

Long Term Side Effects of Radiotherapy in Breast Conservative Surgery: Proposal of a Management Algorithm Based on a Case Series Analysis

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Abstract

Introduction: Breast Conserving Surgery (BCS) is nowadays an oncologically safety surgical management of breast cancer and provides lumpectomy or partial mastectomy followed by radiation therapy (RT). RT is very effective from an oncological perspective, although it comes with complications, mostly derived from damage effects on the surrounding healthy tissue. Despite a lot has been said through the years about the effect of postmastectomy radiation therapy, very few data can be found in literature of the effect of radiation therapy in breast conserving surgery. We could assume that the same solutions valuable for postmastectomy radiation therapy complications can be performed (such as autologous conversion or fat grafting sessions). Our case series evaluate serious tissue damage of post breast conserving surgery radiation therapy and we would try to access an algorithm of treatment in patients with severe complications.

Material and methods: Patients were analyzed retrospectively, in particular patients who presented to the Plastic, and Reconstructive Surgery department of Cattinara Hospital, Trieste between January 2019 and October 2022. All the included patients undergone BCS and subsequent RT and at the time of first presentation at our department showed long term RT side effects, and so they were coherently treated.

Results: From January 2019 to October 2022, 5 patients have been surgically treated, they presented long term side effects of radiation therapy after BCS. All patients reported a LENT-SOMA score of 3 or 4: in particular two patients

showed only a single skin lesion (without any other aberration of the breast), instead the other three patients presented a huge fibrosis of the mammary gland associated with an important skin retraction (especially around the scar area of previous surgery) and tissue atrophy. One of these cases showed bilateral severe retraction and fibrosis associated with intense pain and hypersensitiveness. According to our experience, patients who presents with long term side effects caused by radiation therapy that state in a LENT-SOMA score between 3 and 4 are suitable for surgical procedures. In case of a single skin lesion with impaired wound healing process, with no other apparent tissue damage or with little damage, this can be treated with fat grafting sessions, in local anesthesia. In cases with severe, wide fibrosis involving all the breast, with skin atrophy and edema, it is often needed to proceed to demolitive surgery instead. In such patients it is suitable and appropriate to remove all the affected glandular tissue along with the skin and perform an autologous reconstruction. In the last group considered in our algorithm, we contemplate patients with less severe condition or patients that refuse autologous reconstruction. In these cases, it is possible to infiltrate fat tissue extensively along all subcutaneous surface of the breast.

Conclusion: We review our cases of severe radiation damage post breast conserving surgery and we create an algorithm of treatment in order to standardize our future management of those conditions.

Introduction

Breast Conserving Surgery (BCS) is nowadays an oncologically safety surgical management of breast cancer and provides lumpectomy or partial mastectomy followed by radiation therapy [1]. Radiation Therapy (RT) is one of the most important advancements in breast cancer treatment, actually it decreases local tumor recurrence increasing the overall survival [2]. RT is very effective from an oncological perspective, although it comes with complications, mostly derived from damage effects on the surrounding healthy tissue. In fact, the goal of radiation therapy is to hit cancer cells causing their death, since they cannot easily repair their DNA damage. The problem is that still nowadays RT inevitably injures healthy cells close to the cancer [3]. Thanks to the progress made in oncoplastic surgery techniques: BCS, compared to the mastectomy, allows patients to afford a better quality of life. Anyway, radiation therapy also brings acute complications (such as erythema, ulceration, and pain) and chronic (such as skin atrophy, edema, lymphedema of the arms and fibrosis). At the end with these kinds of complications a great part of the benefit of this procedure is lost, and patients have a very high discomfort, pain, hardening of the breast and aesthetic problems. As said before the adverse reaction could be acute – immediately after the radiotherapy session – with inflammation and skin desquamation, but long-term effects can appear even years after the RT and that are mainly fibrosis, skin atrophy, dryness, that can lead to ulceration [4]. These adverse side effects are classified by the LENT-SOMA score, proposed by the Cancer and Radiation Therapy Oncology Group [5]. It is made by an objective scale and a subjective one, one about management and one analytical that allows a quantification of the long term side effects of radiation therapy in healthy tissues [6]. Despite a lot has been said through the years about the effect of postmastectomy radiation therapy, very few data can be found in literature of the effect of radiation therapy in Breast Conserving Surgery. We could assume that the same solutions valuable for postmastectomy radiation therapy complications can be performed (such as autologous conversion or fat grafting sessions) [7], anyway the same complications could happen in Breast Conserving Surgery, given the fact that the damage is carried onto the tumor bed such as on the surrounding healthy tissue, and the same effects of edema, fibrosis, pain and induration of the breast could verify. Our case series evaluate serious tissue damage of post Breast Conserving Surgery radiation therapy and we would try to access an algorithm of treatment in patients with severe complications, stated that there is very few data in literature about this topic.

Materials and Methods

Patients, who presented to the Plastic and Reconstructive Surgery department of Cattinara Hospital (Trieste, Italy) between January 2019 and October 2022, were analyzed retrospectively. All the included patients underwent BCS and subsequent RT. At the time of first presentation at our department showed long term RT side effects, and so they were coherently treated. Patient demographics, RT dose data, previous surgeries, comorbidities, smoke status were noticed. Clinical examination was described, photos with patients' consent have been collected, and all features have been classified according to the LENT-SOMA scale (Table 1). Due to the small number of patients, no statistical analysis has been made, but only a descriptive statistics.

Table 1: LENT-SOMA score, proposed by the Cancer and Radiation Therapy Oncology Group (5).

	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Subjective Pain	Occasional & minimal Hypoesthesia, Pruritus	Intermittent & tolerable	Persistent & intense	Refractory & excruciating
Objective				
Edema	Asymptomatic	Symptomatic	Secondary dysfunctions	
Fibrosis /Fat necrosis	Barely palpable increased density	Definite increased density and firmness	Very marked density, retraction and fixation	
Teleangiectasia	<1/cm ²	1-4/cm ²	> 4/cm ²	
Lymphedema, arm (circumference)	2 cm - 4 cm increase	> 4 cm -6 cm	> 6 cm increase	Useless arm, angiosarcoma
Retraction/Atrophy**	10% -25%	> 25% - 40%	> 40% - 70%	Whole breast
Ulcer	Epidermal only, <1 cm	Dermal, > 1 cm	Subcutaneous	Bone exposed, necrosis
Management				
Pain	Occasional non-narcotic	Regular non-narcotic	Regular narcotic	Surgical intervention
Edema			Medical intervention	Surgical intervention/ mastectomy
Lymphedema, arm		Elevate arm, elastic stocking	Compression wrapping, intensive physiotherapy	Surgical intervention/ amputation
Atrophy				Surgical intervention/ mastectomy
Ulcer		Medical intervention	Surgical intervention, wound debridement	Surgical intervention/ mastectomy
			x*	
Analytic				
Photographs	Assessment of skin changes as atrophy, retraction or fibrosis, ulcer			
Tape measure	Assessment of breast size and forearm diameter			
Mammogram	Assessment of skin thickness and breast density			
CT/MRI	Assessment of breast size, fat atrophy, and fibrosis density			

Results

From January 2019 to October 2022, 5 patients, who have been surgically treated with BCS and subsequent RT, presented to our department with long term side effects of radiation therapy. Median patients age at surgery was 63 years, median time follow up from RT to the presentation at our department was 5 years, all patients did not have any comorbidities such as diabetes, vascular disease, none of them smoked. All patients reported a LENT-SOMA score of 3 or 4. In particular two patients showed only a single skin lesion (without any other aberration of the breast), instead the other three patients presented a huge fibrosis of the mammary gland associated with an important skin retraction (especially around the scar area of previous surgery) and tissue atrophy. One of these cases showed bilateral severe retraction and fibrosis associated with intense pain and hypersensitiveness. All of them demonstrated an important reduction in terms of quality of life and psychological features.

Proposed Algorithm (Figure 1)

According to our experience, patients who present with long term side effects caused by radiation therapy that state in a LENT-SOMA score between 3 and 4 are suitable for surgical procedures. In case of a single skin lesion with impaired wound healing process, with no other apparent tissue damage or with little damage, this can be treated with fat grafting sessions, in local anesthesia. In these cases, the collected adipose tissue – after being purified of oil, blood components, and infiltration fluid – is infiltrated subcutaneously under the bed ulcer. It is also possible to put a part of the lipoaspirate directly on the wound bed (nano-fat). In cases with severe, wide fibrosis involving all the breast, with skin atrophy and edema, it is often needed to proceed to demolitive surgery instead. In such patients it is suitable and appropriate to remove all the affected glandular tissue along with the skin and perform an autologous reconstruction. In the last group considered in our algorithm, we contemplate patients with less severe condition or patients that refuse autologous reconstruction. In these cases, it is possible to infiltrate fat tissue extensively along all subcutaneous surface of the breast. Our algorithm provides for 3 sessions of lipofilling or less if there is a clear improvement in symptoms after the first or second session. Generally, we let 3-4 months pass by between one session and the next one. Using this simple method all treated patients have experienced a complete resolution of signs and symptoms, both considering aesthetic aspect and pain, along with other features. Here follows briefly three illustrative clinical cases.

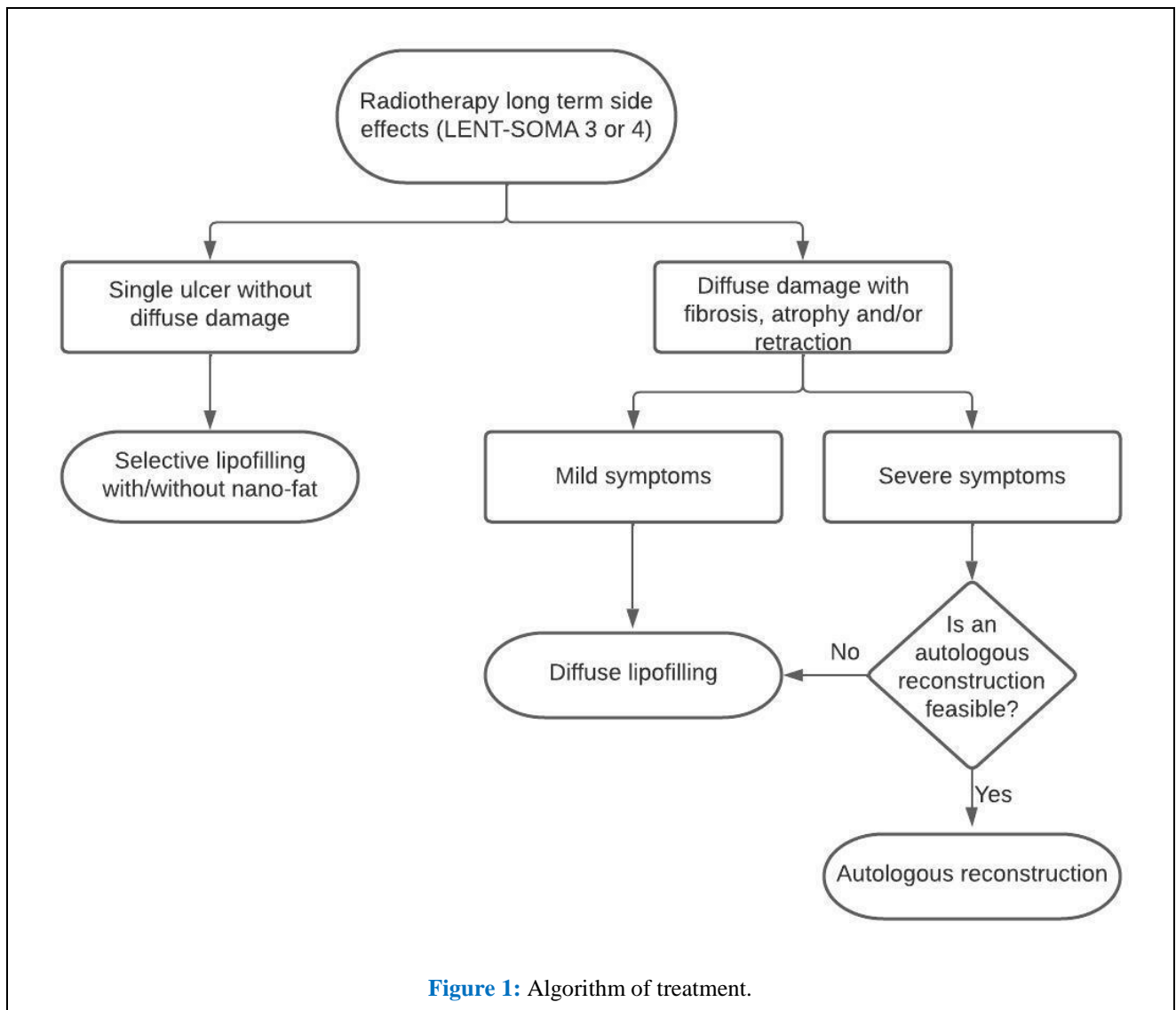


Figure 1: Algorithm of treatment.

Case 1

Patient of 78 years old, presented at an outpatient visit with an ulcer on the breast. She underwent a lumpectomy with subsequent radiation therapy 17 years before. She told us she has been treating this lesion without success for ten years. She has also been submitted to multiple biopsies and pathological examination that assure the neoplastic, infectious and autoimmunity nature of the wound. Lots of attempts have been made in order to surgically remove the lesion with as result an increase in ulcer's width and skin atrophy. We performed three sessions of lipofilling of the ulcer's region, every 3-4 months that led to a complete resolution of the wound and the associated symptoms (**Figure 2**).

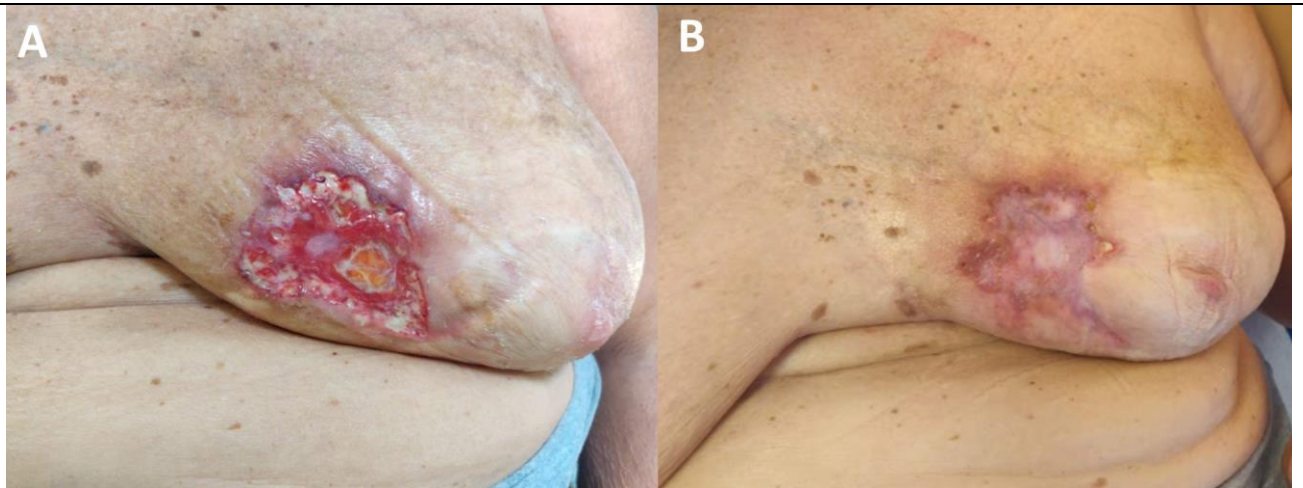


Figure 2: S.E. (78 y.o.) underwent lumpectomy with subsequent radiation therapy 17 years before (A). Results after three sessions of lipofilling of the ulcer's region (B).

Case 2

Patient of 63 years old that have been submitted to bilateral lumpectomy and oncoplastic breast surgery with subsequent radiation therapy. A few months after the radiation therapy she developed skin retraction, atrophy and massive skin hypersensitivity that became after intense pain. She underwent ultrasound and mammogram, that tested negative for disease recurrence, and then skin biopsies that ruled out other possibilities, like autoimmune diseases, hence the damage has to be considered as a post-radiation therapy one. Considered the width of the damage (bilateral breast and sternum area), patients was proposed a bilateral DIEP flap reconstruction but she refused, so she underwent multiple sessions of lipofilling. The surgeries were done every 3- 5 months and have led to an improvement in breast texture (which was much more tender), a huge reduction in pain, without any improvement in aesthetic features, indeed. She is anyway satisfied and doesn't wish for further surgeries (**Figure 3**).



Figure 3: R.A. (63 y.o.) underwent bilateral lumpectomy and oncoplastic breast surgery with subsequent radiation therapy (A). Results after multiple sessions of lipofilling (B).

Case 3

Patient of 57 years old that underwent lumpectomy and radiation therapy 5 years before. She developed, during these past few years, an important skin reduction with fibrosis, atrophy and pain in all the remaining breast glandular tissue. So she was submitted to a mastectomy (that removed all the breast tissue affected along with all the retracted and fibrotic skin, as well as the NAC which was deeply retracted) and autologous reconstruction with a DIEP flap. She healed completely without complication and with complete resolution of the previous pattern of fibrosis and pain (Figure 4).

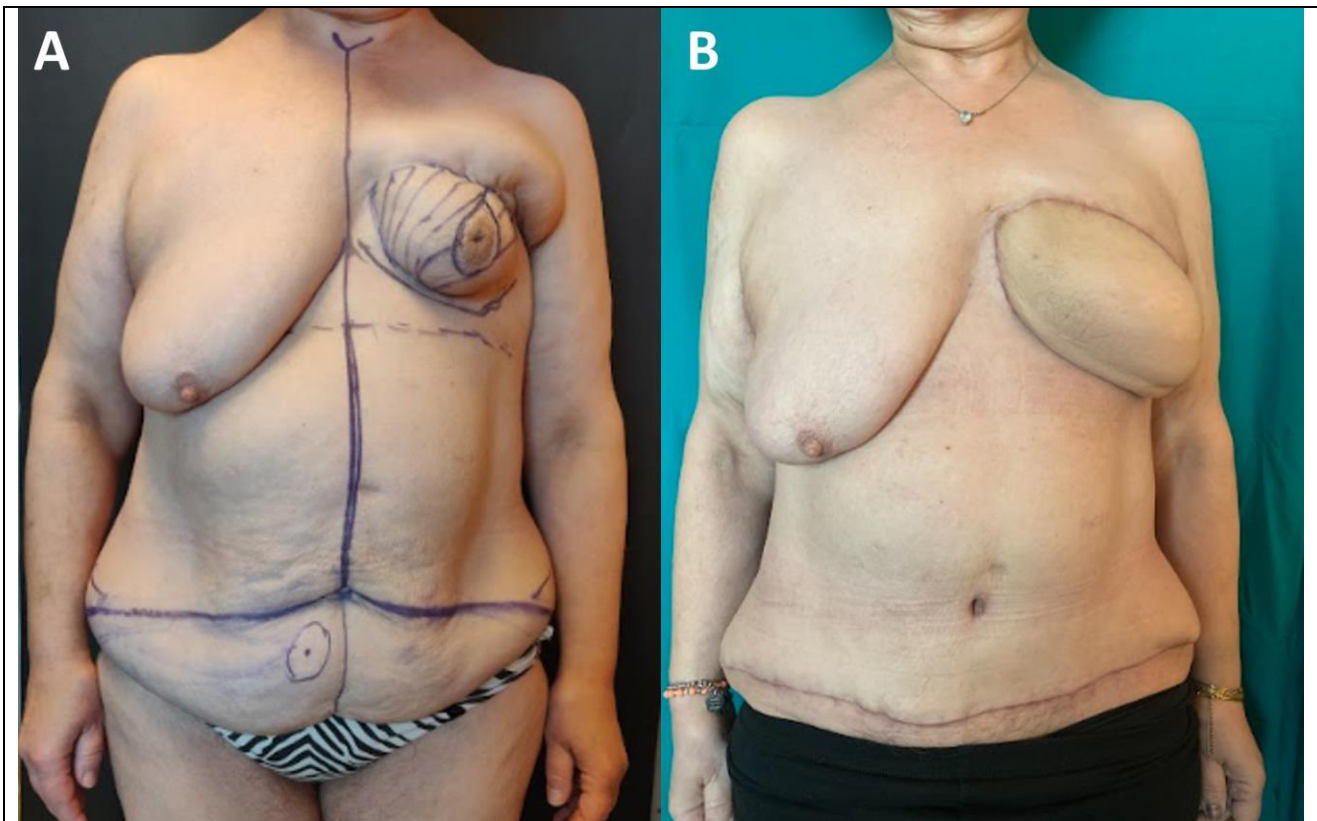


Figure 4: S.L. (57 y.o.) underwent lumpectomy and radiation therapy 5 years before (A). Results after mastectomy and autologous reconstruction with a DIEP flap (B).

Discussion

Breast cancer is the most commonly diagnosed cancer among American. Women, about 30% of all newly diagnosed cancers in women each year are breast cancer [8]. Breast cancer accounts for 12.5% of all new annual cancer cases worldwide. About 13% (about 1 in 8) of American women are going to develop invasive breast cancer in the course of their life. Early diagnosis is the only real weapon that women have to defeat breast cancer and also to get conservative treatment to obtain a better aesthetic breast shape. The possible curative treatment range has changed in the last twenty years, it has modified and evolved: from total mastectomy to minimally invasive surgery (lumpectomy). Rather than rely on systemic interventions in response to inadequate surgical approaches, surgeons now place greater emphasis on meticulous planning and skilled execution combined with radiotherapy to minimize local relapse while maintaining cosmesis [9]. Breast Conserving Surgery followed by radiotherapy has become less invasive without compromising survival and aimed at improving Quality of Life (QoL) in terms of satisfaction with cosmesis. Despite that, short-term patient-perceived aesthetic results after BCS can still be displeasing [10] because some patients suffer from chronic late side effects of RT: atrophy of the breast, skin damage, breast edema, lymphedema of the arm or pain [2]. Although radiation therapy is one of the most significant evidence-based advancements of modern cancer care, decreasing local tumor recurrence and increasing overall survival rates for a variety of malignancies. It is estimated that around 50% of cancer patients receive RT. A major area of concern is the damaging effect of RT on normal neighboring tissues. As cancer survival rates continue to improve, increasing numbers of patients will live with the long-term effects of RT. Mechanisms of radiation injury are induced by ionizing radiation directly or indirectly (via reactive oxygen species) damages DNA, prompting a cascade of events that may lead to cell death. The degree of cell killing and resistance varies based on properties such as degree of differentiation and mitotic rate, and also cumulative and fractional radiation

dose. Fibrosis are caused by inflammation and acute injury, leading to fibroblast proliferation and increased extracellular matrix deposition, along with vascular insufficiency [11]. The treatment of the effects of RT has been studied and analyzed in many studies in its repercussions in prosthetic and autologous breast reconstruction. Also regenerative surgery with multiple autologous fat grafts has been proven to be a satisfactory approach in the radio-damaged breast [12-14]. As far as we know, there are no articles in the literature regarding the treatment of long-term damage from radiotherapy in Breast Conserving Surgery.

Solutions for this kind of patients could be the conversion to autologous breast reconstruction or multiple sessions of fat grafting [15]. Speaking of fat grafting, this has gained more attention both for the ease of the procedure, and for Adipose Derived Stem Cells (ADSC) properties, which are the most important fat components [16]. Fat grafting can improve thickness and tissue adhesion [17], in particular ADSCs are believed to have the main role in all the benefits of the procedure, compared with other stem cells (such as the bone-marrow stem cells) they are helpful especially in the wound healing process and tissue regeneration [18-21]. In particular, the Stromal Vascular Fraction (SVF) from the adipose tissue contributes to the creation of a mature vascular network composed of arteries, capillaries, veins, as well as lymphatics, structurally and functionally connected with the host circulation, also with a paracrine angiogenic activity, that results in an improvement of tissue revascularization. This paracrine activity is given by SVF, in particular by endothelial cells ECs (CD45–CD31+CD146+CD34+), pericytes (CD45–CD31–CD146+CD34–CD90+) and a large proportion of mesenchymal cells, also named fibro-adipogenic progenitors FAPs (CD45–CD31–CD146–CD34+) [22]. According to our experience, it is reasonable to argue that the optimal treatment of radiotherapy complications classified as LENT-SOMA 3 and 4 is lipofilling with or without breast nano-fat, especially in the case of single ulcer. Ulcerectomy surgery is followed by a high risk of local recurrences in relation to the diffuse tissue damage caused by radiotherapy. In agreement with the proposed algorithm, in case of more severe and extensive complications (diffuse tissue damage with fibrosis, atrophy and/or detracton) we believe that the therapeutic gold standard is, in case of moderate symptoms, multiple sessions of diffuse lipofilling, while in case of severe symptoms eventual breast reconstruction with autologous tissue. Bearing in mind our experience we assumed that our algorithm could be a good tool for the treatment of cutaneous side effects of RT after BCS.

Conclusions

We review our cases of severe radiation damage post breast conserving surgery and we create an algorithm of treatment in order to standardize our future management of those conditions.

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