Incidence of capsular contracture on irradiated acellular dermal matrices (ADMs)-assisted prepectoral breast reconstructions

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Background: Recently, the advent of acellular dermal matrices (ADMs)-assisted prepectoral breast reconstruction has shown good aesthetic results and a fast recovery, with a low rate of capsular contracture. However, little is known about the effect that radiation therapy has on the surgery outcomes. The aim of this study is to analyse the influence of radiotherapy on the occurrence of capsular contracture in prepectoral ADM-assisted breast reconstruction.

Methods: The retrospective observational study was conducted at the Venetian Oncological Institute of Padova, where 84 ADM-assisted prepectoral breast reconstructions with Braxon have been conducted in 78 patients between April 2014 and October 2018. Complications (seroma, infection, pain, fever, skin necrosis, dehiscence, implant loss and implant migration) were recorded, with particular attention to capsular contracture.

Results: Patients had an average age of 67.6 years (31.1–83.3 years) and mean BMI 26.2 kg/m^2 (19.5–39.3 kg/m^2), mean follow-up 12 months. Comorbidities were recorded as: 5 active smokers and 3 ex-smokers; 18 hypertensive, 18 vascular diseases (coagulation problems, hypercholesterolemia, diabetes), 10 obese (BMI >30 km/m^2). Mastectomies were mainly skin-sparing [50], followed by nipple-sparing [20] and 16 skin-reducing, 7 with NAC preservation and 7 without; symmetrisation was needed in 24 patients. In our series, 18 breasts were irradiated (22.2% pre-operative, 72.2% post-operative, and 5.5% both treatments). The occurrence of capsular contracture was evaluated comparing non-irradiated patients with those who were. This complication occurred in 3 cases on the total reconstructions (3.6%); 11.1% of the patients who were irradiated experienced capsular contracture at the mean follow-up of 11.2 months (7.5–15 months) while the not-irradiated woman had incidence of 1.5% at 8 months after the surgery. The rates of other complications (seroma, infection, pain, fever, skin necrosis, dehiscence, implant loss and implant migration) were analysed as well.

Conclusions: The outcomes are promising and led us to consider the use of ADM in prepectoral breast reconstruction as a relevant tool in the prevention from capsular contracture, even in irradiated patients.

Keywords: Radiotherapy; prepectoral breast reconstruction; acellular dermal matrices (ADMs); capsular contracture

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Introduction

As a result of a long history of research and different surgical advancements, breast reconstruction (BR) is now an integral part of the oncological treatment of breast cancer (1). Among the different feasible options, prosthetic BR is currently the most common form of surgery offered to women who undergo mastectomy (2,3). Implantation of medical devices for breast reconstruction purposes is a trend that has been dramatically increasing over the past three decades. The emergence of device-related complications came along due to the host foreign body response (FBR), that results in a fibrotic capsule formation (4-6). Capsular contracture (CC) is, in fact, a major complication of implant-based breast reconstruction (IBBR). Its occurrence is driven by a prosthesis-induced FBR and has a cumulative incidence of 6–18% over a 3–6-year period, as reported in core clinical studies of implant manufacturers (5,7). With the aim of decreasing capsule visibility, BR has been performed by placing the prosthesis in a subpectoral position, using the chest wall muscles to cover the implant. Such technique, however, has been proven to lead to deep functional consequences as well as poor aesthetic result (8,9).

Recently, the development and use of bioactive materials for soft-tissue reconstruction such as acellular dermal matrices (ADMs) derived from either allogeneic or xenogeneic sources has markedly increased (4,10). In contrast to synthetic materials, these scaffolds, made of extracellular matrix, perfectly bio-mimic the structure and composition of human subcutaneous tissues thus actively guiding the host response towards a cellular ingrowth of the implanted biomaterial (4,10-12). Mechanistic studies in animal models, as well as human histopathologic studies, suggest that chronic inflammation, capsule fibrosis, and fibroblast cellularity are lower in ADM capsule compared to native breast capsule (13-15). Indeed, although originally intended to provide support and coverage of the breast lower pole, numerous studies have demonstrated that the use of ADMs in breast reconstruction is associated with reduced CC (7,16-19).

A technique involving complete implant coverage using ADM allowed plastic surgeons to revisit the concept of prepectoral surgery, abandoned in the 1980s due to high subcutaneous fibrosis (17,20). In fact, starting from 2012, a substantial number of studies have demonstrated the feasibility, safety, and advantages of this approach, so much so that today the prepectoral breast reconstruction (PPBR) has been widely documented and has become the gold standard of reconstructive breast surgery (19,21-23).

To date, modulation of capsule formation and capsular contracture onset by ADMs has been widely confirmed, with documented prevention even up to 4 years of follow-up (16). What is currently missing is a clear framework regarding the effect of radiation therapy (RT) on IBBR, and more precisely on ADMs and capsule formation in RT settings (12,24). Despite the success achieved so far, RT remains a sort of Achilles heel of the reconstructive process, since it is a well-known risk factor affecting complications and proven to cause increased fibrosis and myofibroblast conversion (12,25,26). Notably, in this setting literature reports a reconstructive failure rate of 20–50%, a major corrective surgery rate of 40%, but most of all it is recognized to increase capsular contracture rates with incidences of 17–60%, hence decreasing the patient satisfaction and aesthetic outcomes (2).

Although some data are available, most of the published research on this topic involves subpectoral reconstruction and postmastectomy radiation therapy (PMRT), leaving however inconclusive and contradictory guidelines (9,24,27). Given the established prepectoral trend and the increasing awareness of biomaterial requirements within biological mechanisms, today a real gap to fulfil in this surgical field is the effect of RT treatment in the context of prepectoral reconstruction with bioactive materials which serves as a protective barrier against FBR. With this study we aim to analyse the influence of RT on the occurrence of capsular contracture in prepectoral ADM-assisted breast reconstruction. We present the following article in accordance with the STROBE reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-141/rc).

Methods

Study design and participants

A retrospective analysis was performed on consecutive patients who underwent ADM-assisted prepectoral implant-based breast reconstructions from April 2014 to October 2018 at the Venetian Oncological Institute of Padova. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written consent has been obtained from the patients. Ethical approval was not required given the retrospective nature of the analysis. Patients' inclusion criteria were defined according to the criteria suggested for the PPBR procedure. They include women with a pinch test >1 cm and a viable skin flap, without tumours involving skin or chest wall. Some of the selection criteria were however less rigid (history of radiation therapy, obese women, smokers, or diabetics). All cases who underwent pre- or post-operative radiation therapy during their cancer treatment were included in the study. Patients with incomplete data were excluded. Attention was directed to patients' age, body mass index (BMI), comorbidities, smoking status, and use of drugs, previous breast surgeries, type of tumour, neo-adjuvant or adjuvant chemotherapy, irradiation treatment (pre-, post-operative, both), type of surgery and mastectomy, breast implant size and hospital stay. Complications of seroma, capsular contracture, infection, fever, pain, hematoma, skin necrosis, dehiscence, implant loss and implant migration were analysed.

Surgical procedure

All reconstructions were performed with the same pig-derived Braxon ADM (Decomed, Venice, Italy) to warrant a standardised approach and reduce variability. Such ADM is a chemical-free, 0.6 mm thick, collagen membrane of dermal origin specifically designed for pre-pectoral breast reconstruction. The operational technique of using Braxon ADM has been previously described (17). Preparation of the ADM involves matrix hydration in room-temperature saline solution for 5 min, to facilitate its handling. Then, anatomical implant wrapping is done cutting away the excess matrix and closing the membrane flaps with adsorbable 3/0 sutures. The ADM-covered implant is then placed in the breast pocket and fixed with cardinal stitches to the un-detached pectoralis major muscle. It is also fixed with multiple quilting sutures to the subcutaneous tissue to eliminate dead spaces and ensure mechanical rest, which favour Braxon ADM integration.

Statistical analysis

Data are presented as mean or frequency (percentage) as appropriate. The reconstruction outcomes (post-operative complications) were calculated both on the total number of breasts and on the total number of breasts present in the two groups, divided as non-irradiated and irradiated. Group comparisons were made using χ^2 test for categorical variables. P-values were considered significant when less than 0.05. Statistical analysis was conducted using Microsoft Excel (Office 365).

Results

Eighty-one patients were eligible for the retrospective analysis. Due to incomplete data for three of them, the study was conducted on 84 pre-pectoral breast reconstructions performed with Braxon ADM on 78 patients. No patients were lost upon follow-up. Data collection started in April 2014 and ended in October 2018. In *Table 1*, patients' details, demographics, clinical and surgical specifics are shown. Patients undergoing skin/nipple-sparing and skin-reducing mastectomies had a mean follow-up of 12 months (range, 1–27 months). Mean age was 67.4 years and mean BMI was 26.2 kg/m^2. Comorbidities were recorded as follows: 10 obese, 18 hypertensive, 18 vascular disease (including coagulation problems, hypercholesterolemia, diabetes) and 16 had multiple comorbidities. Smoking habit was present in 5 patients while 3 were ex-smokers. Chemotherapy (CT) was administered to 35 patients (6 underwent neoadjuvant CT, 25 adjuvant CT and 4 both treatments). Irradiated breasts were the 21.4% (18 breasts) of the total. Of these, 22.2% (4 breasts) were treated pre-operatively, 72.2% (13 breasts) were treated post-operatively and 5.5% (1 breast) were treated both times.

Total complications were calculated as breast-related and are reported in *Table 2*. Considering together non-irradiated and irradiated breasts, the most frequent complications were pain and implant loss, both observed in the 11.9% of the cases. Infection, dehiscence, and seroma were at 9.5%, 8.3% and 7.1% respectively. Hematoma was recorded at 5.9%. Only 3 breasts (3.6%) developed capsular contracture. Low incidence of skin necrosis was observed (1.2%) and no implant migration was recorded. Two patients (2.4%) experienced fever.

A comparison of complication rates between non-irradiated (No-RT group, n=66) and irradiated (RT group, n=18) patients was performed in order to unravel which complications are more likely to occur when ADM-assisted PPBR is performed in a radiation setting. Data are collected in *Table 3*. Complications that were observed with similar rates and not statistically significant between the two groups were seroma, fever, hematoma, and skin necrosis (P>0.05). Radiation therapy seemed to negatively influence the incidence of pain and dehiscence: 9.1% No-RT *vs.* 22.2% RT group, 6.1% No-RT group *vs.* 16.6% RT group. However, none of these differences resulted statistically significant (P>0.05). A higher incidence of capsular contracture was observed in the radio-treated group: 11.1% RT group *vs.* 1.5% No-RT group. These data did

Table 1 Patients' details, demographic, clinical and surgical characteristics

Details	Value
No. of patients	78
No. of breasts	84
Follow-up (months), mean ± SD [range]	12±8.2 [1–27]
Demographic/clinical	
Age (years), mean ± SD (range)	67.4±9.5 (31.1–83.3)
BMI (kg/m^2), mean ± SD (range)	26.2±4.4 (19.5–39.3)
Comorbidities, n (%)	
Obese	10 (12.8)
Hypertension	18 (23.1)
Vascular disease	18 (23.1)
Hypothyroidism	6 (7.7)
Others	13 (16.7)
Multiple	16 (20.5)
Smoking status, n (%)	
Active smokers	5 (6.4)
Ex-smokers	3 (3.8)
Use of drugs, n (%)	
Anticoagulants	9 (11.5)
Other not defined	27 (34.6)
Type of tumour (per breast), n (%)	
DCIS	13 (15.5)
IDC	46 (53.4)
ILC	16 (19.0)
Multiple/mixed	10 (11.9)
Other	0 (0.0)
None	0 (0.0)
Chemotherapy, n (%)	
Neoadjuvant	6 (7.7)
Adjuvant	25 (32.0)
Both	4 (5.1)
Radiotherapy (per breast), n (%)	
Pre-operative	4 (22.2[†])
Post-operative	13 (72.2[†])
Both	1 (5.5)
Surgical (per breast)	
Mastectomy, n (%)	
Nipple-sparing	20 (23.8)
Skin-sparing	50 (59.5)
Skin-reducing (NAC removal)	7 (8.3)
Skin-reducing (NAC preservation)	7 (8.3)
Not defined	0 (0.0)
None	0 (0.0)
Breast implant size (cc), mean ± SD [range]	314.1±77 [125–470]
Hospital stay (d), mean ± SD [range]	2.2±0.3 [1–3]

[†], calculated on the total number of irradiated breasts. SD, standard deviation; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; NAC, nipple-areolar complex.

Table 2 Total complication rates

Complications	Total complications, n (%)
Seroma	6 (7.1)
Capsular contracture	3 (3.6)
Infection	8 (9.5)
Fever	2 (2.4)
Pain	10 (11.9)
Hematoma	5 (5.9)
Skin necrosis	1 (1.2)
Dehiscence	7 (8.3)
Implant loss	10 (11.9)
Implant migration	0 (0.0)

not prove, however, to be statistically significant (P>0.05). Capsular contracture onset was observed to be on average 11.2 months after surgery (range, 7.5–15 months) for the RT group while it occurred 8 months after surgery in the patient that did not undergo radiation therapy. From our analysis only infection and implant loss resulted affected by radiotherapy. The first occurred in the 22.2% of the cases in the RT group (*vs.* 6.1% No-RT group, P<0.05) while the second occurred in the 33.3% of the RT-treated breasts (*vs.* 6.1% No-RT group, P<0.01).

Table 3 Comparison of complication rates in non-irradiated and irradiated patients

Complications	Non-irradiated, n (%)	Irradiated, n (%)	P value
Seroma	5 (7.6)	1 (5.5)	0.767995
Capsular contracture	1 (1.5)	2 (11.1)	0.051822
Infection	4 (6.1)	4 (22.2)	0.038403
Fever	2 (3.1)	0 (0.0)	0.4548
Pain	6 (9.1)	4 (22.2)	0.127285
Hematoma	4 (6.1)	1 (5.5)	0.936018
Skin necrosis	1 (1.5)	0 (0.0)	0.5993
Dehiscence	4 (6.1)	3 (16.6)	0.148982
Implant loss	4 (6.1)	6 (33.3)	0.000961

Discussion

Breast cancer treatment can nowadays rely also on radiation therapy, an established tool that in some cases can reduce the risk of recurrence and improve overall survival (5,28,29). According to a meta-analysis done by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), PMRT reduces loco regional cancer recurrence by 19%, and this translated into a 9% reduction in breast cancer mortality (30). Nevertheless, RT is one of the crucial factors that increase the risk of CC, and often, before mastectomy, it cannot be told *a priori* if the patient is going to need it (24,29). Although not life-threatening, CC has been a challenge in BR surgery calling for preventive strategies since the introduction of breast implants, more than half a century ago (19). Numerous studies have investigated the cause of such fibrotic reaction, and though FBR involvement has been ascertained, today it is common scientific opinion that its aetiology may be multifactorial (7). Consulting the current literature, an interesting recent position on this debated topic ascribes the causes of CC mainly to the use of the pectoralis major muscle, and therefore to the choice of the reconstruction plane (31). However, this perspective does not seem to take account of the historical evolution of breast reconstruction, which, since the 'eighties, has exploited the coverage provided by chest muscles precisely to obviate the high fibrotic rates obtained with subcutaneous prostheses placement (8). Furthermore, recently published data by Spengler *et al.* on the use of different ADMs such as Epiflex®, Strattice® and Braxon® in submuscular direct-to-implant cases, report decidedly improved incidences of CC compared to those occurring with surgeries on the same reconstructive level using the synthetic prostheses alone (32). More than the reconstructive plan, then, a fundamental aspect to fight the onset of CC rather seems to be the choice of reconstructive materials (4,12-15).

Over the last 50 years, the use of implantable materials and devices has risen dramatically, making it necessary to optimise the rationale behind biomaterials through a better understanding of the biological mechanisms involved in the FBR (4,6,10,11). This scientific trend has led to an evolution of the concept of biocompatibility (11). Today, according to D.F Williams and other experts, a material can be defined as biocompatible only in relation to its specific implant site, meaning that a material must interact in a specific way with the contiguous tissues, through similar structure and composition (11). Unlike synthetic materials, ADMs are de-antigenised collagen, perfectly biomimetic with structure and protein composition of mammary soft tissues (4,11,33). Histopathological studies confirm that ADM diminishes the inflammatory and profibrotic signalling hallmark of breast capsule development, thus leading to remodelling and regeneration (4,34,35). Clinically, it is now well recognized that ADM mitigates CC (2,19,36). What is currently under investigation is if this type of biological material, given its bioactive properties, can effectively prevent the onset of CC also in irradiated breasts, which remains a great challenge in the reconstructive process (12,28).

Though most would agree that failure rates with ADM-assisted reconstructions in the setting of any form of RT are higher compared to reconstruction without radiation, there is a significant discrepancy in the actual rates of complications reported even in more recent studies (3). For example, in the context of submuscular surgery, a study by Spear *et al.* on 56 acellular dermis-assisted subpectoral reconstructions, PMRT was associated with a reconstructive failure rate of 21% and a capsular contracture (grade III/IV) rate of 61% (37). On the other hand, in the same setting, Salzberg collects in his retrospective study the largest reported cohort of 104 irradiated breast, highlighting an increase in the incidence of CC in irradiated patients, which however was not statistically significant (19). A few possible explanations for these discrepancies include differences in the materials or technique used or differences in the delivery of RT (3).

In the specific setting of RT, beyond the materials used, the choice of the reconstructive plan can play a role in the onset of CC. In fact, when the pectoralis major is radiated, it becomes fibrotic, it shortens and tightens, elevating any underlying device as the implant pocket starts to contract (2,28,38). Therefore, prepectoral reconstruction, when indicated, could once again demonstrate an extra gear with respect to submuscular reconstruction (2,38). Nevertheless, data on outcomes after one-stage prepectoral BR in the setting of pre-mastectomy or postmastectomy RT are limited (24). This is precisely why our prepectoral case series aims to investigate the impact of radiation treatment on the onset of CC, in order to facilitate clinical practice and potentially improve outcomes. In fact, if the prepectoral approach is now the reconstructive gold standard, there are still no clear guidelines regarding the effects of RT on ADM-assisted breast reconstruction (12). In 2017, Elswick *et al.* demonstrated comparable data between ADM-assisted prepectoral reconstruction with expander and submuscular reconstruction in PMRT setting (9). As the prepectoral technique began being coupled with RT, however, promising data appeared in the literature. Sigalove, for example, recently observed 34 ADM-assisted PPBR with partial implant matrix coverage, in which PMRT seems to be very well tolerated (2.9% implant loss, significant capsular contracture 0%, reoperation rate 2.9%) (2). This result led the author to hypothesise that perhaps the complete coverage of the prosthesis with an ADM combined with the sparing of the pectoral muscle could provide greater protection against the adverse effects of RT than a partial coverage (2). The study from Polotto *et al.* confirms this hypothesis. Authors have investigated a series of one-step PPBR reconstructions with complete ADM-implant coverage followed by PMRT. In this case, apart from a low rate of CC, the authors did not register significant differences in complication and failure rates between PMRT patients and non-radiated ones. Moreover, they ascertained in 87.7% of radiated patients a stability of softness and shape of reconstruction without fat grafting (28).

In relation to such data, our results seem to confirm this positive trend. In our series of 84 ADM-assisted PPBR including radio-treated patients, the overall incidence of CC recorded was 3.6%, perfectly in line with literature results obtained with the same standardized technique (21). When considering RT, we recorded an increased rate of CC in irradiated patients, although in our cohort this result was not significant, likely due to the small sample size. Similarly, most of the complications observed were not significantly different between irradiated and non-irradiated breasts. However, it is worth highlighting the incidence of seroma considering both irradiated and non-irradiated patients, which is set at 7.1%. This result seems in fact to challenge a common prejudice on biological matrices, which some surgeons believe being implicated in seroma formation (20). In this regard, Caputo *et al.* recently conducted a standardised analysis using the complete ADM-implant coverage highlighting the poor correlation between the onset of postoperative serum-related complications and the use of ADM (20). Our data support this last clinical position, especially considering that our patient sample includes both pre- and post-mastectomy irradiated patients, historically related to inflammation and higher post-operative complications (19,24,29). The incidence of seroma in our case series also appears in line with the data reported by the iBAG study, the largest collection of prepectoral cases in the world that defines a clinical-aesthetic standard (21). Among the various complications encountered, however, statistically significant differences between irradiated and non-irradiated patients were the incidences of infections and of implant loss. Contrary to literature evidence (21), we found a higher rate of infection, which significantly worsens in irradiated patients, and which likely correlates with the implant loss data. Nonetheless, it must be considered that all irradiated cases who experienced an infection were elderly patients, and all received chemotherapy.

These findings could help designing more patient-specific antibiotic protocols minimizing this type of complication. Furthermore, our results could be useful to update patient selection criteria, leading to considering RT not as an absolute contraindication to PPBR (the patients' age or administered adjuvant chemotherapy must be taken into account). Patient selection has always been of vital importance in BR, as the presence of risk factors is well known to be associated with adverse outcomes (39).

Our results, together with other publications with this standardized technique (21,28), would seem to lay the groundwork to a cautious opening of patient selection criteria, allowing a wider pool of patients to safely benefit from the advantages of PPBR.

The size of our cohort of irradiated patients is limited and definitive conclusions would require a larger sample. Longer follow-up and a bigger cohort of irradiated patients are needed to better understand if this effect of RT on ADM-assisted prepectoral breast reconstruction is stable and reproducible. Yet, it is becoming increasingly evident that we must tune the reconstructive process with an appropriate choice of the reconstructive materials in order to gain in predictability of the results.

Conclusions

Literature analysis on RT and PPBR still outlines a paucity of high-quality evidence that may guide safe clinical practice. In the last decade, the lowering of CC rates noted with the use of ADMs has increased the awareness on the importance of the biologic response at the interface between implant surface and breast tissue. A total ADM-implant cover technique was therefore chosen and helped us standardising our series of 84 one-stage PPBRs including pre- and post-mastectomy RT cases. Even if our results suggest that RT may be well tolerated in this setting. However, when combined with chemotherapy, care should be exercised when considering PPBR. These findings lead us to consider that the use of ADM in PPBR can be a relevant tool in the prevention against CC, even in irradiated breast.

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Footnote

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