Radiotherapy as an adjuvant to mastectomy is integral to the treatment of breast cancer for both late-stage and early-stage disease. In patients with early-stage disease, the addition of postmastectomy radiotherapy has been shown to improve locoregional control, disease-free survival, and overall survival.1,2 Consequently, postmastectomy radiotherapy is increasingly offered to women with early disease during the early stages of immediate postmastectomy breast reconstruction.3,4

Radiotherapy, however, adversely affects breast skin and tissue. Radiation injury to breast skin and tissue usually manifests in two phases, with the acute phase occurring within days to weeks after irradiation and the delayed phase occurring several months or years after irradiation.5 The acute effects of irradiation on breast skin usually include edema from leaking capillaries, inflammation, and desquamation. They are dose- and time-dependent. The delayed response usually manifests as atrophy and fibrosis, with replacement of the adipose tissue with collagen. Irradiation may also cause permanent damage to fibroblasts and fibroblast stem cells, thus impeding revascularization of tissues. Consequently, infection, delayed healing, wound breakdown, and fat necrosis may occur following radiotherapy.

Approximately 70% of breast reconstructions are currently performed with implants, with a two-stage tissue expander/implant (TE/I) reconstruction being the most popular approach.6 Implant-based breast reconstruction, however, is not ideal in the setting of adjuvant radiotherapy. The literature is replete with studies documenting increased complications in implant-based reconstructions when performed in conjunction with radiotherapy, compared with reconstructions without adjuvant radiotherapy (Table 1).3,7-11 In general, radiotherapy increases the incidence of total complications by two- to 15-fold. Capsular contracture (CC), implant loss, wound dehiscence, and infection all occur at a higher incidence and may contribute to poor outcomes often associated with radiotherapy.3,12 Even when the latest prosthetic materials and modern radiation delivery techniques are applied, the postoperative complication rate remains high in irradiated breasts, at greater than 40% with an extrusion rate of 15%.13 Some patients, however, may still undergo implant-based reconstruction despite radiation risks either due to patient choice or lack of tissue for autologous options.3

Acellular Dermal Matrix in Breast Reconstruction in the Setting of Radiotherapy

Ron Israeli, MD, FACS; and Randall S. Feingold, MD, FACS

Abstract

Acellular dermal matrices (ADM) are becoming an integral component of immediate implant-based breast reconstruction, providing inferolateral coverage and support of the implant. Currently, five ADM products are available on the market for this purpose. Although their application has resulted in improved aesthetic results with low complication rates, the clinical performance of ADM when radiotherapy is a component of breast cancer treatment has yet to be defined. In this article, we present a thorough review of the current literature on the performance of ADM in the setting of radiotherapy from both animal and human studies, including our own experience with two proprietary ADM products. The other three products have little literature documenting their application for this type of reconstruction, and further studies specifically evaluating the performance of all ADM formulations in the setting of radiotherapy are still needed.

Keywords

acellular dermal matrix, ADM, breast reconstruction, radiotherapy

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In the last five years, the technique of TE/I reconstruction has evolved to include the acellular dermal matrices (ADM) as an interpositional graft between the pectoralis major muscle (PMM) and the chest wall to better secure the inferolateral aspect of the device pocket as well as to provide soft tissue coverage of the lower pole of the breast. This technique was pioneered with AlloDerm (LifeCell Corp., Branchburg, New Jersey), with the first published report in 2005.14 Since then, several published series have studied AlloDerm both in direct-to-implant as well as TE/I reconstructions and have reported low complication rates and improved aesthetic outcomes, attesting to the reliability and reproducibility of the technique.15-23 Recently, other ADM products have become available and have been placed for this purpose, including NeoForm (Mentor Corp., Santa Barbara, California),24 DermaMatrix (Synthes Inc., West Chester, Pennsylvania),23 Strattice (LifeCell Corp.),25 and FlexHD (Ethicon, New Brunswick, New Jersey).25,26 Initial experience with NeoForm, DermaMatrix, and FlexHD has also indicated low complication rates.23,24,26

With the increasing applications of ADM in immediate implant-based reconstructions and the increasing use of postmastectomy radiotherapy in early disease, the performance of these matrices (ie, their viability and ability to integrate into host tissue) in the setting of radiotherapy has not yet been fully elucidated. It is also not clear whether the combination of ADM with adjuvant radiotherapy would increase or decrease the rate of postoperative complications associated with reconstruction. In this article, we review published animal and human studies on the clinical performance of ADM in the presence of adjuvant radiotherapy in an attempt to evaluate the benefit and safety of these matrices in this setting. In addition, we discuss our clinical experience with AlloDerm and Strattice with adjuvant radiotherapy in immediate postmastectomy TE/I reconstruction.

### Animal Data

Two animal studies have investigated the performance of AlloDerm in the setting of radiotherapy. Dubin et al evaluated the viability of AlloDerm in tissue exposed to single-dose external-beam radiation (EBR) in 36 Sprague-Dawley rats.27 One hind leg of each rat was exposed to EBR, while the other limb served as the nonirradiated control. Two animal studies have investigated the performance of AlloDerm in the setting of radiotherapy. Dubin et al evaluated the viability of AlloDerm in tissue exposed to single-dose external-beam radiation (EBR) in 36 Sprague-Dawley rats.27 One hind leg of each rat was exposed to EBR, while the other limb served as the nonirradiated control. Two animal studies have investigated the performance of AlloDerm in the setting of radiotherapy. Dubin et al evaluated the viability of AlloDerm in tissue exposed to single-dose external-beam radiation (EBR) in 36 Sprague-Dawley rats.27 One hind leg of each rat was exposed to EBR, while the other limb served as the nonirradiated control. Two animal studies have investigated the performance of AlloDerm in the setting of radiotherapy. Dubin et al evaluated the viability of AlloDerm in tissue exposed to single-dose external-beam radiation (EBR) in 36 Sprague-Dawley rats.27 One hind leg of each rat was exposed to EBR, while the other limb served as the nonirradiated control. Two animal studies have investigated the performance of AlloDerm in the setting of radiotherapy. Dubin et al evaluated the viability of AlloDerm in tissue exposed to single-dose external-beam radiation (EBR) in 36 Sprague-Dawley rats.27 One hind leg of each rat was exposed to EBR, while the other limb served as the nonirradiated control. Two animal studies have investigated the performance of AlloDerm in the setting of radiotherapy. Dubin et al evaluated the viability of AlloDerm in tissue exposed to single-dose external-beam radiation (EBR) in 36 Sprague-Dawley rats.27 One hind leg of each rat was exposed to EBR, while the other limb served as the nonirradiated control. Two animal studies have investigated the performance of AlloDerm in the setting of radiotherapy. Dubin et al evaluated the viability of AlloDerm in tissue exposed to single-dose external-beam radiation (EBR) in 36 Sprague-Dawley rats.27 One hind leg of each rat was exposed to EBR, while the other limb served as the nonirradiated control. Two animal studies have investigated the performance of AlloDerm in the setting of radiotherapy. Dubin et al evaluated the viability of AlloDerm in tissue exposed to single-dose external-beam radiation (EBR) in 36 Sprague-Dawley rats.27 One hind leg of each rat was exposed to EBR, while the other limb served as the nonirradiated control.
of 36 rats; one hind limb of each rat was exposed to EBR, and the other served as control. Grafts were harvested at one, two, four, and 12 weeks after irradiation and were subjected to histological analysis. Although graft thickness was not affected by irradiation at any time point, recellularization and neovascularization were reduced during the early postirradiation period compared with controls. While at 12 weeks recellularization was normalized, neovascularization remained significantly less than in the control group, although ultimate graft survival was not affected.

These animal studies demonstrated that AlloDerm graft survival was not adversely affected when implanted in a previously irradiated field or when exposed to irradiation. There are no published data on the viability of other ADM products in the setting of radiotherapy in animals.

**CLINICAL EXPERIENCE**

**Complications in ADM-Assisted, Implant-Based Reconstruction With Adjuvant Radiotherapy**

Several published series have reported on complications in AlloDerm-assisted breast reconstruction in the presence of adjuvant radiotherapy as part of their clinical experience with AlloDerm (Table 2). Gamboa-Bobadilla evaluated 11 patients (13 reconstructions, eight immediate and five delayed) who underwent AlloDerm-assisted implant-based reconstruction. Two patients had been previously irradiated (prior to breast reconstruction). Both irradiated patients healed without delay or complications in the postoperative period. The mean follow-up was 14 months.

In their series of 41 patients (65 breasts) who underwent immediate AlloDerm-assisted TE/I reconstruction, Bindingnavele et al encountered five patients (five breasts) who had unplanned radiotherapy after expander and AlloDerm placement. One irradiated breast developed a wound infection two months postoperatively that required explantation of the TE and AlloDerm followed by a seven-day course of intravenous antibiotics. There were no postradiation complications in the four other patients during a 10-month follow-up period after TE and AlloDerm placement.

Breuing and Colwell placed AlloDerm in 67 breast reconstructions (43 patients): 10 for immediate TE/I reconstruction, 30 for immediate silicone implant reconstruction, four for delayed TE/I reconstruction, and 23 for revisional implant reconstruction for capsular contracture in conjunction with capsulectomy. Five breasts were irradiated prior to mastectomy, and five were irradiated after mastectomy but before implant reconstruction. During a six-month to three-year follow-up period, there was one complication in irradiated breasts: implant extrusion requiring implant removal. In the nonirradiated breasts, there were two instances of infection.

Spear et al, in their series of 43 patients (58 breasts) who underwent immediate AlloDerm-assisted TE/I reconstruction, reported that radiation after TE reconstruction significantly affected the complication rate. Of 11 irradiated breasts, three were irradiated before mastectomy and eight after mastectomy. Of five irradiated breasts (45.5%) experienced complications (three infection, one partial flap necrosis, and one seroma) compared with two

---

Table 2. Complications in AlloDerm-Assisted Implant-Based Reconstructions, With or Without Adjuvant Radiotherapy, in Published Series

<table>
<thead>
<tr>
<th>Study</th>
<th>Irradiated, % (No. of Patients/Breasts)</th>
<th>Nonirradiated, % (No. of Patients/Breasts)</th>
<th>Difference in Complication Rate (Irradiated vs Nonirradiated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamboa-Bobadilla (2006)16</td>
<td>0% (2)</td>
<td>11.0% (9)</td>
<td>NA</td>
</tr>
<tr>
<td>Bindingnavele et al (2007)19</td>
<td>20.0% (5)</td>
<td>8.3% (60)</td>
<td>2.4-fold</td>
</tr>
<tr>
<td>Breuing and Colwell (2007)17</td>
<td>10.0% (10)</td>
<td>3.5% (57)</td>
<td>2.9-fold</td>
</tr>
<tr>
<td>Spear et al (2008)20</td>
<td>45.5% (11)a</td>
<td>4.3% (47)a</td>
<td>10.6-fold</td>
</tr>
<tr>
<td></td>
<td>0% (8)b</td>
<td>2.0% (42)b</td>
<td></td>
</tr>
<tr>
<td>Breuing and Colwell (2009)29</td>
<td>0% (5)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Nahabedian (2009)28</td>
<td>(23)</td>
<td>(77)</td>
<td>2.2-fold</td>
</tr>
<tr>
<td></td>
<td>Infection: 8.7%</td>
<td>3.9%</td>
<td>10-fold</td>
</tr>
<tr>
<td></td>
<td>Incisional dehiscence: 13.0%</td>
<td>1.3%</td>
<td>5-fold</td>
</tr>
<tr>
<td></td>
<td>Seroma: 13.0%</td>
<td>2.6%</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Skin necrosis: 0%</td>
<td>3.9%</td>
<td></td>
</tr>
<tr>
<td>Nguyen et al (2010)31</td>
<td>(28)</td>
<td>(47)</td>
<td>1.6-fold</td>
</tr>
<tr>
<td></td>
<td>Explantation: 10.7%</td>
<td>6.4%</td>
<td>0.6-fold</td>
</tr>
</tbody>
</table>

IV, intravenous; NA, not applicable.
*Complications after Stage 1 tissue expander reconstruction.
*aComplications after Stage 2 implant exchange.
*Explantation due to infection, seroma, or extrusion.
of 47 (4.3%) (one infection and one partial flap necrosis) nonirradiated breasts ($P = .002$). In addition, of the 11 irradiated breasts, three required autologous tissue salvage during implant exchange; in two breasts, latissimus flaps were added to implant reconstructions, while in the third, a pedicled transverse rectus abdominal muscle (TRAM) flap was dissected to salvage the reconstruction. After second-stage implant exchange, there were no complications that were attributed to adjuvant radiotherapy during a mean follow-up of 18.1 months.

A preliminary report by Breuing and Colwell of immediate AlloDerm-assisted implant or TE/I reconstruction followed by postreconstruction radiotherapy in five patients found no complications associated with this procedure.\(^29\) There were no cases of CC or implant loss in any patient, and no patient required or requested autologous reconstruction following irradiation. Patients were followed for 2.5 to 5.5 years after implant reconstruction and two to five years after radiotherapy.

Nahabedian, in a review of his clinical experience with AlloDerm-assisted prosthetic breast surgery, found a higher incidence of complications in irradiated breasts compared with nonirradiated breasts.\(^30\) In this study, 76 women and 100 breasts underwent reconstruction with AlloDerm assistance; 23 breasts were irradiated (nine preoperatively, 13 postoperatively, and one preoperatively and postoperatively). Patients were followed for a mean of 17 months. Incidence of infection (8.7% vs 3.9%), incisional dehiscence (13.0% vs 1.3%), and seroma (13.0% vs 2.6%) were higher in irradiated versus nonirradiated breasts. However, there were no instances of delayed wound healing or skin necrosis in irradiated breasts.

A recent study by Nguyen et al compared infectious complications as well as explantation rate in AlloDerm-assisted versus traditional implant-based reconstruction.\(^31\) Of 75 breasts that were reconstructed with AlloDerm support, 28 had received adjuvant radiotherapy. The explantation rate due to infection, seroma, or extrusion was higher in irradiated (10.7%) versus nonirradiated breasts (6.4%), while infectious complications were lower in irradiated breasts (3.6% vs 6.4%).

A retrospective review of our initial clinical experience with AlloDerm for immediate TE/I breast reconstruction consists of 72 patients (122 breasts) who underwent mastectomy and first-stage reconstruction between January 2005 and June 2007. Fourteen patients (17 breasts) who underwent adjuvant radiotherapy, and 58 patients (105 breasts) did not. Of the 17 irradiated breasts, nine were irradiated mastectomy, six were irradiated postmastectomy, and two were irradiated premastectomy and postmastectomy. Baseline demographics (age and body mass index) and comorbid conditions (smoking status, diabetes, and obesity) were similar between the irradiated and nonirradiated group, except for the rate of adjuvant chemotherapy, which was significantly higher in the irradiated group (86% vs 46%, $P = .008$). Complications occurred in 18 nonirradiated breasts (17.1%) and four irradiated breasts (23.5%) during the expansion phase. In nonirradiated breasts, complications included 11 seromas, five infections, three expander losses, and three hematomas (Table 3). All three lost expanders were replaced; a latissimus flap was added to one expander at a later stage. Of the five infections, two resulted in expander removal, and three were successfully treated with intravenous antibiotics. In irradiated breasts, complications included three expander losses and one infection. All three were converted to autologous procedures (two free TRAM flap and one latissimus flap). All instances of seroma and hematoma in nonirradiated breasts, were not serious, and resolved without further sequelae. With the exception of the expander loss, all other complications (as well as the overall rate of complications) were not significantly different between the irradiated and nonirradiated groups (Table 3).

Stage 2 implant exchange was performed in 116 breasts. During a mean follow-up period of 21.6 months, complications occurred in six of the 102 nonirradiated breasts (5.9%) and included four seromas, two CC, and two implant removals (due to CC) (Table 4). In the irradiated group, complications occurred in three of the 14 breasts (21.4%): three CC and two infections. Although the rate of total complications was not significantly different between the two groups (21.4% vs 5.9%, $P = .076$), the rate of CC (21.4% vs 2.0%, $P = .012$) and infection (14.3% vs 0%, $P = .014$) were significantly higher in irradiated breasts (Table 4). The final outcomes of a patient who had received mastectomy radiotherapy and a patient who had postreconstruction (after Stage 1) radiotherapy are shown in Figures 1 and 2, respectively.

While some of the studies presented here reported no postoperative complications in AlloDerm-assisted breast reconstruction in the setting of radiotherapy, others have found a two- to 11-times higher rate of complications compared with nonirradiated reconstructions (Table 2). This higher rate of complications in irradiated breasts, however,
is similar to the two- to 15-times higher rate reported in reconstructions without ADM (Table 1). Thus, it appears that AlloDerm does not increase the rate of complications beyond what would otherwise be expected with radiotherapy. In support of this, a recent study that evaluated significant predictors of complications in AlloDerm-assisted TE breast reconstruction found that radiation was not a significant risk factor for the development of complications (seroma and reconstructive failure) after AlloDerm-assisted breast reconstruction. 32

There are limited data on other ADM products in implant-based reconstructions. An initial experience with NeoForm in TE/I reconstruction postmastectomy was reported by Losken in 2009. 24 Of 22 patients (31 breasts) who underwent the procedure, eight received postoperative radiotherapy. There was one complication, native skin flap necrosis, although it was not specified whether this occurred in a nonirradiated or irradiated patient. There were no cases of infection, foreign body reaction, rejection, seroma, or skin erythema. The authors stated that occasionally they placed expanders temporarily when postmastectomy radiation therapy was required before converting to autologous reconstruction at a later stage. The number of such autologous reconstructions was not specified. The average follow-up in the series was 10.2 months.

The initial experience with FlexHD in immediate implant-based reconstruction was recently reported by Rawlani et al. 26 In their cohort of 84 patients (121 reconstructions), three breasts were irradiated premastectomy and 23 were irradiated postmastectomy between Stage 1 and Stage 2 reconstruction. The incidence of total complications was three-times higher in irradiated versus nonirradiated breasts (30.8% vs 13.7%), although the difference was not significant. Complications in irradiated versus nonirradiated breasts included soft tissue infection (11.5% vs 6.3%), partial flap necrosis (15.4% vs 4.2%), exposure (15.4% vs 4.2%), and seroma (0% vs 2.1%); there was no significant difference in the incidences of these complications between the two groups. Patients were followed for a mean of 44 months.

A retrospective review of our entire clinical experience with Strattice in immediate TE/I breast reconstruction examined outcomes in 44 patients (77 breasts) who underwent mastectomy and first-stage reconstruction between March 2008 and February 2009. Of 77 reconstructions, 12 received adjuvant radiotherapy, four before mastectomy and eight postoperatively after tissue expansion. During Stage 1 reconstruction, complications occurred in 11 nonirradiated breasts (16.9%) and included eight TE losses,
several infections, five cases of skin necrosis, three seromas, and one hematoma (Table 5). Of patients who had TE loss, five abandoned reconstruction; one was reconstructed with a latissimus flap/implant, and two were reconstructed with TE. In irradiated breasts, there were two expander losses (one was converted to a DIEP flap, and the other was abandoned) and one each of infection, skin necrosis, and seroma for an overall complication rate of 16.7%.

In this cohort, there was no significant difference in the rate of overall complications or the rate of individual complications between irradiated and nonirradiated breasts. A total of 67 TE were exchanged for implants. During a follow-up period of eight to 345 days, there were significantly more complications in irradiated breasts (50%) than in nonirradiated breasts (30% vs 3.5%, $P = .0005$) (Table 6). Complications in nonirradiated and irradiated breasts included one infection, one seroma, and one implant loss. While there was no incidence of CC in nonirradiated breasts, this was the most frequent complication in irradiated breasts, occurring in three of 10 breasts (30%).

**Evidence of Viability of ADM in the Setting of Radiotherapy**

Histological analyses of AlloDerm biopsies obtained from patients who had received adjuvant radiotherapy as well as gross observations of AlloDerm integration into mastectomy skin flaps have provided evidence of the viability of this tissue matrix in the presence of radiotherapy. Breuing and Colwell performed histological analyses of biopsies taken from the AlloDerm/TE capsule interface during bilateral implant exchange from a patient who had unilateral...
They reported no discernible differences in the collagen architecture of AlloDerm from the irradiated and nonirradiated breast.

The ability of AlloDerm to incorporate into mastectomy skin flaps and revascularize and recellularize in the setting of radiotherapy was demonstrated in the study by Nahabedian. Of the 23 women who had radiotherapy, total incorporation of AlloDerm into the mastectomy skin flaps was seen in 21 patients (91%), while nearly total incorporation of the AlloDerm was seen in two patients (9%). Although histological analyses were not performed in this study, gross incorporation of AlloDerm was demonstrated by intraoperative visualization and palpation, while a visible capillary network on AlloDerm provided evidence of revascularization. Likewise, Gamboa-Bobadilla has also reported AlloDerm to be well-vascularized and fully-integrated into the surrounding tissue in irradiated breasts.

In our patient cohort, during second-stage implant exchange, full incorporation of AlloDerm with revascularization was observed in all patients. In fact, we observed no discernible differences in gross pathology of the incorporated AlloDerm from a nonirradiated, preoperatively irradiated, and postoperatively irradiated breast (Figure 3). Furthermore, hematoxylin and eosin staining of biopsies taken from AlloDerm/capsule junction from a nonirradiated, preoperatively irradiated, and postoperatively irradiated breast indicated abundant recellularization and revascularization of AlloDerm in all three cases (Figure 4). Verhoeff’s staining of all three AlloDerm biopsies showed an abundance of elastin, indicating an absence of scar tissue where the AlloDerm matrices were located. Scar tissue lacks elastin, as seen in the capsules adjacent to the AlloDerm matrices. In fact, a clear line of demarcation between the AlloDerm and capsule was seen in all cases. Collectively, these results suggest that preoperative or
postoperative radiotherapy does not adversely affect the recellularization, revascularization, or integration of AlloDerm within the host tissue and are consistent with those reported in animal studies.27,28 There are limited data on the integration and viability of other ADM products in the setting of radiotherapy. Early results with NeoForm for TE/I reconstruction indicated adequate incorporation of NeoForm during second-stage implant exchange in 16 patients, including patients who had received postoperative radiotherapy.24 The author reported small punctate bleeding on the dermal matrix. Histological analyses of NeoForm biopsied from two randomly-selected patients indicated capillary and fibroblastic tissue proliferation. It was not stated whether any of these patients were irradiated.

Similar to this study, early experience with FlexHD in TE/I reconstruction noted incorporation of this tissue matrix in all 45 patients (51 nonirradiated breasts and 16 irradiated breasts) who underwent second-stage implant exchange.26 Incorporation of FlexHD was evidenced by gross observations of firm adhesion of the graft to the mastectomy skin flap. Further, neovascularization of FlexHD was demonstrated by histological analyses of graft biopsies obtained from four patients, although it was not stated whether any of these patients were irradiated. In our experience with Strattice, we have noted

Figure 4. Histology of AlloDerm/capsule interface biopsy from a nonirradiated (A), preoperatively irradiated (B), and postoperatively irradiated (C) breast. Biopsy was taken at three months after AlloDerm implantation (A), at four months after AlloDerm implantation in a previously irradiated field (B), and at 6.5 months after completion of radiotherapy (C). Left panel: Hematoxylin and eosin staining. Right panel: Verhoeff-van Gieson staining. Magnification: 100x.
Table 7. Rate of Capsular Contracture in Non–ADM-Assisted Implant-Based Reconstructions, With or Without Adjuvant Radiotherapy, in Published Series

<table>
<thead>
<tr>
<th>Study</th>
<th>Irradiated, % CC (No. of Patients/Breasts)</th>
<th>Nonirradiated, % CC (No. of Patients/Breasts)</th>
<th>Difference in CC Rate (Irradiated vs Nonirradiated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persichetti et al (2009)</td>
<td>40% (20)</td>
<td>7% (43)</td>
<td>2.9-fold</td>
</tr>
<tr>
<td>Percec and Bucky (2008)</td>
<td>15% (21)</td>
<td>5% (20)</td>
<td>3.0-fold</td>
</tr>
<tr>
<td>McCarthy et al (2005)</td>
<td>50% (10)</td>
<td>10% (10)</td>
<td>5.0-fold</td>
</tr>
<tr>
<td>Benediktsson and Perbeck (2006)</td>
<td>42% (24)</td>
<td>15% (83)</td>
<td>2.8-fold</td>
</tr>
<tr>
<td>Cordeiro et al (2004)</td>
<td>40% (68)</td>
<td>11% (75)</td>
<td>3.6-fold</td>
</tr>
<tr>
<td>Contant et al (2000)</td>
<td>50% (28)</td>
<td>11% (87)</td>
<td>4.5-fold</td>
</tr>
<tr>
<td>Spear and On-yewu (2000)</td>
<td>32% (40)</td>
<td>0% (40)</td>
<td>NA</td>
</tr>
<tr>
<td>Vandeweyer et al (2005)</td>
<td>100% (6)</td>
<td>3% (118)</td>
<td>33.3-fold</td>
</tr>
</tbody>
</table>

CC, capsular contracture; NA, not applicable.
*CC = Grades 3 or 4.
**CC ≥ Grade 2.

...grossly-incomplete and variable incorporation of this tissue matrix into surrounding breast tissue in the setting of radiotherapy.

**RADIOThERAPy AND CAPSULAR CONTRACTURE**

CC is the most common complication of implant-based reconstruction. It is also a challenging complication because its occurrence is unpredictable, preventive measures are unreliable, and corrective measures do not preclude recurrence. The incidence of CC reported in published series of non–ADM-assisted breast reconstruction ranges from 0% to 15%; in the presence of adjuvant radiotherapy, the incidence increases to 15% to 100% (Table 7). Although the true cause of CC is unknown, inflammation seems to play a critical role. Inflammatory response has been directly correlated to capsule thickness and Baker score. The higher incidence of CC in irradiated breasts may be attributed to radiation effects of inflammation and skin fibrosis.

In breast reconstruction with AlloDerm, clinical evidence to date indicates a low rate (2%) to zero rate of occurrence of CC during a mean follow-up period of 10 to 21 months, suggesting that AlloDerm may mitigate CC. In support of the low CC rate with AlloDerm, in vivo animal (rabbit and primate) studies have demonstrated reduced or no capsule formation around implants covered with AlloDerm. A human histological study suggested that reduced capsule formation around AlloDerm may be due to its ability to reduce the inflammatory response to a foreign body. In this study, biopsies of integrated AlloDerm obtained during second-stage implant exchange from patients who underwent AlloDerm-assisted TE/I reconstruction were found to have significantly reduced levels of granulation tissue formation, vessel proliferation, chronic inflammatory changes, capsule fibrosis, fibroblast cellularity, and foreign body giant cell inflammatory reaction compared with biopsies obtained from native capsules. By inhibiting the inflammatory changes required for the inception of capsule maturation, AlloDerm may thus provide a method for preventing capsule formation.

It is not clear to what extent AlloDerm is able to reduce the rate of CC in the setting of radiotherapy. An animal study that evaluated the pathobiology of capsule formation in the presence or absence of radiation showed that AlloDerm significantly decreased radiation-related inflammation and delayed or diminished pseudopithelium formation around capsules compared with native capsules. As the occurrence of pseudopithelium precedes the transformation of periprosthetic tissue into a more fibrotic capsule, AlloDerm may thus slow the progression of capsular formation, fibrosis, and contraction in the presence of radiation.

In the previously-mentioned clinical studies, both irradiated and nonirradiated breasts were included in the evaluation of CC in AlloDerm-assisted reconstructions. In our clinical experience with AlloDerm, two instances of CC (2%) have been encountered in nonirradiated breasts along with three instances of CC (21%) in irradiated breasts. As the total number of irradiated reconstructions from our series as well as those from published series is approximately 100, further studies are needed to determine the rate of CC in AlloDerm-assisted reconstructions in the presence of radiotherapy.

Whether the ability to decrease inflammatory changes and minimize capsule formation is characteristic of AlloDerm or of all ADM products remains to be seen. As the different ADM formulations are processed with different solvents and decellularization and sterilization techniques, these could potentially influence the biochemical properties of the matrices. The latter, in turn, may influence foreign recognition and antigen presentation, causing a varying response by tissue macrophages to the presence of the tissue matrix. This was shown to be the case in an in vitro study that investigated inflammatory responses to various tissue matrices [AlloDerm, FlexHD, and AlloMax (Bard Davol, Warwick, Rhode Island)] in the presence of human peripheral blood mononuclear cells. Of the tissue matrices investigated, AlloDerm was found to have the lowest statistically-significant inflammatory response (measured by cytokine expression) to human peripheral blood mononuclear cells. Although cytokine expression was not...
correlated with in vivo graft performance, the results of this study suggest that the greater activation of proinflammatory cytokines by FlexHD and AlloMax may negatively impact the performance of these grafts compared with AlloDerm. However, clinical series reporting on initial experiences with NeoForm, DermaMatrix, and FlexHD have reported the absence of CC in breasts reconstructed with the aid of these ADM products during a follow-up period of 10.2 months (mean), 13.5 months (median), and 7.2 months (mean), respectively. In addition, in a clinical study of three different ADM products (AlloDerm, Strattice, and FlexHD), the CC rate was 3.9% during a mean follow-up period of 7.3 months, although this was not segregated by ADM type. In that study, 87% (n = 52) of the patients received AlloDerm, 10% (n = five) received Strattice, and 3% (n = two) received FlexHD. In our clinical experience with Strattice, the total incidence of CC was 4.5% (0% in nonirradiated breasts and 30% in irradiated breasts) during the follow-up period.

**Revision of Capsular Contracture in the Irradiated Breast with ADM**

Apart from its applications in primary reconstructions, AlloDerm is also being placed during corrective or revisionary surgery. With respect to revision of CC in irradiated breasts, our clinical experience indicates that placing AlloDerm in conjunction with capsulectomy provides an effective means to correct and minimize recurrence in irradiated breasts.

**Technique**

The essential steps of corrective surgery for CC include capsulectomy followed by expansion of the implant pocket with a sheet of AlloDerm, along with redefinition of the inframammary and lateral mammary folds. The implant or expander is usually accessed and removed via the previous mastectomy incision. A circumferential capsulotomy is completed along the perimeter of the implant pocket at the level of the chest wall. After mobilizing the inferolateral border of the PMM, a partial anterior capsulectomy is performed, the extent of which depends on capsule thickness. This recreates the original inferolateral defect postmastectomy prior to primary reconstruction. Steps are then taken to correct this defect by recreating the inframammary and lateral mammary folds, as in a primary reconstruction. For this purpose, a sheet of rehydrated AlloDerm of standard thickness is utilized. We routinely rinse AlloDerm in an antibiotic solution, followed by a saline rinse. The rehydrated AlloDerm is then placed at the inferolateral border of the breast and is secured laterally, inferiorly, and medially to the chest wall with running 2-0 Vicryl (Ethicon Inc., Somerville, New Jersey) sutures. The AlloDerm is oriented such that the deep dermal surface is facing the overlying soft tissue. The size of AlloDerm required is dependent on the extent of capsulectomy performed.

A new implant is then introduced into the pocket. After verifying proper implant and fold placement with the patient in a sitting position, the superior edge of AlloDerm is trimmed as needed and sutured to the PMM (Figure 5). Whereas in AlloDerm-assisted primary reconstruction we typically utilize two drains, in this case, only one drain is placed. Through a separate lateral stab incision, the drain is placed along the inframammary fold between the AlloDerm and the skin flap inferiorly, where the capsulectomy was completed. Placing a second drain superiorly is not required because the superior breast skin is not elevated and remains adherent to the PMM. Final incision closure is then performed, completing the corrective surgery.

**Outcomes**

Since 2005, the senior author (RI) has been successfully performing this technique of mastectomy pocket expansion.
with AlloDerm for the correction of CC in patients following TE/I breast reconstruction. The initial clinical experience with this technique includes both radiated and nonradiated reconstructed breasts that required surgical correction of Baker Grade 3 or Grade 4 CC. In the properly-selected patient, this technique has allowed correction of CC (ie, achieving a Grade 2 or less) and has obviated the need for conversion to autologous procedures. A typical outcome of a patient who underwent corrective surgery for CC following radiotherapy is shown in Figure 6.

For a successful outcome, attention to several technical details during corrective surgery is important. AlloDerm acts as an “internal bra”, and it should be trimmed as needed to achieve a “hand-in-glove” fit over the implant and below the overlying skin flap. This reduces the dead space between the AlloDerm and the skin flap, thereby reducing the risk of seroma. When properly fixed, AlloDerm should appear smooth and taut, without gross wrinkles that may affect integration. Further, to reduce the risk of seroma, adequate drainage from the space between AlloDerm and the skin flap is necessary; the drain should be maintained until there is less than 30 mL of drainage over a one- to two-day period.

**CLINICAL DECISION MAKING**

Several factors, including timing of radiotherapy (preoperative or postoperative), patient anatomy, quality of remaining breast skin and tissue, and patient preference, must be taken into consideration when selecting the best reconstructive approach following mastectomy. With this in mind, we have designed an algorithm for selecting patients for AlloDerm-assisted implant-based reconstruction.
in the setting of radiotherapy (Figure 7). In patients with a history of breast irradiation, the decision to perform tissue expander reconstruction with AlloDerm support is based on the quality of tissue remaining after mastectomy as well as the degree of radiation damage to the tissues. In these patients, single-stage implant reconstruction is usually not recommended because of inadequate tissue quality. In patients with planned postmastectomy radiotherapy, AlloDerm-assisted tissue expander reconstruction can be offered following mastectomy, and radiotherapy is usually initiated after tissue expansion has been completed. In patients with no prior radiotherapy and for whom postmastectomy radiotherapy is not planned, autologous or implant-based reconstructions are possible options, and the reconstructive choice may be dictated by patient anatomy and preference. In all patients who undergo AlloDerm-assisted tissue expander reconstruction, the quality of reconstruction is assessed after completion of expansion. If the patient develops CC after tissue expansion, whether or not they have had radiotherapy, corrective surgery may require flap reconstruction or may be performed during implant exchange, as described above.

**CONCLUSIONS**

ADM products are emerging as an integral part of implant-based reconstruction because of the benefits associated with their placement. Early experience indicates that the benefits of ADM formulations, particularly AlloDerm, are maintained when adjuvant radiotherapy is a component of breast reconstruction. Of the ADM products currently available for breast reconstruction, AlloDerm has the most reported clinical experience. Evidence to date indicates that AlloDerm can be safely combined with adjuvant radiotherapy, as it does not increase postoperative complications beyond what would be expected with radiotherapy alone. Animal and human data indicate that AlloDerm remains viable in the presence of radiotherapy. Preoperative or postoperative radiotherapy does not appear to adversely affect its recellularization, revascularization, or integration into host tissue. Further, the incidence of CC appears to remain as low in AlloDerm-assisted reconstructions in the presence of radiotherapy as in the absence of radiotherapy. Animal data suggest that AlloDerm may slow the progression of capsule formation, fibrosis, and contracture in the presence of radiation. Our clinical experience similarly
indicates that AlloDerm, in addition to reducing the incidence of CC in primary reconstructions with or without irradiation, can also be successfully placed for the revision of CC in conjunction with capsulectomy. While further studies are needed to confirm the safety and benefit of AlloDerm in the setting of radiotherapy, animal and clinical studies for other ADM products for breast reconstruction are eagerly awaited.

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**REFERENCES**


