

Acellular Dermal Matrix in Prosthetic Breast Reconstructive Surgery with Prepectoral Technique: A Literature Review

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Received date: October 21, 2020, **Accepted date:** November 21, 2020

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Abstract

Breast reconstruction after surgery for cancer has more and more become crucial for patients' satisfaction and quality of life. Lately, thanks to the spread of medical devices like synthetic and biological meshes (Acellular Dermal Matrices: ADMs) and surgical techniques such as skin-sparing and nipple-sparing mastectomies, surgeons are allowed to perform immediate breast reconstruction, avoiding the use of tissue-expanders. ADMs-assisted breast reconstruction can be divided into prepectoral and submuscular dual-plane technique. In the last decade, many surgeons adopted the prepectoral technique, in order to avoid the direct contact between the silicone implant and the host tissues and complications such as animation deformity, muscular impairment and migration of the prosthesis. ADMs create a scaffold that the host cells can colonize, thus allowing prosthetic integration and encapsulation and promoting at the same time new vascularization. We performed a brief review of the literature about the use of ADMs in prepectoral direct-to-implant breast reconstruction, also discussing about the costs and their impact on the healthcare system, and finally mentioning which may be the direction of future technology in this promising field of research.

Introduction

Breast cancer is the second most commonly diagnosed cancer worldwide, with an incidence of 2.088.850 and a mortality rate of 627,000. Incidence and mortality rate in Europe were 522,513 and 92,000, respectively [1], while in Italy accounted for 53,000 diagnoses and 12,000 deaths [2].

Advances in early diagnosis, identification of patients at high risk of developing cancer in familial-hereditary status, oncological and breast studies are progressively extending patients overall survival (OS) and disease-free survival (DFS) highlighting the importance of quality of life concept [3]. In fact, approximately 35-40% of women diagnosed with breast cancer undergo a surgical mastectomy and about 75% of them receive breast reconstruction (BR) after mastectomy [4,5].

BR after surgery for cancer has indeed become crucial for patients' satisfaction and quality of life. Delayed breast reconstruction using tissue expanders has demonstrated to cause dissatisfaction towards body image and emotional and social distress [6].

Lately, thanks to the spread of devices to assess blood flow intraoperatively, of medical devices like synthetic and biological meshes (Acellular Dermal Matrices: ADMs) providing complete covering of implants [7-9], surgical techniques such as skin-sparing (SSM) and nipple-sparing mastectomies (NSM), surgeons are allowed to perform immediate breast reconstruction (IBR), avoiding the use of tissue-expanders [10].

Meshes used in IBR can be divided in synthetic and biological, which can be further classified in human-

derived ADM and xenografts, made from fetal bovine, porcine dermis and bovine pericardium. Tissue processing removes the cellular antigens responsible for immunologic response, while preserving the structural matrix that stimulates angiogenesis and tissue regeneration. In fact, they create a scaffold that the host cells can colonize, thus allowing prosthetic integration and encapsulation and promoting at the same time new vascularization [11-13].

There is a great amount of meshes available for breast reconstruction but still no clear guidelines about their use. John Y.S. Kim published a review in 2017 in order to provide a summary of the latest biologic and synthetic mesh innovation. He concluded that additional studies were necessary to help clarify the true advantages and disadvantages associated with both biologic and synthetic mesh and their different ways of integration [14].

ADMs-assisted breast reconstruction can be divided into prepectoral and submuscular dual plane technique. Many authors agree that the submuscular approach has the best long-term cosmetic results, is less expensive while ensuring a better coverage of the upper-pole of the breast, but it has the big disadvantage of causing animation deformity, upper migration of the prosthesis and more post-operative pain [15,16].

During the last decade, many surgeons adopted the prepectoral technique, assuming the possibility to avoid the use of the pectoralis major muscle for implant coverage and performing a complete wrapping of the prosthesis with a sheet of ADM, in order to avoid the direct contact between the silicone implant and the host tissues [17,18].

This review briefly analyzes current literature about the use of ADMs in prepectoral direct-to-implant breast reconstruction.

Literature Search

Literature search was performed using MEDLINE®. Key words searched were “acellular dermal matrix” OR “biological mesh” OR “ADM” OR “pericardial mesh” in combination with either “breast” OR “mammoplasty” OR “breast reconstruction” AND “prepectoral”. A total of 24 articles were found. We excluded papers with comparison between prepectoral and subpectoral techniques, or between use versus no-use of ADMs. We also excluded articles regarding synthetic meshes, articles related to chest wall or abdominal reconstruction and articles on basic science. We finally selected 6 papers.

Discussion

Breast reconstruction represents an essential step of the

therapeutic process in women with breast cancer treated with mastectomy, since it reduces negative effects on body image deriving from the destructive surgical procedures [6,19]. Then follows a brief excursus on different techniques and materials used in BR, so far.

Reconstruction can be performed both using implants or autogenous tissues.

Implant-based reconstruction has the advantages of shorter procedure time, hospital stay and recovery as well as lower costs [20]. It can be performed as a two-stage technique, using a tissue expander followed by the implant of a permanent prosthesis, or as an immediate single-stage technique with direct implant of a prosthesis with or without the use of an autologous tissue [21].

Immediate single-stage reconstruction, while improving patient's compliance, has some limits: it can be performed only for non-large and ptotic breast patients with good quality of tissues. Aesthetic outcomes are sometimes worse than in delayed-breast reconstruction and a second surgical procedure is often required [22].

Capsular contracture is the most common complication associated with prosthetic breast reconstruction following mastectomy for cancer, with a frequency of 21.8 and 34% at 5 years, respectively [23-25].

Acellular dermal matrices (ADMs) have been recently introduced to avoid direct contact between silicone implants and host tissues, in order to decrease capsular contracture rates [24,26]. In particular, acellular bovine pericardium-derived collagen matrix membranes (APMs) have been used in immediate-breast reconstruction, improving the definition of the inframammary and lateral mammary fold and reducing capsular contracture [27].

Bernardini et al. published a paper in 2019 [28], in which they analyzed tissue remodeling occurring after implantation of two different bovine pericardium-derived biological meshes BioRipar® (ASSUT EUROPE, Rome, Italy), and Tutomesh® (Tutogen Medical GmbH, Neunkirchen am Brand, Germany) and three different types (smooth, texturized and polyurethane) of mini-silicone round prosthesis in a rat model.

Mechanical properties of the two meshes were previously compared by using two mechanical tests, namely uniaxial tensile test and burst test, and the BioRipar® mesh demonstrated to be more extensible and resilient than the commercial control ones [29].

Results from rat model suggested that differences in composition and/or structure of AMP likely influence tissue remodeling after their implantation alone or in

combination with different prostheses. The authors concluded that additional studies were needed in order to develop a new biological mesh capable to further reduce prostheses-induced adverse events, like postsurgical periprosthetic fibrosis, following breast reconstruction [28].

In this regard, the exaSHAPE® is a particular sheet of BioRipar® mesh, especially designed for prepectoral implant placement. It covers the whole front surface and approximately 1/3 of the rear surface of the implant. The exaSHAPE® allows, without altering the mechanical characteristics of the BioRipar® mesh, thus maintaining its strength, a perfect and simple fit, with less matrix. This need of a new shape, specific for a prepectoral approach, was due to the fact that most of complications, such as seroma and infection, are related to the amount of biological mass used [30]. Moreover, this mesh can be positioned using a “no-touch” technique: the surgeon passes a 2-0 Vicryl® thread through the pre-formed holes on the mesh to create a purse-string suture and touches it only when applying it to the implant, then tightens the suture, thus fixing the mesh to the prosthesis and making it ready for positioning in the prepectoral pocket. Reducing the unnecessary handling of the mesh may help to decrease the risk of post-operative infections, which still represent a challenge even using biological devices [31-33].

Prosthesis can be positioned with a subpectoral approach, using the traditional dual plane technique, or with a prepectoral approach, above the pectoralis major.

The prepectoral placement of the implant, as compared to the submuscular dual plane approach, avoids the complications associated with pectoralis major muscle dissection and mobilization. These include impaired functionality, muscle spasms, animation deformity, and “window-shading” among others [17,18,34,35].

Historically, the prepectoral approach was left behind in 1970s, due to excessively high complication rates, including capsular contracture, flap necrosis, implant descent/migration, implant loss and implant rippling at the upper pole [36]. However, recent progress in both surgical technique and materials, including new generation expanders and implants, the use of ADMs, intraoperative flap perfusion analysis, and fat grafting, made the prepectoral technique again feasible and allowed its spreading among oncoplastic surgeons.

Nevertheless, the prepectoral approach is not without its drawbacks as well. As previously said, the most common complication is capsular contracture, with a rate of 8.8% in a recent systematic review of prepectoral breast reconstruction complications. Upon subgroup analysis,

however, the rate of capsular contracture with the use of an ADM was decreased to 2.3% as compared to 12.4% without. However, while ADMs demonstrated to lower capsular contracture and overall complications rates, their use was correlated with a higher rate of implant loss, infection, and mastectomy flap necrosis. ADMs are also associated with the red breast syndrome, with an incidence of 6.4% [37]. This entity is characterized by erythema directly overlying the ADM and is thought to be secondary to lymphedema and lymphatic obstruction postoperatively. All cases of breast erythema are empirically treated with antibiotics, but they are discontinued after one week if no change is observed, and red breast syndrome is presumed. Most cases are self-limiting, but prolonged red breast syndrome is occasionally treated with explantation of ADM and implant and conversion to autologous breast reconstruction.

Other important complications to consider are infection, seroma, hematoma, implant loss, mastectomy flap necrosis, and NAC necrosis. It should be noted that long-term comparative studies between prepectoral and subpectoral implant placement complications are not yet available. However, there are many studies, mostly retrospective, that published complication rates with prepectoral reconstruction [18,38-40].

Another concern is the risk of visible implant rippling at the upper pole, given thinner, soft tissue coverage as compared to submuscular reconstruction. During two-stage prepectoral reconstruction, the tissue expanders should be underfilled, taking into account the anticipated final implant size, in order to avoid rippling due to redundant skin during the expander-to-implant exchange operation. The rippling effect is also mitigated by performing fat grafting to the upper pole mastectomy flap during the second-stage expander-to-implant exchange operation. It is important to counsel patients who are undergoing immediate, direct-to-implant prepectoral breast reconstruction that they may need a later procedure for fat grafting over the implant to reduce rippling and implant visibility. Direct-to-implant breast reconstruction was in fact made possible with prepectoral implant placement as the muscle does not need to be expanded to accommodate a big implant [41].

A new interest in prepectoral reconstruction has started since Sigalove et al. first published their results of 353 procedures in 207 patients, of which 89% were two-stage prepectoral reconstruction [42].

Thanks to the spread of techniques like skin-sparing and nipple-sparing mastectomies, direct-to-implant prepectoral reconstruction using ADMs has become more feasible with good results [43-46].

Author, Year, Country	Study Design	Study Duration (Months)	Type of ADM	Patients (N), Breasts (N)	Mean Age (Yrs)	Adjuvant Radiotherapy (% of Patients)	Type of Surgery	Complications	Mean Follow-Up (Months)
Reitsamer et al. 2015, Austria	Retrospective	Not specified	Strattice_ Porcine ADM (LifeCell Corporation, Bridgewater, NJ, USA)	P=13 B= 22	45	15%	NSM and single-stage direct-to-implant breast reconstruction with prepectoral implant placement and complete coverage with ADM	Partial nipple necrosis (9%); hemorrhage with evacuation (4,5%)	6 (median)
Vidya et al. 2017. UK, Spain, Italy, Poland	Prospective data collection, multicentric	16	Braxon® porcine ADM (Decomed S.r.l., Venezia, Italy)	P=79 B=100	55,8	3,80%	SSM or NSM and single stage direct-to-implant breast reconstruction with prepectoral implant placement and complete coverage with ADM	Hematoma (2%); dehiscence (3%); necrosis (1%); seroma (5%); implant loss (2%)	17.9
Jafferbhoy et al. 2017. UK	Prospective multicentric	11	Braxon® porcine ADM (Decomed, Maron, Venezia, Italy)	P=64 B=78	50 (median)	Not specified	SSM or NSM and single stage direct-to-implant breast reconstruction with prepectoral implant placement and complete coverage with ADM	Seroma (23%) Erythema needing antibiotics (29.6%) Hematoma (6.25%) Infection (6.25%) Skin necrosis (3.12%) Wound dehiscence (1.56%) Readmission within 30 days (20.3%) Re-exploration (21.9%) Implant loss (10.2%)	9,98 (median)

Jones G, Antony AK. 2019. USA	Retrospective	Not specified	AlloDerm® Allergan Inc.	P=234 B=305	Not specified	NSM and single stage direct-to-implant breast reconstruction with prepectoral implant placement and anterior tenting technique using ADM	Hematoma (0.9%), capsular contracture (0.9%), minor contour deformities (57.8%), seromas (5.2%), cellulitis (5.7%), explantation (6.7%).	15,1	
Safran T et al. 2020. Canada	Retrospective	24	AlloDerm® Allergan Inc.	P=201 B=313	48, 6	18, 50%	Major complications 8,6%; Hematoma (2.9%); Infection (2.2%); Seroma (2.2%); Implant displacement (0.6%); NAC full-thickness necrosis (0.6%)	Not specified	
Masià J; iBAG Working Group. 2020. Spain, Italy, UK	Retrospective multicentric	72	Braxon® porcine ADM (Decomed, Marcon, Venezia, Italy)	P=1186 B=1450	52, 4	10, 60%	<p>Nipple-sparing (49.7%)</p> <p>Skin-sparing (32.1%)</p> <p>Skin-reducing with NAC removal (5.6%)</p> <p>Skin-reducing with NAC preservation (1.3%)</p> <p>None (revisions: 2.8%)</p> <p>Not defined (8.9%) and single stage direct-to-implant breast reconstruction with prepectoral implant placement and complete coverage with ADM</p>	<p>Seroma (7,7%), dehiscence (4,6%), hematoma (2,1%), necrosis (3,2%), infection (4,8%), extrusion (1,2%), RBS (3,3%), fever (1,7%), implant rotation (0,2%), capsular contracture (2,1%), rippling (2,8%), other complications (3,3%), implant loss (6,5%)</p>	22,7

In particular, Cattelani et al. in 2018 compared prepectoral and subpectoral direct-to-implant techniques in 86 patients and found lower rates of postoperative pain, less impact on upper extremity function, higher aesthetic BREAST-Q scores and economic benefits [41]. Baker et al. in 2018 reported no statistically significant differences in pain scores, early complications, or hospital stay in a series of 40 patients when comparing direct to implant pre- and subpectoral breast reconstruction groups, while some patients complained about implant rippling in the prepectoral group [45].

Benefits and risks with ADMs in immediate breast reconstruction, regardless of implant positioning, whether pre-or subpectoral, were extensively analyzed in a meta-analysis by Hallberg et al. in 2018. The authors, after reviewing and comparing 51 studies, concluded that their results were uncertain due to the lack of high quality studies comparing use of ADMs VS no ADMs in IBR. In particular, they found out that data about recurrence of cancer, delay of beginning of adjuvant therapy and Health related quality of life (HRQoL) were missing and that the risk of bias in the selected studies was high, underlining the need for controlled trials [47].

Our research specifically focused on papers about prepectoral reconstructions using ADMs. In the table 1 we report a selection of papers about prepectoral reconstructions using ADMs.

Reitsamer, from Austria, first published a paper in 2017 describing a complete ADM coverage of breast implants (Strattice® Porcine ADM, LifeCell Corporation, Bridgewater, NJ, USA) with good results in terms of muscle function, absence of breast animation, postoperative pain, and length of stay, but with a short follow up [38]. Vidya et al., in their multicentric study, based on prospectively collected data, reported in 2017 two hematomas, three dehiscences, one necrosis, five seromas and two implant losses (2%) after 100 procedures, the latter considerably lower than similar reports in literature about the use of ADMs in subpectoral breast reconstruction (5.0%-19.2%) [48].

Jafferbhoy et al. in 2017 published results from a prospective, multicentric experience of 78 prepectoral implant based immediate breast reconstructions using Braxon® porcine ADM (Decomed S.r.l., Venezia, Italy) and concluded that it was an effective technique with complication rates similar to the traditional technique of subpectoral implant using ADM, while variables like effects on adjuvant radiotherapy were still to analyze [46].

Jones et al. in 2019 reported retrospective data about their 234 patients treated with IBR and prepectoral breast reconstruction using AlloDerm® (Allergan Inc.) with a

mean follow-up of 15 months and stated that this kind of reconstruction demonstrated maintenance of the integrity and quality over time with low rates of capsular contracture (0,9%) and complete absence of animation deformity [39].

The last two papers selected were about retrospective large series of patients.

The first, written by Safran et al. in 2020, reported data from 313 IBR with prepectoral implant placement, either performed without ADMs or with anterior wrapping with AlloDerm® (used in 77.6% of cases). Their bivariate analysis and logistic regression demonstrate that surgical complications did not differ in terms of a-cellular dermal matrix use, incision selection, and use of postmastectomy radiation therapy [40].

Briefly speaking of post-operative radiation therapy, it should be underlined that, while lifesaving, it is a known risk factor for implant-based reconstruction complications, namely capsular contracture and reconstruction failure. In a recent retrospective review, Sinnott et al. reported that subpectoral breast reconstruction had a three times greater rate of capsular contracture compared to prepectoral breast reconstruction following postmastectomy radiation therapy (52.2 versus 16.1%). Moreover, 10 of the 12 cases of capsular contracture in the subpectoral group were grades 3 or 4 compared with 2 of the 9 cases in the prepectoral group. It has been proposed that the increased surface area coverage of the implant by ADM is protective [43].

Following two-stage reconstruction, the migration of the tissue expander is higher in the dual plane than the prepectoral group during postmastectomy radiation. This is thought to occur due to radiation-induced fibrosis and contraction of the pectoralis major muscle, which causes superior displacement of the expander. Prepectoral breast reconstruction is not subject to this phenomenon as there is no muscle coverage of the expander.

Finally, Masià J. and the International Braxon Audit Group (iBAG) working group published in April 2020 about a large multicentric case series from Spain, Italy and UK, with 1450 immediate prepectoral implant placements and complete coverage with Braxon® ADM, performed over a period of 6 years in 30 hospitals. After a mean follow-up of 22 months, the authors reported durable results with low complication rates, especially capsular contraction, and statistically confirmed the well known correlations between patients' risk factors and the development of postoperative complications (i.e. smoking status, diabetes and the use of immunosuppressive drugs) [18].

About the costs of ADMs, and their impact on healthcare system, not only the raw price of the meshes but also the outcomes after using them should be considered, as the

length of post-operative hospital stay, the complications and need for a re-intervention, contribute to the total economic burden.

Only a few studies about this topic have been published so far. Two of them reported a cost-minimization analysis, comparing the traditional 2-stage technique with one-stage reconstruction using ADMs. However, outcomes were estimated considering averages of results from previous literature and, therefore, more high-quality studies are needed to understand the real results of this novel technique [49-51].

Buendia and Olivas-Menayo published a paper in 2019 about their series of 11 patients treated with one-stage subpectoral bilateral reconstruction using a single sheet of ADM (Surgimend® bovine acellular dermal collagen matrix, LifeSciences), cut in 2 pieces, making the hypothesis that using less matrix could lead to a faster integration with less inflammatory response, avoiding or reducing the complications related to the use of ADM, such as seroma or infection, with the additional advantage of improving cost-efficiency [30].

A multicentric randomized trial was also published in 2019, from the Netherlands, comparing one-stage immediate implant-based breast reconstruction with ADM to the two-stage procedure without ADM: the first was more expensive with comparable complication rates, so the authors did not recognize its cost-effectiveness value, though the study had several limitations, as socioeconomic burden of multiple operations, absence from work and travel expenses, was not taken into account [52].

Finally, Viezel-Mathieu et al. reported in 2020 on a retrospective series of 77 patients receiving either a two stage subpectoral reconstruction using ADM or a single stage ADM-sparing prepectoral intervention. The ADM-sparing technique consisted in a fenestration of the matrix, in order to increase its surface and still ensure anterior covering of the prosthesis. Prepectoral reconstruction costed 25% less than the subpectoral technique [53].

Current technologies in experimental stage are mainly addressed to produce meshes that ensure the same biomechanical strength with less biological mass, like the exaSHAPE® previously cited, and to enhance oncological safety and efficacy in breast reconstruction. An interesting and promising topic, which can be further developed, was first discussed in 2017 by Wu et al., who analyzed outcomes after fat grafting following lumpectomy in animal models using a peptide hydrogel scaffold loaded with Tamoxifen, attached to human adipose-derived stem cells after liposuction. The authors noted that the scaffold provided support for stem cells engraftment and proliferation while carrying out a selective cytotoxic effect on tumor cells [54].

Conclusions

The international bibliography is continuously enriched with new studies concerning prepectoral breast reconstruction and the results are very encouraging. Prepectoral implant positioning offers less pain, less morbidity and faster recovery, while the percentages of capsular contracture and animation deformity are almost zero in all studies. The need of a very close collaboration between all the specialists involved (radiologist, breast surgeon, plastic surgeon, anatomo-pathologist, oncologist, radiotherapist) is very high, in order to achieve oncological safety and the best aesthetic result.

It is still very early to draw conclusions and more multicenter and prospective studies, together with further studies on animal models, are needed to better understand the indications and contraindications, the detailed guidelines for oncological follow-up, the guidelines for postoperative radiotherapy. In addition, the definition of the economic costs of this approach, is an important issue to define, especially in countries where insurance does not cover this cost and patients are forced to pay out of their own pockets.

We are at the beginning of a new era in breast reconstruction and our duty is to achieve the best for our patients.

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