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Improving Long-Term Projection in Nipple Reconstruction Using a New Human-Derived Acellular Dermal Matrix

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ABSTRACT

Background: Loss of projection is a very common complaint after nipple reconstruction. In this paper, we present our experience with the use of a novel human cadaver-donor-derived acellular dermal matrix, named MODA (Matrice Omologa Dermica Acellulata) from the Regional Skin Bank to improve and stabilize nipple projection after oncoplastic breast surgery.

Methods: We did a retrospective analysis of patients undergoing nipple reconstruction with local flap and MODA graft after breast reconstruction between February 2019 and May 2021. The analysis was done following the Declaration of Helsinki and was approved by the ethics committee; written consent was sought from all the participants. The main evaluation criterion was nipple projection measurement, performed immediately after surgery, 6 and 12 months postoperatively. The secondary endpoints were complications and patients' satisfaction.

Results: In this study, 50 patients underwent nipple reconstruction, with 57 reconstructed nipples. All cases except six followed delayed breast reconstruction. The patients were divided into 3 groups, according to the breast reconstructive technique. There were three cases of delayed wound healing and two cases of partial necrosis, but all of the cases healed by secondary intention. Five percent of the patients (3/57 reconstructions) presented more than 60% of nipple projection loss and required another procedure. The other reconstructed nipples maintained an average of over 60% projection after 12 months.

Conclusion: The described technique presents a high success rate associated with low complications. Indeed, it provides the advantages of nipple reconstruction with ADM with low costs, appears safe after radiotherapy, and has similar results when used after different reconstructive techniques.

INTRODUCTION

Nipple-areola complex (NAC) reconstruction is the final stage to complete breast reconstruction,[1] traditionally done by composite grafting of the opposite nipple or a local flap. However, loss of nipple projection is commonly observed after NAC reconstruction, which is mainly caused by lack of rigid connective tissue support and wound contracture.[2] Maintaining nipple projection is challenging for surgeons, leading to the introduction of numerous techniques throughout the years.[3–6] One of these techniques is the creation of a local flap using

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a graft (autogenous or alloplastic) to maintain projection.[7,8] Autogenous grafts, such as rib cartilage, auricular cartilage, dermal grafts and fat grafts have been successfully used but can result in donor site morbidity and increased operative time for tissue harvesting.[7] With advancements in materials engineering, surgeons have turned to allogenic tissue as a possible source of structure for long-lasting nipple projection.[9]

Acellular dermal matrix (ADM) use in breast reconstructions is well-documented as an implantable material for projection in nipple reconstruction.[10,11] Particularly, the use of rolled ADM as an internal augmentation to maintain projection in nipple reconstructions has previously been reported in an animal model[9] and a series using cylindrical blocks of extracellular, completely absorbable, porcine-derived collagen nipple cylinders has been previously described in humans.[12] The main problem with non-human ADM use in NAC reconstruction, compared to autologous approaches, is the possibility of xenogenic transplant rejection and the relative cost. In this study, we report our preliminary experience with the use of a new human cadaver-donor-derived ADM (named with the Italian acronym, MODA, for Matrice Omologa Dermica Acellulata) from the Regional Skin Bank ("M. Bufalini" Hospital, Cesena, Italy), to enhance and stabilize nipple projection after oncoplastic breast surgery.

METHODS

We performed a retrospective analysis of the patients undergoing nipple reconstruction with local flap and MODA graft after breast reconstruction in our department between February 2019 and May 2021. The analysis was done based on the Declaration of Helsinki and was approved by the ethics committee; written consent for human-derived ADM use was obtained from all the participants. Nipple reconstruction lasted at least 3 months after the breast reconstruction and always before areola tattoo. The main evaluation criterion included the measurement of nipple projection, performed immediately after surgery, 6 and 12 months postoperatively. The secondary endpoints were complications (infections, delayed wound healing, necrosis, etc.) and patients' satisfaction, rated by a visual analogue scale between 1 and 5 (1, poor; 2, disappointing; 3, satisfactory; 4, good; 5, excellent). The same researcher was responsible for making the measurements using a caliper and collected all the data.

Human-Derived ADM Confectioning

The Skin Bank of the Bufalini Hospital obtained the approval for the production and distribution of a new human cadaver-donor-derived ADM (MODA) in 2009 from the Italian National Transplant Center and National Health Institute. Human dermis for MODA confectioning was obtained from the back of multi-organ and/or multi-tissue donors based on Italian national rules on harvesting, processing and distributing tissues for transplantation. In sterile conditions, 10cm dermal patches were dissected using an electric dermatome. Human dermis was decellularized at the Skin Bank of the Bufalini Hospital (Cesena, Italy). Under sterile conditions, the dermis was subjected to a combined treatment of decellularization: first, pretreatment, overnight with 2.5% trypsin 10 (Gibco Invitrogen SRL, San Giuliano Milanese, MI, Italy) in an incubator (5% CO_2 at 37 °C), and second, treatment with a series of washes for at least 15 min each with sterile 0.9% NaCl in order to remove trypsin remnants carefully. Finally, the dermis was irradiated with gamma-rays (100 Gy), frozen and stored in azote vapors at - 180 °C. This human-derived ADM (H-ADM) had to be stored at 4–6 °C for a maximum of 72 h.[13,14]

Surgical Methodology

Surgical design was done with the patient standing up. Height and diameter of the target nipple were determined with regard to the contralateral nipple in the standing position. Expecting the loss of projection, we designed the projection 30 to 40 percent higher than the contralateral nipple. In case of bilateral nipple reconstruction or giant contralateral nipple, the diameter and the height did not exceed 12mm and 10mm, respectively. We used an arrow flap (Figure 1A).

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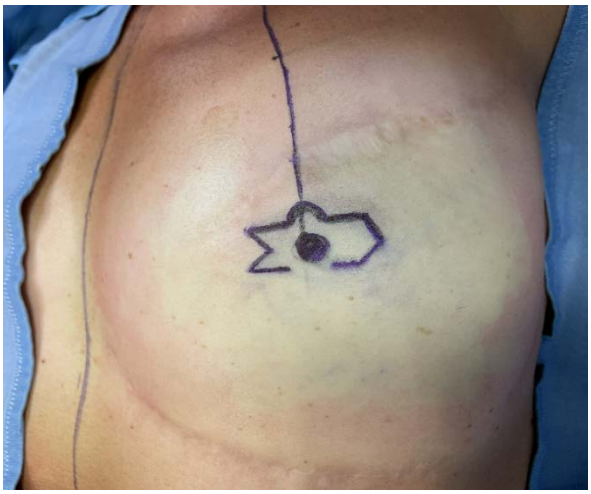

Figure 1A. For this nipple reconstruction series, we used an arrow flap. Expecting the loss of projection, we designed the projection 30 to 40 percent higher than the contralateral nipple.

After local anesthesia using 1% ropivacaine, an incision was made with a no. 11 blade, and the flap, along with the subdermal fat, was carefully elevated (Figure 1B).

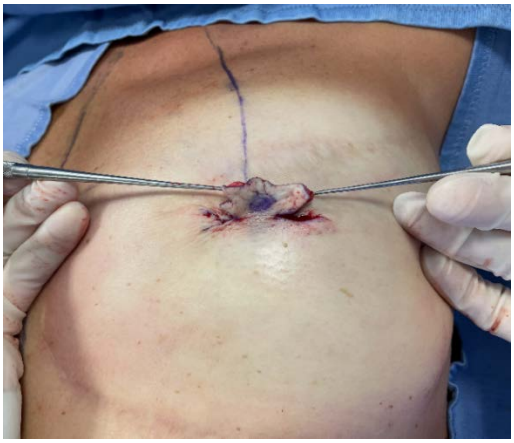

Figure 1B. After local anesthesia using 1% ropivacaine, an incision was made with a no. 11 blade, and the flap, together with the subdermal fat, was carefully elevated.

A 10mmx20mm MODA rectangle (Figure 1C) was shaped as a cigarette and sutured using absorbable sutures (Figure 1D).

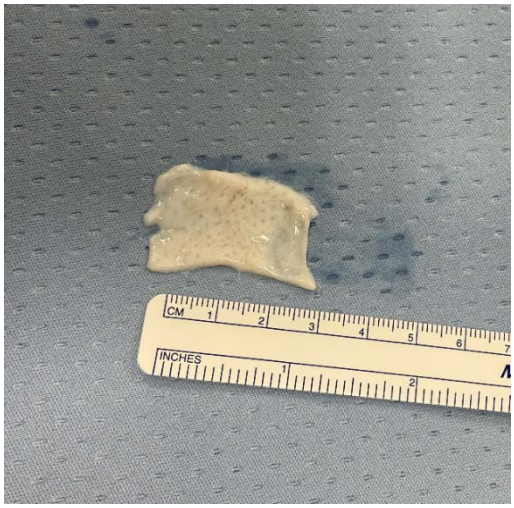

Figure 1C. For each reconstruction, a 10mmx20mm MODA rectangle was used.

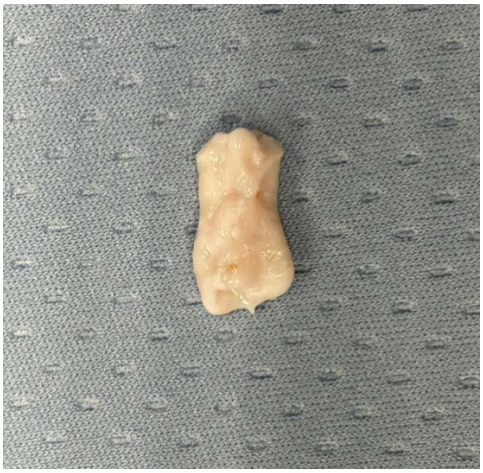

Figure 1D. The MODA rectangle was shaped as a cigarette and sutured using absorbable sutures

The cigarette-shaped H-ADM was placed in the nipple column made up of the two lateral flaps, sutured together (Figure 2A).

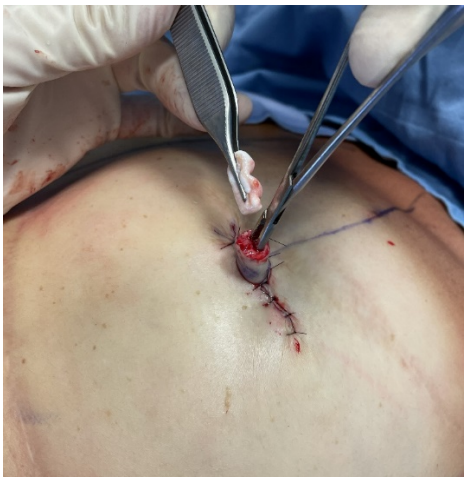

Figure 2A. The cigarette-shaped H-ADM was placed in the nipple column composed of the two lateral flaps sutured together.

Lastly, the donor site and the cap flap were sutured with absorbable and non-absorbable sutures (Figure 2B, 2C).

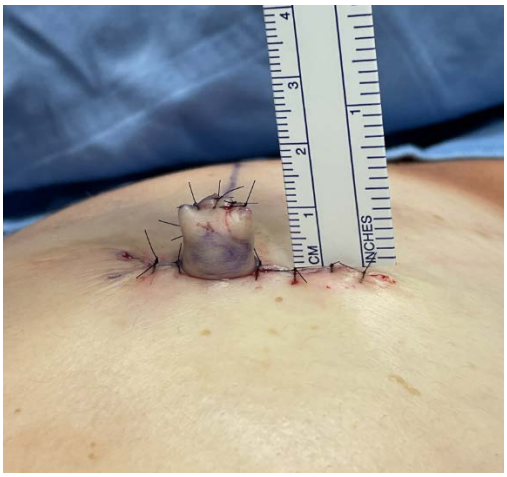

Figure 2B. Lastly, the donor site and the cap flap were sutured with absorbable and non-absorbable sutures

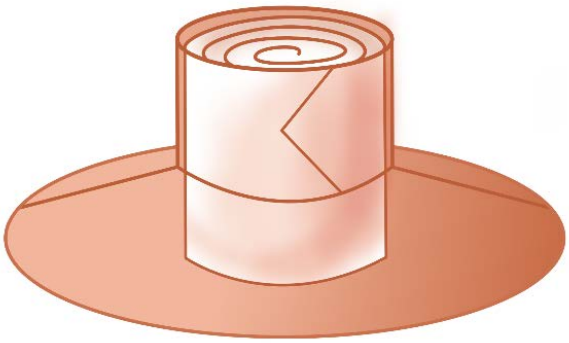

Figure 2C. Scheme of the nipple reconstructive technique described.

After dressing the site with vaseline gauze, a nipple protector was applied to prevent pressure on the new nipple. We used a silicone-based nipple protector, which had a hole in the center with a sufficient diameter and height to protect the new nipple during the early phase of wound healing. The stitches were removed after 10 days and the nipple protector stayed on for 3 weeks postoperatively. The patients were cautioned against applying direct pressure, and areolar tattoo was not performed before 3 months postoperatively.

RESULTS

A total of 50 patients went through nipple reconstruction in the study (Table 1).

Table 1. Demographics of patient cohort

Characteristics	N = 50 (%)
Age (mean, in years)	51.27 (range 28-68)
Chemotherapy	
Adjuvant	12 (24%)
Neoadjuvant	2 (5%)
Radiotherapy	
Adjuvant	16 (33%)
Neoadjuvant	0 (0%)
Reconstruction timing	N = 57 (%)
Immediate	6 (10%)
Delayed	51 (90%)

Seven patients had bilateral reconstruction, so the total number of reconstructed nipples was 57 (Table 2).

Table 2. Surgical characteristics of patient cohort

Surgical characteristics	Number (%)
Number of patients (N = 50)	
Unilateral	43 (86%)
Bilateral	7 (14%)
Reconstructive technique (N = 57)	
Skin expander	31 (55%)
Reverse expansion	15 (27%)
Implant	11 (18%)

All cases except six followed delayed breast reconstruction. Twelve patients underwent adjuvant and 2 neoadjuvant chemotherapy (CT), while 16 patients received adjuvant radiotherapy (RT). They were split into 3 groups: two-stage implant reconstruction using an expander (expander group), reverse expansion (reverse expansion group), and one-stage implant reconstruction (implant group). There were 28 patients (n=31) in the expander group, 13 patients (n=15) in the reverse expansion group, and 9 patients (n=11) in the implant group.

Regarding adverse events, there were three cases of delayed wound healing and two cases of partial necrosis, but all of them were resolved with a secondary closure. No case of infection or hematoma was reported. Five percent of the patients (3/57 reconstructions) had a loss of nipple projection greater than 60% and required a further procedure. The other reconstructions maintained an average of over 60% projection at 12 months (Figure 4). The patients rated the aesthetic result as “Excellent” in 39 cases (77%) and “Good” in 11 cases (23%), with no “Fair” (0%) and no “Poor” results (0%). The results for the three groups are summarized in Table 3.

DISCUSSION

The reconstruction of the NAC may be the simplest step of breast reconstruction from a technical viewpoint, but is considered one of the most important steps from an aesthetic perspective. NAC reconstruction is used to match the contralateral breast in nipple projection and areola size, texture and pigmentation.[15] Reconstruction of the nipple traditionally consists of the composite grafting of the opposite nipple or a local flap.

The former method involves a large opposite nipple and is limited by potential morbidity of the opposite nipple and significant reduction in the volume of the new graft after its survival. In any case, loss of projection is a commonly observed problem which is often difficult to predict. Several methods have previously been found to improve nipple reconstructions and reduce or treat loss of projection. These have included numerous autologous materials use, such as rib cartilage,[16] auricular cartilage,[17] dermal grafts[18] and fat grafts.[19]

Table 3. Comparative results for the three study groups: two-stage implant reconstruction using an expander (skin expander group), reverse expansion (reverse expansion group), and one-stage implant reconstruction (implant group)

	Skin expander	Reverse expansion	Implant
Total number of nipples	31 (55%)	15 (27%)	11 (18%)
Nipple projection	One loss greater than 60%.	Two loss greater than 60%.	None,
Complications	Two delayed wound healing, one partial necrosis.	None.	One delayed wound healing, one partial necrosis.
Patient’s satisfaction	Excellent 26 cases, good 5 cases.	Excellent 12 cases, good 3 cases.	Excellent 8 cases, good 3 cases.

Many of these materials involve introducing a donor site for graft harvest. Nipple reconstructions are usually local anesthetic procedures in skin with reduced sensation and are thus exceptionally well-tolerated by patients. The use of these extra donor sites can be painful, and less well-tolerated, and require longer procedures and sometimes general anesthesia. They also tend to have more variable results and higher complication rates, and therefore they are now largely of historical interest only. Non-autologous methods of nipple augmentation have included the use of artificial bone,[20] polyurethane coated silicone,[21] and the injection of polymethacrylate microspheres suspended in bovine collagen.[22] However, the clinical experiences of many surgeons who have used synthetic products have been different, with some reporting problems of extrusion as the most common challenges.

The use of AlloDerm to increase nipple projection following reconstruction was first described by Nahabedian in 2005.[11] Usually, the AlloDerm is cut into a 10mmx6mm piece although the dimension can vary depending on the size of the skin flaps and the available space. It is then folded and fixed with sutures to maintain its position and shape with the skin flap.[23–26] ADM provides high tissue compatibility, has a proven track record, does not require donor sites, and is available commercially. Although more extensible compared to rigid materials such as cartilage, it is strong enough to resist tension, making it soft yet hard enough to resist nipple widening. Moreover, it has been reported that ADM undergoes a gradual neovascularization when rolled into a cylinder.[27] Holton *et al.* described their experience with human-derived ADM to improve long-term projection in nipple reconstruction in an animal model: complications included ADM migration and extrusion.[9] However, these complications were because of the presence of looser subcutaneous tissue in rats compared to humans, and the authors themselves expected that in humans, the injected ADM would be more likely to stay in the nipple flap as the dermal attachments in humans are formidable.

An important limitation of the use of alloplastic materials in NAC reconstruction, compared to autologous approaches, is the relative cost.[28] However, the cost of MODA is 14€ per cm^3, and 28€ per patient. Indeed, the described technique, in addition to presenting the advantages of using ADM, also presents a low cost. Additionally, because MODA is made from tissue harvested from humans, it does not stimulate a xenogenic response when used in human patients.

Sisti *et al.* observed that the use of flaps with autologous graft/alloplastic/allograft augmentation resulted in less loss of nipple projection (Figure 3, 4); however, they reported that the use of such material might also increase the rate of postoperative flap necrosis.[1]

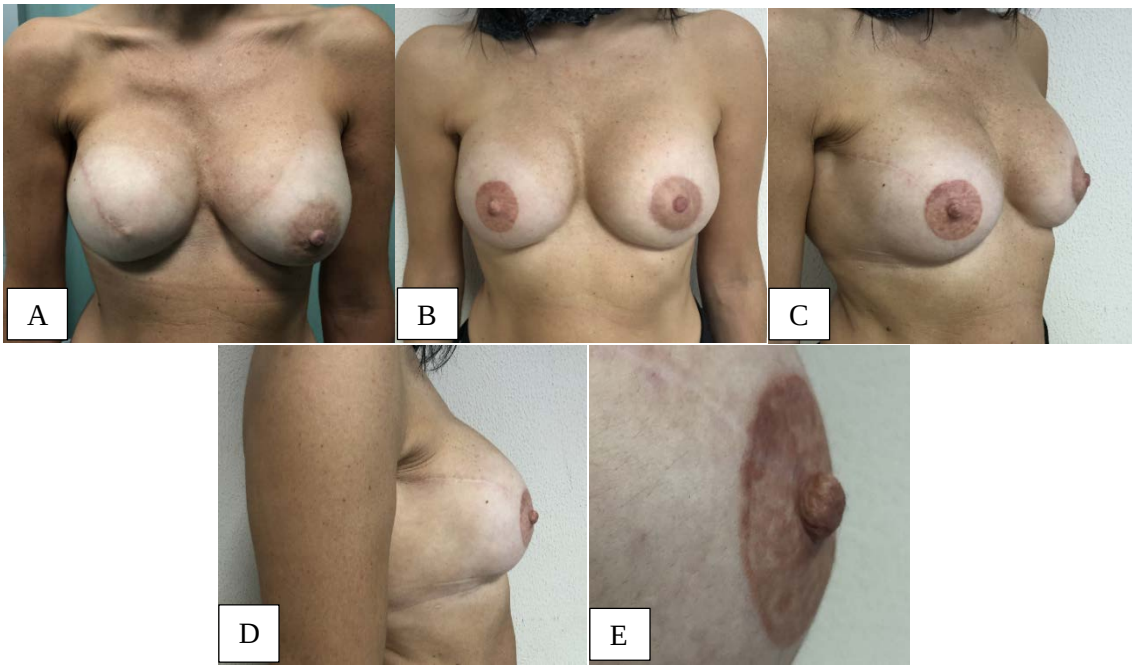

Figure 3. A 47-year-old woman presented with invasive breast carcinoma of the right breast following right mastectomy and two-stage implant reconstruction using an expander. The patient underwent adjuvant chemotherapy and radiotherapy (**A**). Twelve months after nipple reconstruction with H-ADM and areola tattoo, front view (**B**), three quarter view (**C**) and lateral view (**D**). The nipple maintained its projection over time, assuming a very natural appearance (**E**).

In our series, only two reconstructed nipples underwent partial necrosis and therefore loss of projection. The technique also appears safe in radiotherapy fields and has similar results when used after different reconstructive techniques. This demonstrates that the described technique presents a high success rate associated with low complications.

Due to the retrospective nature of this study, the data we collected from the medical record were limited and the analysis we were able to perform was constrained. Likewise, because the study was performed at a single center, the generalizability of our findings is limited. However, our results are valuable and warrant debate, since this is the first study to describe the use of MODA as graft for nipple reconstruction in humans.

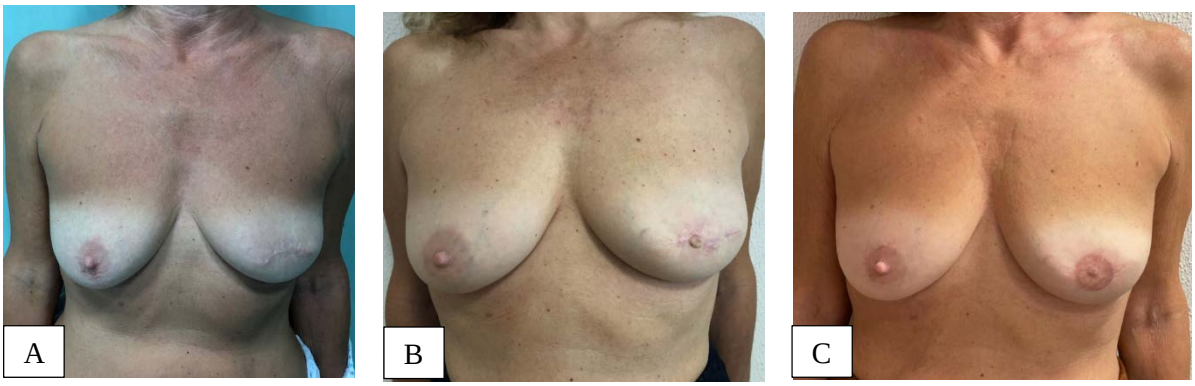

Figure 4. A 58-year-old woman presented with invasive breast carcinoma of the left breast following quadrantectomy and breast parenchyma remodeling (**A**). Twelve months after nipple reconstruction with H-ADM, front view (**B**). Three months after areola tattoo, front view (**C**).

CONCLUSION

In conclusion, we present a promising technique for nipple reconstruction with local flap and human-derived ADM. The reconstructions were successful in both irradiated and nonirradiated patients with only two cases of partial necrosis and loss of projection. Sustaining the nipple projection over time remains to be a challenge.

ETHICAL CONSIDERATIONS

The analysis was done based on the Declaration of Helsinki and was approved by the ethics committee; written consent for human-derived ADM use was obtained from all the participants.

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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