be an independent risk factor for complications. While both BMI and bra volume were found to be significant variables in the univariate analysis, only bra volume was found to be significant in the multivariate analysis. Bra volume may, therefore, be a more specific indicator for breast-related outcomes, as a large BMI does not always correspond with large breast size.5,24

The MSFN rate in both ADM and non-ADM patients is greater than that reported in the literature.10,22,23 However, it should be noted that for a given bra volume, both ADM cohorts (irradiated and non-irradiated) had intraoperative fill volumes that were 100 cc higher on average than those of the non-ADM cohorts. While ADM allows for a greater intraoperative fill volume, this advantage can place additional pressure on thin, ischemic flaps, contributing to higher rates of MSFN. Judicious clinical assessment of skin viability, and perhaps the use of SPY can offer additional assistance in determining tissue tolerance to fill volumes. PMRT was also found to be a significant risk factor for MSFN, and this may be secondary to more aggressive mastectomies being performed in the setting of advanced disease (as indicated by the need for PMRT). Other contributing risk factors to mastectomy skin necrosis—bra volume and the nipple-sparing technique—are fixed variables and should therefore be included in preoperative discussions with the patients.

Both PMRT and ADM were found to be significant risk factors for infections; however, other factors may have either over- or underreported the true incidence of infection. It should be noted that we have a “red breast clinic” at our institution where patients with suspected infections undergo immediate ultrasonographic evaluation, an infectious disease consult, and drainage of any fluid collection by interventional radiology as part of a standard protocol. Our approach to diagnosing and treating cellulitis with intravenous antibiotics likely differs from that of other practices and might lead to the overestimation of the true incidence of infection, particularly in our ADM patients. However, given that infection is the leading cause of explantation, it is possible that our aggressive approach might also increase our ability to salvage reconstructions.

Explantations occurred in 8.6% of our patient population, the majority of which was in irradiated patients treated without ADM. Radiation is a known risk factor for

### Table 6. Multivariate Everything

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<td>Overall complication</td>
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<td>3.16 (2.28-4.39)</td>
<td>1.95 (1.19-3.19)</td>
<td>4.61 (2.72-7.83)</td>
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Multivariate analysis examining the role of ADM and radiation on overall complications, dehiscence, infection, necrosis, seroma, and explantation. Odds ratios (OR) were not performed if statistical significance was not present. The non-ADM and non-radiated cohort was used as a point of reference for OR determinations. OR reported as OR (95% CI).
Figure 2. Example of prosthetic reconstruction of the radiated breast with acellular dermal matrix. Patient is a 41-year-old female who required bilateral skin-sparing mastectomy and tissue expander reconstruction with ADM as a pectoralis major extension for soft tissue support. (A, B, C) Appearance of skin 6 months following 3D conformal 50 gy external beam radiation therapy with incision and internal mammary boost. Patient received device exchange and one round of autologous fat grafting. (D) Appearance of incisions (E) at 1 month of the right non-radiated breast (F) and slower healing of the left radiated breast. Implant choice was a shaped gel extra projection 650 mL implant on the right breast and a 700 mL implant on the left breast. Postoperative course was uncomplicated with no further revisions, (G, H, I) appearance at 2 years postoperatively and (J) by 3D surface imaging (taken with 3dMD LLC Camera Systems, Atlanta, GA).
infection, but its impact on ADM is relatively unknown. The effect of radiation on patients reconstructed without ADM was profound, increasing the infection rate 3 times. Similarly, the explantation rate of patients reconstructed without ADM who underwent PMRT was 3 times higher than that of non-ADM patients who did not undergo PMRT (20.4% vs 5.9%, respectively). In contrast, patients reconstructed with ADM experienced no difference in infection or seroma rate in response to radiation. Radiation therapy is a known risk factor for complications in non-ADM
reconstructions; however, studies are just beginning to report the effects of radiation on ADM reconstructions. An evidence-based review performed by Clemens and Kronowitz suggests a potentially protective effect of ADM in the setting of PMRT, with decreased cellular infiltrates and decreased capsular contracture rates.\textsuperscript{5,13,19,21,25,27–32} Seth et al published a case-control series in 2012 with 592 ITE reconstructions and found no significant increase in complication rate following PMRT in patients reconstructed with ADM.\textsuperscript{33} This is in contrast to the observed threefold increase in complication rate experienced by the non-ADM group following PMRT ($P = 0.003$). Unfortunately, a contrast analysis was not performed between the irradiated ADM and non-ADM groups to evaluate how ADM reconstructions behave with respect to traditional techniques in the setting of radiation. In addition, the ADM and non-ADM cohorts had varying demographic profiles that may have confounded their outcomes. While this study lends support to previously reported data, questions still remain regarding the true impact of PMRT on ADM in breast reconstruction, how this compares to traditional techniques, and how this influences patient selection criteria.

Our data support the conclusions by other authors that ADM plays a protective role in irradiated patients by limiting explantation.\textsuperscript{23,26} Among these, our study is the largest study to date using cohort comparisons to illustrate the impact of ADM on patients undergoing PMRT.\textsuperscript{34–38} We theorize that ADM has a higher infection and seroma rate prior to its incorporation. Use of antibiotics, aggressive treatment of “red” breasts, and prolonged use of drains are imperative for promoting incorporation. Once incorporated, the ADM may serve as an additional vascularized layer over the TE, protecting it from bacterial contamination. Patients without ADM do not experience an “incorporation period,” and therefore have initially lower infection and seroma rates. However, in the setting of radiation, non-ADM patients do not have the advantage of an additional vascularized ADM layer and are thus more susceptible to bacterial contamination, leading to higher explantation rates.

In 2012, Nahabedian published the following indications for ADM: women with A to D cup size breasts, regardless of age, who are not morbidly obese, have not had prior radiation, and are not active smokers.\textsuperscript{14} Similarly, Ganske et al described changes in their patient selection criteria and postoperative management that played a critical role in the success of their implant-based reconstructions with ADM.\textsuperscript{4} Intraoperative tailoring of the ADM to eliminate folding and dead space, aggressive mastectomy skin flap excision and debreadment, and more conservative drain removal thresholds successfully decreased their complication rates to those equivalent to their non-ADM reconstructions.\textsuperscript{12}

We recognize that our study has limitations. This is a retrospective review and is subject to type II error. Capsular contracture rates were not included in our study or data collection because it was reported in a subjective and inconsistent manner. Our incidence of PMRT may be low compared to other studies; however, this may in part be explained by the relatively high incidence of prophylactic...
mastectomies (31.4%). In addition, the non-ADM group comprised both partial and total muscle coverage. One could argue that partial muscle coverage places patients at greater risk for bacterial contamination and explantation as compared to total muscle coverage. However, only a few patients had partial muscle coverage and are believed to not have significantly impacted this group as a whole. In addition, there was some variability in the timing of drain removal and duration of antibiotics in our group practice that could potentially impact seroma and infection rates, although with 1367 reconstructions, we believe these small differences were likely inconsequential. Patients who completed PMRT at outside institutions were included in this study, allowing some variability in radiation dosing treatments. Again, the majority of patients received their treatment at our institution, making any patients treated outside the institution negligible in such a large cohort.

CONCLUSIONS

The key to success in breast reconstruction is patient selection and patient education. With the introduction of ADM, we now have another tool to consider and evaluate its utility in each patient. The data presented in the current study can be used to further guide patient selection, and educate patients about their risk profile for complications when using ADM. The decision to use ADM for expander-based breast reconstruction should be performed with caution, given higher overall rates of complications, including infections and seromas. There may, however, be a role for ADM in cases requiring PMRT, as the overall incidence of implant failure is lower than non-ADM cases. The choice to use ADM should be individualized, with particular attention paid to the risk factors presented in our study.

Disclosures

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