5

The Role of Free Fat Graft in Breast Reconstruction After Radiotherapy

Pietro Panettiere, Danilo Accorsi and Lucio Marchetti
Dipartimento di Scienze Chirurgiche Specialistiche ed Anestesiologiche, University of Bologna
Italy

1. Introduction

Free fat grafts in plastic surgery and in regenerative medicine are extremely promising. Their use in breast reconstruction and in particular after radiotherapy is radically changing the approach to the problem.

2. Radiotherapy and tissue damage

Radiotherapy is a fundamental therapeutic resource in a large majority of neoplastic diseases. But adverse reactions and complications can severely damage the irradiated tissues. Adverse effects can be distinguished into early (within few weeks to 90 days from treatment) and late ones (months to years from exposure). Late adverse effects are primarily the result of radiation-dependent reduction of stem cells or progenitors (Brush, 2007; Rodemann & Blaese, 2007). Fibrosis, teleangiectasias and atrophy are the most common late effects for skin and subcutaneous tissues and those most frequently observed in irradiated breast cancer patients. The mean concentrations of collagen are two times higher in irradiated skin than in non-irradiated skin thus leading to fibrosis (Autio et al, 1998; Riekki et al, 2002). There seems to be a genetic predisposition for fibrosis and teleangiectasias as a response to radiotherapy. Fibrosis risk is also associated with an inflammatory response, whereas telangiectasia is linked to endothelial cell damage. Atrophy is related to an acute response, but no genetic predisposing factors have yet been identified. (Quarmby et al, 2003; Andreassen et al, 2005; Giotopoulos et al, 2007). The reconstructive properties of adipose tissue are also significantly altered (Poglio et al, 2009) as the stromal microenvironment is unable to self-repair the injury suffered. Depletion of the stromal compartment leads to a loss of the precursor reservoir, thus compromising its ability to maintain tissue homeostasis. In response to ionizing radiation, fibroblasts and macrophages remain in an activated state, continuously generating growth factors and free radicals (Barcellos-Hoff et al, 2005) which are the main reasons for fibrosis. Radiations also severely harm the homeostatic network connecting parenchymal, mesenchymal, and vascular cells within tissues and normal interactions between cells are therefore altered (Barcellos-Hoff et al, 2005; Bentzen, 2006). Late adverse effects of radiotherapy in breast reconstructions can consequently cause flap failure, implant exposure, and capsular contracture in prosthetic breast reconstructions. The final aesthetic results can also be compromised due to liponecrosis.

The Late Effects of Normal Tissue-Subjective Objective Management Analytical (LENT-SOMA) scale (Pavy et al, 1995) is considered the gold standard when evaluating radiation injury (Hoeller et al, 2003), as it provides both subjective and objective analyses and a detailed and specific description of the nature and severity of the injury.

3. Adipose-Derived Stem/Stromal Cells (ADSCs)

3.1 The features of the ADSCs

The ideal stem cell for use in tissue regeneration needs to be abundantly available, harvested with minimal morbidity, reliably differentiated down various pathways and able to be safely and efficaciously transplanted. Adult human adipose tissue contains a population of mesenchymal stem cells (MSC), named "adipose-derived stem cells" or "adipose-derived stromal cells" (ADSC), which seem to fulfil most, if not all, of these criteria. They are part of the stromal vascular fraction (SVF) that also contains a large amount of mature endothelial and hematopoietic cells. ADSCs can be harvested readily, safely, and in relative abundance by liposuction techniques. Their abundance in adipose tissue is 100 to 500 fold higher than that of MSCs in bone marrow. Their functional properties are: multipotency, functional cell support (stromagenesis), and modulation of immuno-inflammatory functions. Most of these effects are believed to be mediated via paracrine activity (Caplan & Dennis, 2006; Phinney & Prockop, 2007), so that the fat is considered as a true endocrine tissue (Casteilla et al, 2005; Gimble et al, 2007; Uccelli et al, 2008; Wang et al, 2008). The multipotency of ADSCs was first proved *in vitro* by Zuk (Zuk et al, 2002) and several works proved that they can differentiate into other mesenchymal tissue types, including adipocytes, chondrocytes (Erickson et al, 2002), myocytes and osteoblasts (Cowan et al, 2004) as well as they are claimed to differentiate also into nerves (Kang et al, 2003), cardiomyocytes, hepatocytes and pancreatic endocrine cells, even if their *in vivo* potential still remains unclear. Therefore, fat cells are supposed to effectively supply any tissue texture both in trauma reconstruction and for aesthetic needs (Wickham et al, 2003; Gimble & Guilak, 2003). Angiogenic properties were also observed, even more efficient than the bone marrow MSCs one (Y. Kim al, 2007), probably linked to the secretion of vascular endothelial growth factor (Cousin et al, 2003; Planat-Benard et al, 2004; Mazo et al, 2008; Ebrahimian et al, 2009) or other cytokines/chemokines (HGF, placental growth factor, FGF-2, TGF-β, and angiopoietin-1). This suggests that ADSCs may have a potential as cell sources for therapeutic angiogenesis (Murohara et al, 2009). Angiogenic activity was shown to increase in hypoxic conditions (Rehman et al, 2004; Weil et al, 2009), but aging could reduce angiogenic potentials (Efimenko et al, 2011). A very efficient immunosuppressive capability and modulation of inflammation both in vitro and in vivo were also shown (Puissant et al, 2005; Yañez et al, 2006; González et al, 2009; Constantin et al, 2009) as demonstrated in healing chronic wounds in Crohn's fistulae (Garcia-Olmo et al, 2008, 2009; Ebrahimian et al, 2009).

3.2 Adipose-tissue Derived Stem Cells (ADSCs) in irradiated tissues

An increasing number of studies addressed lipofilling in irradiated tissues (Rigotti et al, 2007; O. Amar et al, 2008; Phulpin et al, 2009; Faghahati et al, 2010). The rationale for the use of ADSCs in irradiated tissue repair stems from the consideration that late adverse effects of radiotherapy derive from the destruction or the loss of functionality of ADSCs and, in

particular, the loss of self-repair properties, chronic inflammation and destruction of microcirculation. The fat grafts can replace atrophic functional niches (the complex made of cell, extracellular and biochemical elements whom the adipose cell interacts with) with physiologic ones, thus playing their normalizing role on the receiving tissue. The normalizing role of free fat grafts in tissue regeneration was pointed out by several clinical studies (Moseley et al, 2006; Rigotti et al, 2007; Locke & de Chalain, 2008; Panettiere et al, 2009; Sarfati et al, 2011). In a recent work (Panettiere, 2011), USG and MR of a free fat grafts reconstructed breast suggested that the proliferation and differentiation of the ADSCs allowed the formation of a perfectly normal structural tissue. Moreover, a quite high density of perivascular stem elements was found, demonstrating a persistent regenerative potential.

An important reduction of fibrosis was also observed (Rigotti et al, 2007; Panettiere et al, 2009, 2011). The immunoregulatory activity and the capacity to modulate inflammation displayed by ADSCs can at least partially explain such behaviour. Recent studies therefore started challenging the dogma of the relative contraindication of prosthetic reconstruction after radiotherapy (Percec, 2008; Panettiere et al, 2009; Salgarello et al, 2010).

3.3 Neoplastic degeneration of the ADSCs or activation of dormant neoplastic cells

The immunosuppressive effect associated with angiogenic properties of ADSCs, as well as their paracrine activity, raised questions about their interactions with cancer cells. A positive correlation between obesity and cancer is well-known (Roberts et al, 2010). Some authors observed that ADSCs can promote tumour growth (Zhang et al, 2009; Lin et al, 2010; Prantl et al, 2010; Zhao et al, 2010; Nomoto-Kojima et al, 2011; Zimmerlin et al, 2011). Tumour growth beyond the size of 1-2 mm is angiogenesis-dependent. Therefore, it was hypothesized that the angiogenic spike induced by MSCs or ADSCs could awake dormant cancer cells (Naumov et al, 2006; Vessella et al, 2007; Indraccolo et al, 2006; Favaro et al, 2008); but more recent studies (Donnenberg et al, 2010; Zimmerlin et al, 2011) concluded that ADSCs could trigger tumour growth from active cancer cells, but not from dormant ones. Moreover, ADSCs promoted tumour growth only when transplanted at the beginning of the neoplastic process. An unusual cell line was observed to emerge from a culture of human ADSCs. Though being proved to be unable to form tumours, they presented alarming similarities with human angiosarcoma (Ning et al, 2009). At present, there is no firm evidence that ADSCs can directly promote tumorigenesis and some works showed an even inhibitory effect of ADSCs when implanted in pre-existing tumours (Cousin et al, 2009). It was thus suggested that reactive cross-talk can take place between ADSCs and other cell types that maintain a proper tissue development and a correct balance between proliferation and differentiation (Casteilla et al, 2011).

Some works addressed the angiogenic capability and suspected that ADSCs respond to chemotactic factors and migrate to the sites of injuries, inflammation, and/or tumour (Kubis et al, 2007; J.M. Kim et al, 2007; Constantin et al, 2009; Lamfers et al, 2009; Lee et al, 2009; Lin, 2010; Gehmert et al, 2010; U. Kim et al, 2011). This property was used in a recent experimental work where engineered ADSCs (able to convert 5-fluorocytosine into the 5-fluorouracil) engrafted into tumours and micro-metastases, activating prodrugs directly within the neoplastic mass (Cavarretta et al, 2010). The secretion of anti-apoptotic factors, and the T cell-mediated immune response suppression have been blamed for a tumour-supporting role (Jones & McTaggart, 2008; Fox et al, 2007; Wels et al, 2008). ADSCs can be

found everywhere in the body and their ability to migrate is not a peculiarity of transplanted cells. So, any ADSC in the body could migrate and promote cancer growth and not only transplanted ones. In irradiated patients very few ADSCs can be found in the site of possible residual tumour cells due to radiotherapy itself. So fat grafts implanted directly in the irradiated site could restore a tumour-supporting environment. But this could happen also with flap reconstructions where the ADSCs present in the subcutaneous fat of the flap are transferred to the irradiated areas. Much concern could be raised by *in vitro* stimulated ADSCs. Anyhow, a potential different behaviour between native and cultured cells remains an open question. A recent limited clinical study with a good follow up found no increase in the recurrence rates in patients treated with fat grafts (Petit et al, 2011). A single case of a late osteosarcoma recurrence 18 months after free fat graft was reported (Perrot et al, 2010). In any case, the risk for possible cancer promotion in the context of cancer related diseases cannot still be ruled out at present.

4. The free fat grafts

Free fat grafts were first described by Neuber (Neuber, 1893). In 1914, Bruning (Bruning, 1914) was the first to inject autologous fat into the subcutaneous tissue. Liposuction provided large volumes of autologous fat that could be re-injected. Since 1985 the first works about fat re-implantation from liposuction were published (Illouz, 1985, 1986a, 1986b; Chajchir & Benzaquen, 1986).

4.1 Techniques for fat harvesting

The keystone of fat graft is to transplant as many vital cells as possible in the best survival conditions, while injecting more (nonviable) graft material is useless. The keys for graft survival are well known: adequate donor site, atraumatic harvesting, short time between collection and re-implantation, suitable host bed and adequate stabilization.

As far as regards the best donor site, there is no clear evidence in the literature. In a recent survey, the most preferred site for fat harvest was the abdomen (89%), followed by thighs (34%), flanks (25%), gluteal regions (12%), and knees (9%) (Kaufman et al, 2010). Rohrich found no significant difference in the viability of fat cells collected from the abdomen, flank, thigh, and medial knee (Rohrich et al, 2004). Similar conclusions were obtained by other authors using preadipocytes from the abdomen, breast, and buttock (Von Heimburg, 2004) or from thigh, abdomen, and breast (Ullmann et al, 2005). The donor site choice seems to play a negligible role in graft take. When they are used as fillers, site choice should be based on ease and safety of access, fat distribution and abundance, and patient's preference. When treating critical host beds (as irradiated tissue) or when ADSCs are paramount (as in regenerative surgery), donor site choice could be more significant. Some animal model works showed that the potential of ADSCs differs according to the location of adipose tissue from which they are purified (Prunet-Marcassus et al, 2006). In a recent experimental study, we reported function related structural specializations of adipose tissue, depending on the harvesting site. Large cells and few blood vessels with rare stem niches are present in deposit adipose tissue (large fatty depots like the abdominal area), while good vascularity and adequate staminality can be found in structural adipose tissue (limbs, hips, knees or the trochanteric areas) (Sbarbati et al, 2010).

Another consideration stems from the possible effects of local or general cancer therapies on the number or the viability of ADSCs. A recent work proved that adipose tissue can be severely damaged by radiotherapy, so that the number of ADSCs is deeply reduced and its potential for use in regenerative therapies is dramatically limited (Poglio et al, 2009). Therefore, the donor site should be chosen distant from irradiated areas. No work studied the effects of chemotherapy, monoclonal antibodies or hormone suppression on the number, viability and functionality of ADSCs. Therapies addressing angiogenic activity of tumours or directly interacting with adipose tissue may be relevant and there may be differences in the regenerative effectiveness of fat grafts in patients treated with such therapies. Specific studies may be advisable.

The possible damage induced by harvesting technique has widely been studied. When maximum vacuum levels were comparable, mechanical suction and handheld syringe aspiration showed no difference in injury to fat cells. But histologic studies of human fat grafts demonstrated that relative vacuum levels greater than -500 hPa caused cell membrane expansion and deformation, while membrane rupture and fat cells vaporization occur with higher levels (Niechajev & Sevcuk, 1994). When using large syringes (20-60 mL), extraction normally produces less than -600 hPa vacuum levels and rapidly decreases as the fluid and fat are pulled. Fournier (Fournier, 1988a, 1988b, 1990a, 1990b, 1996, 2000) and Coleman (Coleman, 1995, 1997, 2001) clinically showed that relatively high level suction decreased viable cells concentrations compared to manual aspiration; therefore, they underlined the need for atraumatic harvesting. Tholen observed that very few viable fat cells were present in fat from standard liposuction (large cannula, high vacuum) due to a significant damage (mainly cell membranes rupture) in a large number of lipocytes. On the contrary, a significantly higher rate of intact and viable adipocytes was found when fat was harvested with atraumatic, low-vacuum syringe technique. (Tholen et al, 2010).

Surface adipocytes are nourished from the surrounding recipient bed before vascular in-growth from the bed occurs, while the core cells rely on diffusion only. So the distance between the core and the surface is critical and therefore fat particles dimensions are vital for graft take as larger particles are more prone to central necrosis (Carpaneda & Ribeiro, 1993; Niechajev & Sevcuk, 1994). This is significant only when excisional harvesting is compared to liposuction. On the contrary, smaller liposuction cannulas provide less viable fat grafts (Erdim et al, 2009) probably due to higher cell damage or to damage to the microvascular structure and to the niche.

Some liposuction techniques including ultrasonic emulsification, power- or laser-assisted lipoplasty, or high volume fluid administration ("tumescent" or "super-wet" technique) are blamed to additionally damage the aspirate thus reducing the viable cell rate. Our preference goes to syringe aspiration (20 cc) with a wet technique via open tip or 1-hole bullet tip, 3 mm large cannulas.

4.2 Fat processing

The rationale for fat processing before re-injection stems first of all from the need to remove blood, fluids, debris and free lipid fractions in order to improve the actual volume of viable fat, and to reduce the inflammatory reaction which may jeopardize long term uptake. Secondarily, processing can improve graft take by adding promoting agents or by *in vitro* activation. Finally, some studies are trying to preserve the adipocytes for future uses.

The most common processing techniques are centrifugation (Asken, 1988; Toledo, 1991; Coleman, 1995, 1997, 2001; Fulton et al, 1998; R. Amar, 1999; Locke & de Chalain, 2008), sedimentation and washing/rinsing. In a recent consensus survey, various spin rates centrifugation was preferred by 47% of the respondents, 29% favoured fat washings, 12% opted for "other" unspecified treatment techniques, whereas 12% used no preparation (Kaufman et al, 2010). The concentration of viable fat cells in centrifuged vs. sedimented samples seems to be similar. A reliably high concentration of fat cells after centrifugation was seen (Boschert et al, 2002), but maybe the cell damage was underestimated due to the low centrifugation spin rate. An improved long term graft persistence with decanted samples compared to centrifuged ones (1,500 rpm for 5 min) was suggested (Ramon et al, 2005). A recent work showed interesting results with the "squeezing centrifugation lipotransfer system" to concentrate healthy fat cells, the ADSCs, the patient's own peptides (growth factors), and scaffolds (extracellular matrix) through a combination of squeezing, centrifugation and filtration (Yang & Lee, 2011).

Sample washing after centrifugation (Chajchir & Benzaquen, 1986) or sedimentation (Toledo, 1991; Klein, 1993; Niechajev & Sevcuk, 1994; Fagrell et al, 1996; R. Amar, 1999) or in place of either (Rubin & Hoefflin, 2002) was proposed. Its rationale stems from the dilution of detrimental substances combined to an improved sedimentation. In particular, serial washing with saline can reduce cellular remnants and free lipids (Alexander, 2010). Different washing solutions were proposed: sterile water (Rubin & Hoefflin, 2002), 5% glucose solution (Fournier, 2000) or saline (Carpaneda & Ribeiro, 1993; Niechajev & Sevcuk, 1994). A decrease in the survival of normal saline washed grafts vs. unwashed ones was found (Baran et al, 2002). Moreover, sample washing removes fibrin (Chajchir & Benzaquen, 1986) that could be important in stabilizing adipocytes within the wound bed.

Different processing methods significantly correlated with neither viable adipocytes rates nor grafts longevity (Sommer & Sattler, 2000), while other works (Rose et al, 2006) found that sedimentation was associated to almost double the mean concentration of intact cells than centrifugation (3,000 rpm for 3 min) with or without washing. The limit of almost all these *in vitro* studies is the assumption that morphologically intact cells are viable and that viable adipocytes rate correlates to graft survival.

Lidocaine was proved to reversibly inhibit glucose transport, causing lipolysis as the cells fully regain their function after washing (Moore et al, 1995) or centrifugation (Shoshani et al, 2005), regardless of exposure duration. Serial rinsing with normal saline can also significantly reduce the intracellular lidocaine concentration (Alexander, 2010).

Another reason for fat processing is to add substances that may increase graft take. Even if somewhat controversial, insulin can stabilize cell membrane and enhance the survival rate by increasing intracellular glycogen and lipid formation (Asaadi et al, 1993; Yuksel et al, 2000). Bovine fibroblastic growth factor in an animal model was shown to improve weight retention of the grafts (Eppley et al, 1992); IL-8 reduced fat necrosis due to its angiogenic action, cellular proliferation stimulation, and cytokine and growth factor synthesis (Shoshani et al, 2005). A higher survival rate was noted suspending the aspirate in enriched cell culture medium (Har-Shai et al, 1999) or in vascular endothelial growth factor (Nishimura et al, 2000). Platelet-rich plasma was added to the grafts by some authors with

quite contradictory results: some works observed an effective reduction of the inflammatory response and a fat survival improvement (Pires Fraga et al, 2010; Nakamura et al, 2010), while others found no significant positive effect (Por et al, 2009; Salgarello et al, 2011). Freezing aspirate for later use causes the adipocytes rupture, further decreasing viable cell counts: after 8 weeks the cell survival rate is only 5% (Son et al, 2010).

Our preference goes to serial washing and decantation. Normal saline is aspired in the harvesting syringe (half filled with fat) that is gently tilted to improve washing and then it is decanted for about five minutes. The heaviest fraction is discarded and the procedure is repeated two or three times until the fat turns to yellow. The upper fraction (free lipids) is also discarded. This technique gave us good results (Panettiere et al, 2009, 2011).

4.3 Techniques for implantation

Interstitial fluids nourish fat grafts for the first 4 days after transplantation, but during this period oxygen supply and nutrition may be insufficient for graft survival. Graft take can be improved by placing small grafts surrounded by as much as possible healthy recipient tissue, thus maximizing the interface between the graft and the recipient bed. This can be achieved by implanting the fat in multiple tunnels or in single spots (less than 0.1 mL), injecting it linearly while withdrawing the cannula or the needle. Large fat clogs can obstruct the needle/cannula during injection and morre pressure applied to the plunger can cause a large bolus to be inadvertently delivered. Injection guns were therefore proposed to improve control and precision of delivery (Agris, 1987; Newman & Levin, 1987; Niechajev, 1992; Asaadi & Haramis, 1993; Niechajev & Sevcuk, 1994; Berdeguer, 1995; Fulton et al, 1998; Niamtu, 2002, 2010).

Subcutaneous tension should also be always prevented. More than one session of fat grafting is advisable in large defects (Tholen et al, 2010) or when tissue fibrosis is significant (Panettiere et al, 2011), but no sound evidence is available about the minimum interval between them. There is some evidence that newformed blood vessels are similar to normal ones 21 days after free fat graft (Missana et al, 2007). In our experience (Panettiere et al, 2009) a 20 days interval between sessions is generally safe and efficient.

Local anaesthetics should be injected only at the injection point in order to preserve the positive effects of sample washing (Shiffman, 2010). The injection site should be chosen far enough from the recipient area to prevent fat extrusion. In our experience, there is usually no need for suturing the injection point, while sterile taping is advisable. The diameter of the delivery cannula or needle should be at least as large as the one used for harvesting in order to limit graft damage. Although infection of the transplanted fat is not a common event (Valdatta et al, 2001; Dessy et al, 2006; Delay et al, 2009; Talbot et al, 2010), absolute sterility is imperative and antibiotic prophylaxis may be advised.

Our preference goes to large diameter (18-14G) needles for delivery. We gently mould the graft with the fingers to improve its uniform distribution and we place Steri-Strips® to encircle the grafted area in order to limit graft's dislocation. Compression dressings can worsen graft take (blood flow reduction) and cause graft's displacement. On the other hand, mostly when using needles, local bleeding in the recipient site can occur thus hindering

graft's survival. In our experience adhesive soft pads (Reston® by 3M®) applied for five days can balance the risks from both recipient site bleeding and graft ischemia.

4.4 The survival rates of fat grafts

The differences in the method of harvest, processing, storage and so on created a great confusion and an extreme variability in the reported results and resorption rates which, mostly in the early lipofilling era, were extremely high, up to 70% (Fournier, 1988, 2000; Carpaneda & Ribeiro, 1993; Coleman, 1995, 1997). But many studies relied on subjective evaluations that cannot provide comparable results. In an MR study, the long-term volume persistence of autologous fat grafts in facial defects was 51% 3 months after the implant and 45% at 6 months. Nine - twelve months after implantation the volume was stabile. Therefore, a one stage overcorrection protocol was suggested to balance the resorption rate (Horl, 1991). CT scan studies found a 47.5% survival rate nine months after injection (O. Amar et al, 2008). In a recent MR study by our group, eight months after the last session of serial fat grafting the fat survival rate was about 62% (Panettiere et al, 2011).

Several techniques were also proposed to improve grafts survival rates (Hiragun et al, 1980; Bircoll & Novack, 1987; Eppley et al, 1992; Niechajev & Sevcuk, 1994). An experimental study proved that fat resorption was lower with excised fat compared to lipoaspirate (Fagrell et al, 1996). It was suggested that the preservation of fat microvascular structure could improve adipocyte viability and subsequently graft take. In a very recent work, the survival rate of ADSCs was significantly improved when they were implanted along with their collagen scaffold (Mojallal et al, 2011).

Some considerations are crucial in our opinion about the concept itself of fat survival rate. The first ambiguous point is how many are the elements whose survival is about to be calculated. All the studies generally assume that the total injected volume is the same as the graft volume. But, while non-viable adipocytes contribute to the total injected volume, their persistence is obviously null, so they cannot contribute to the long term implanted volume at all. Another undetermined variable is the amount of fluids injected (and accounted) with fat (Alexander, 2010), so it is arduous to discriminate between carrier fluids extraction and fat resorption. In other terms, if the first term of a proportion is uncertain, what will it be the meaning of the proportion itself? Consequently, real fat survival rates (i.e. how many implanted vital cells survive) in *in vivo* studies are unpredictable in our opinion, and the comparison of such data between different studies is aleatory.

5. Applications of lipofilling to irradiated breast: personal experience

The personal experience with three different applications of free fat grafts to irradiated breasts is presented. Data are expressed as mean±95% confidence interval. Statistical evaluations were made using the Kruskal-Wallis test for rank variables, the Student's t test for continuous data and the Fisher's exact test for proportions.

5.1 The salvage of pre-exposed prostheses and expanders

Exposition is the worst adverse effect of radiotherapy in implant breast reconstruction. In the present preliminary study we hypothesize a possible role for free fat grafts in the rescue of pre-exposed expansion flaps and prosthetic reconstructions.

5.1.1 Patients and methods

14 patients presenting with pre-exposed expanders and 19 patients with pre-exposed prostheses were offered free fat grafts to prevent reconstruction failure. 10 patients with expander pre-exposure (expanders active branch, EAB, age: 53.2±5.5 years) and 8 ones with implant pre-exposure (prostheses active branch, PAB, age: 52.5±6.2 years) adhered. The remaining patients (4 pre-exposed expanders, age: 49.6±28.8 years, p=0,53 and 11 pre-exposed prostheses, age: 49.9±6.8 years, p=0,55) who refused were treated with local flaps (control branches). The expanders in the EAB were partially deflated before graft. Fat was harvested by syringe from the abdomen, the hips or the trochanteric areas through a 3 mm open tip cannula, washed with saline and implanted around the pre-exposure area and successively in the thinned area too, through an 18G needle.

5.1.2 Results

The flaps in the EAB received 33.8±5.3 cc (range 12-70 cc) of fat per session (total implanted volume: 90.2±35.9 cc, range: 24-161 cc in 2.5±0.7 sessions per patient, range: 1-4 sessions in 2.9±1.3 months). The flaps in the PAB received 24.9±2.9 cc (range 14-40 cc) of fat per session (total implanted volume: 80.9±31.7 cc, range: 27-135 cc in 4.1±1.6 sessions per patient, range: 1-7 sessions in 9.3± 5.5 months). In the active branches, the prosthesis could not be saved in 1 case (failure rate: 12.5%, 0.3-52.7%), while all the expansion flaps were saved (failure rate: 0, 0-30.8%). On the contrary all the expansion flaps (failure rate: 100%, 39.8-100%, p=0.001) and 6 of the prosthetic reconstructions in the control groups failed (failure rate: 54.5%, 23.4-83.3%, p=0.14).

5.1.3 Discussion

Expansion is undoubtedly critical in irradiated patients because even modest volumes can cause high tension, severe ischemia and a high exposition risk, due to flap stiffness. The present study demonstrates that free fat grafts can play an interesting role in expansion flaps salvage, while a significant positive effect in prosthetic reconstruction rescue failed to be proved. In our opinion, the key is that all expanders were at least partially deflated, while the same could not obviously be done with prostheses. This is a limited preliminary study, so the results should not be generalized. The main advantage of free fat grafts is that they are a closed procedure minimizing the risk of expander/prosthesis infection or further flap loss. The main risk is inadvertent expander/prosthesis rupture.

5.2 Aesthetic and functional improvements in reconstructed irradiated breasts

5.2.1 Patients and methods

137 irradiated breast implant reconstructed patients were offered free fat grafts. 48 of them (active branch, AB, mean age 50.6±2.8 years) adhered, while the remaining 89, who refused (control branch, CB, mean age 51.5±2.4 years, p=0.32), received a conservative treatment. The autologous fat was harvested by syringe from the abdomen, the hips or the trochanteric areas using a 3 mm cannula (1-hole, bullet tip) and processed by gentle washing with saline. Then it was implanted using a 14G needle in depressed areas (10-15% overcorrection), under the scars, and in dystrophic sites. Functional results were compared using the LENT-SOMA score, while a five-points scale (5: very good, 1: very poor) was used to compare the aesthetic results.

5.2.2 Results

The patients in the AB received 28.2±2.0 cc of fat per session (range: 8-70 cc) in 3.3±0.6 sessions (range: 1-9) with a 86.0±14.6 days interval (range: 20-392 days) between sessions. The initial LENT-SOMA scores in the two branches were comparable, but they significantly improved in the AB after lipograft (fig. 1). 3 months after the last fat graft all the parameters except oedema were better in the AB than in the CB (table 1). A significant improvement was recorded also comparing homogeneous subgroups with similar initial LENT-SOMA ranks (excluding only breast oedema in the lower rank subgroup) as reported in table 2. Two patients in the AB presenting with Bk3 capsular contracture downgraded to Bk1 after respectively 2 and 4 fat graft sessions (fig. 2). The initial aesthetic outcome was similar in the two branches (2.5±0.2 vs. 2.5±0.2, p=0.624), while it significantly improved in the AB 3 months after the last fat graft session (2.5±0.2 vs. 2.9±0.2, p=0.00137). In particular, a great improvement in superficial irregularities and scars, reduction of fibrosis related deformities, and a general improvement of skin appearance and trophism were observed. The aesthetic result in the CB was significantly worse (2.5±0.2) than in the AB 3 months after the last session (2.9±0.2, p=0.00274).

	Initial evaluation			Active branch			Three months after graft		
	Active	Control	p	Before	3 m. after	p	Active	Control	p
P	0.8±0.3	1.0±0.2	0.09	0.8±0.3	0.4±0.2	**0.02**	0.4±0.2	1.0±0.2	**0.00003**
T	1.0±0.3	1.0±0.2	0.93	1.0±0.3	0.6±0.3	**0.01**	0.6±0.3	1.0±0.2	**0.007**
A	1.5±0.3	1.6±0.2	0.97	1.5±0.3	0.9±0.3	**0.002**	0.9±0.3	1.6±0.2	**0.0004**
O	0.9±0.2	0.8±0.2	0.58	0.9±0.2	0.5±0.2	**0.03**	0.5±0.2	0.8±0.2	0.108
F	1.5±0.3	1.7±0.2	0.20	1.5±0.3	1.0±0.2	**0.01**	1.0±0.2	1.7±0.2	**0.00002**

Table 1. The LENT-SOMA ranks comparison between the two groups at initial evaluation, in the AB before and 3 months after the last fat graft, and between CB and AB 3 months after the last fat graft (P: Pain, T: Teleangiectasias, A: Atrophy, O: Oedema, F: Fibrosis). Statistically significant results are in bold characters.

	Lower ranks subgroup (initial score 0-1)			Higher ranks subgroup (initial score 2-3)		
	Before	3 m. after	p	Before	3 m. after	p
Pain	0.4±0.2	0.2±0.1	**0.007**	2.3±0.4	1.6±0.4	**0.01**
Teleangiectasias	0.6±0.2	0.3±0.1	**0.001**	2.6±0.4	2.0±0.5	**0.04**
Atrophy	0.7±0.2	0.3±0.3	**0.002**	2.5±0.2	1.5±0.3	**0.00007**
Oedema	0.5±0.2	0.3±0.2	0.06	2.1±0.2	1.4±0.6	**0.014**
Fibrosis	0.8±0.1	0.6±0.2	**0.03**	2.6±0.3	1.6±0.3	**0.0002**

Table 2. The LENT-SOMA ranks comparison in homogeneous subgroups of the AB before and 3 months after the last fat graft. Statistically significant results in bold.

Local recurrence occurred in 3 patients in the AB (6.3%, 1.3-17.2%) after a mean interval of 16.0 months (range: 8.2-29.1 months) from fat graft (33.8 months after cancer treatment, range: 23.8-53.5 months) and in 4 patients in the CB (4.5%, 1.2-11.1%, p=0.805) after a mean of 136.0 months (range: 49.7-235.6 months, p=0.109) from mastectomy. Distant metastases were observed in 2 patients in the AB (4.2%, 0.5-14.3%) respectively 10.7 and 21.4 months

after fat graft (35.3 months after mastectomy, range: 20.9-50.0 months) and in 3 patients in the CB (3.4%, 0.7-9.5%, p=0.779) 22.4 months (range: 17.0-29.4 months, p=0.350) after mastectomy. The mean follow up after mastectomy was 41.2±9.8 months in the AB and 36.6±11.2 months in the CB (p=0.587).

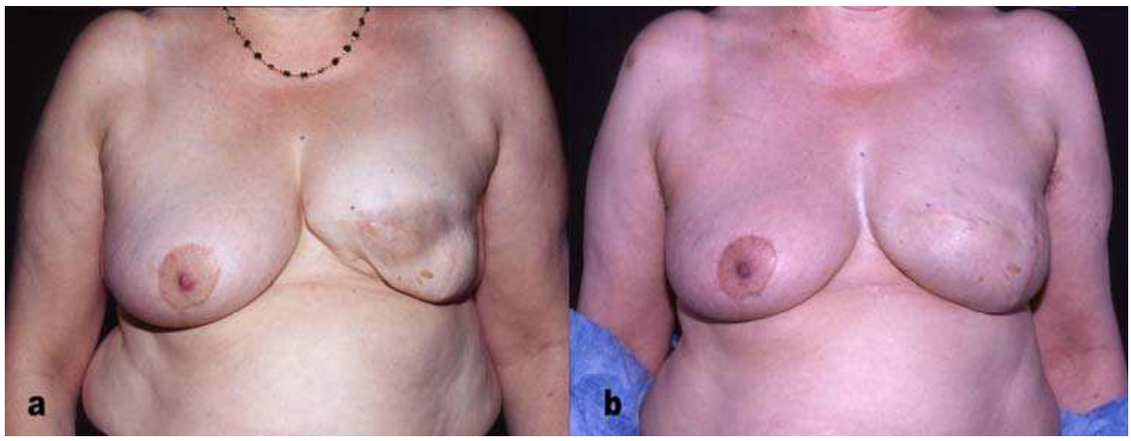


Fig. 1. a: initial severe atrophy and fibrosis; b: dramatic improvement of both parameters 6 months after lipofilling (106 cc in 3 sessions)

5.2.3 Discussion

The present study substantially confirms the results of our previous, more limited published series (Panettiere et al, 2009), but as the present series is more than two folds larger than the previous one, the results appear even more convincing. In particular, a reduced effect of lipofilling on the oedema was confirmed. A possible explanation could be that oedema depends more significantly on the axillary nodes status (sentinel node vs. total dissection, axillary radiotherapy) than on the local tissues. So, a reduced beneficial effect of free fat grafts can be expected. Anyhow, a significant improvement was observed in the subgroup where oedema was initially more severe. Improvement in tissue vascularization and reduction of local inflammatory factors could explain it. In 2 cases a significant improvement of capsular contracture was observed after fat graft. This may be an interesting option for breast augmentation too and, maybe, also to help understand the physiopathology of this challenging adverse event. A possible action mechanism is that ADSCs interact with the inflammatory response as leukotriene antagonists do. Such a hypothesis should obviously be addressed by specific studies. In one case, an accidental prosthetic rupture occurred, due to an inadvertent patient's movement during lipofilling. This was the only procedure-related complication observed, but it should be prevented mostly when dealing with very thin coverage tissues. The data about local and distant recurrence in the present series show no significant difference between the patients who received free fat grafts and those who did not, as far as regards neither incidence, nor distance from cancer surgery. The current series presents some possible biases besides the relatively small number of patients. First of all, 15 patients in the CB (16.9%) were lost at follow up before 3 months. So a higher recurrence rate in the CB could be expected. Secondarily, this study was not specifically designed to address oncologic data. In particular, the patients were not actively and uniformly studied in search for recurrences,

and the data here reported relied only on their individual oncologic follow up programs. So, these results should be considered with caution and specific prospective studies should address the relationship between free fat grafts and cancer recurrence.

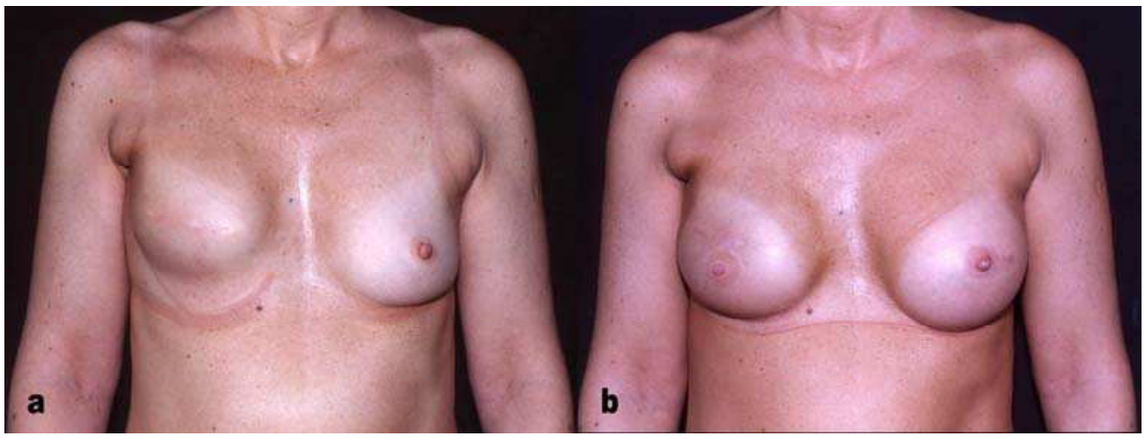


Fig. 2. a: severe fibrosis with Bk3 capsular contracture; b: 4 months after lipofilling (56 cc in 4 sessions), nipple-areola complex reconstruction and contralateral augmentation.

In our opinion, autologous free fat grafts should be routinely offered to all the irradiated implant reconstructed breasts because they can greatly improve both functional and aesthetic results and reduce the incidence of complications.

5.3 The total breast reconstruction with fat grafts only: case reports

Prostheses and autologous flaps are the most common options in breast reconstruction after mastectomy. Autologous flaps are the gold standard in reconstruction failures, but when they are contraindicated, no validated option is available.

5.3.1 Case 1

A 36-year-old patient underwent prophylactic bilateral nipple sparing mastectomy and immediate prosthetic reconstruction 6 years after a left breast quadrantectomy and radiotherapy. Eight months later, the reconstruction failed due to fatal exposure even if several salvage attempts using local flaps were tried. Three years later, the patient asked for reconstruction, but obesity (BMI: 36), and severe asthma contraindicated general anaesthesia. Free fat graft was thus considered the only viable reconstructive option. This case was particularly tricky because of the large breast and the stiffness due to both radiotherapy and the multiple salvage attempts. 700 cc of fat were implanted in 9 sessions in 13.5 months (40 days minimum interval between sessions). The fat was harvested by syringe through a 3 mm open tip cannula from the abdomen, the hips, the thighs, the buttocks or the trochanteric areas and it was washed with saline. The grafts were then implanted using the same syringes and a 14G needle. In the first 4 sessions, small fat volumes were implanted accurately avoiding any significant skin tension (average volume 42.5 cc) under a quite wide surface, in order to release the scar and regenerate the tissues. A great reduction of fibrosis (LENT-SOMA score 3 before session #1; score 1 before session #4) was observed. In a second phase (the last 5 sessions), larger volumes (average: 106 cc) were implanted to

improve volume and shape. The overall fat survival rate was 62% measured at MR eight months after the last grafting session. The aesthetic result was pleasant and stable 14 months after the last session (fig. 3). A great improvement in irradiated skin quality and scars was also achieved (LENT-SOMA score before the first session: 8; 8 months after the last session: 3) with improvements in fibrosis (-2), pain (-1), atrophy (-1) and oedema (-1).

5.3.2 Case 2

A 58-year-old woman underwent modified radical mastectomy and prosthetic reconstruction. During expansion she received radiotherapy, but reconstruction was completed with a good result (total LENT-SOMA score: 0, 6 months after the prosthesis was implanted). 8 months later, an infection occurred (Pseudomonas sp.) imposing implant removal. 2 months later (negative blood and tissue cultures) a new reconstruction procedure was performed, but 15 months later the breast suddenly inflated. Pseudomonas was found, so the implant was removed once again. The patient was asking for breast reconstruction, but she then rejected general anaesthesia and local flaps. Therefore, she was proposed a free fat breast reconstruction. A total 367 cc of fat (52.9% larger than the explanted prosthesis) was implanted in 6 sessions (total time: 11.0 months, 61.2±8.5 cc per session) with a 54.8±10.1 days average interval between the sessions. The aesthetic result was pleasant 10.4 months after the last session (fig. 4), with no sign of infection.

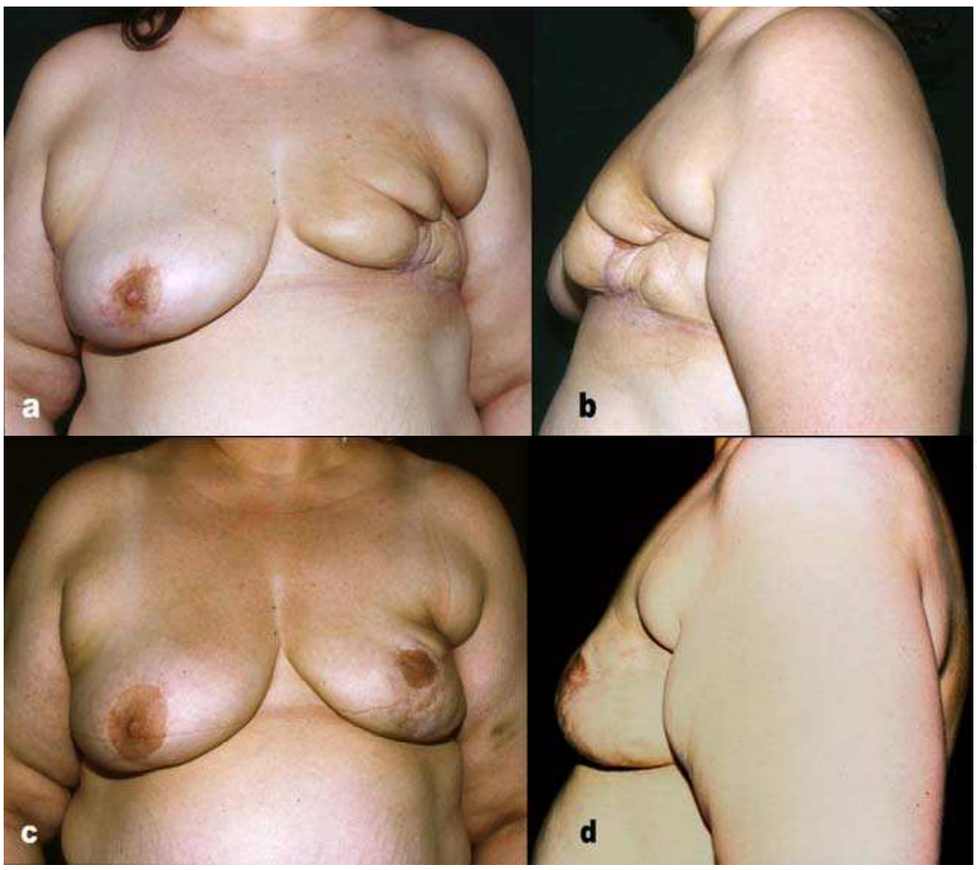


Fig. 3. a, b: case 1, initial status; c, d: 14 months after the last fat graft session

5.3.3 Discussion

The cases here reported offered rather different reconstructive challenges. In the first one, quite a large volume needed to be restored, but a severe fibrosis was present and any attempt to place large volumes of fat under such a stiff skin could cause dangerous tension. In breast reconstruction using free fat only, the grafts usually act as both expanders and vital fillers. Del Vecchio (Del Vecchio, 2009; Khouri & Del Vecchio, 2009) proposed pre-expansion using the BRAVA® system. Even if suction induced by external pre-expansion system was stated to improve blood supply and graft take, in our knowledge, the stiffness observed in the present case was never addressed before with BRAVA® system in published works and its safety on irradiated tissues was not assessed. In case 1, we were concerned about possible risks of pre-expansion as the tissues were extremely thin (mostly in the lower pole). Moreover, we were worried that suction could worsen pain and oedema (both LENT-SOMA score 1). So we opted for a two-step procedure: in the first four sessions we aimed at tissue regeneration, hoping that ADSCs could reduce fibrosis and improve vascularity, so that in the last five sessions larger volumes of fat could be safely implanted. The stable final results demonstrate that this approach is a valuable option.

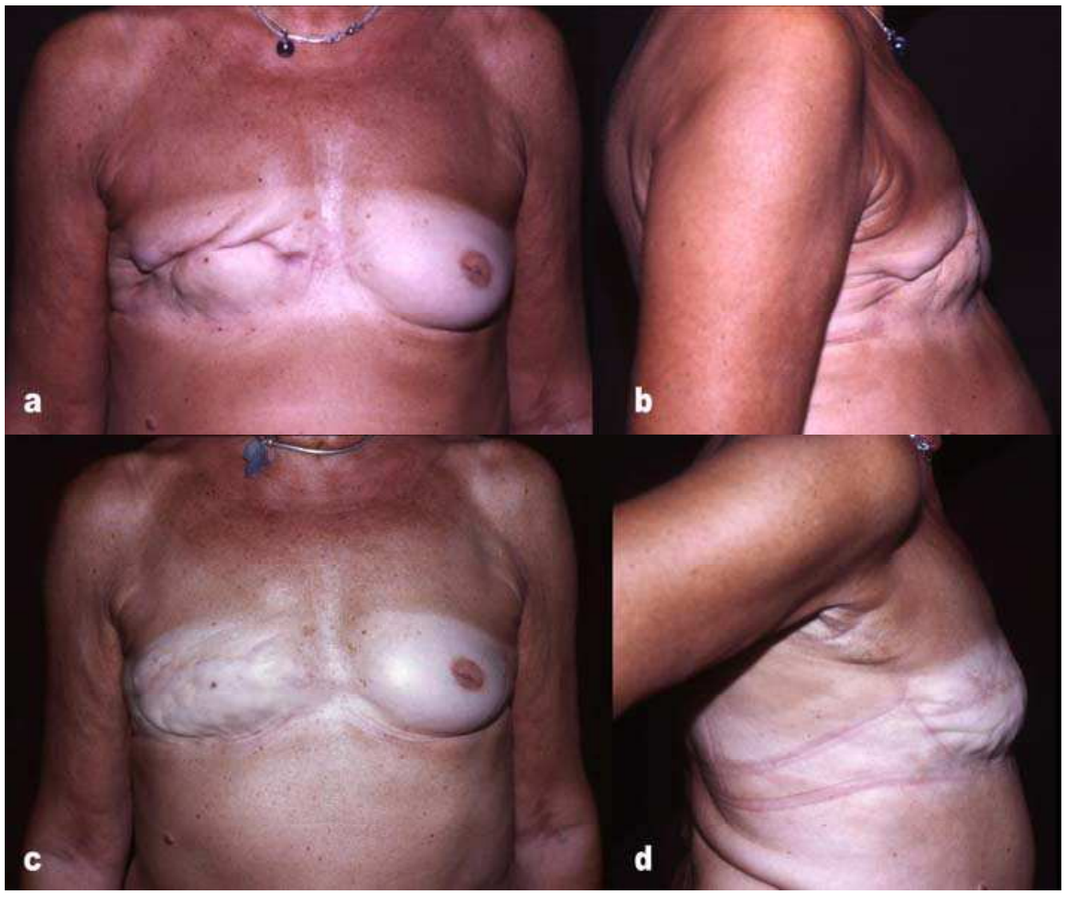


Fig. 4. a, b: case 2, initial status; c, d: 10.4 months after the last fat graft session

In case 2, breast volume was not very large and the tissues showed no significant adverse effect of radiotherapy, but some fibrosis and stiffness developed later due to infections and

multiple procedures. So the two-step approach was successfully applied in this case too. But the main concern was possible recurrent infection. In our knowledge there is no specific work addressing fat grafts in potentially infected areas. The patient was administered an antibiogram driven antibiotic treatment to eradicate the infection. A 5-days antibiotic prophylaxis was also empirically administered after the first fat graft session. Standard one-shot prophylaxis was then applied in the following sessions. No sign of re-infection was observed after a 10.4 months follow up. In the present case, free fat grafts proved to be safe also in high infection risk patients.

The long overall reconstruction time is undoubtedly the greatest limit of breast reconstruction using fat grafts. In the present cases respectively 9 sessions in 13.5 months and 6 sessions in 11.0 months were necessary; a mean of 3 sessions were needed in other studies (Delaporte et al, 2009). Moreover, no immediate reconstruction with fat grafts can be planned, even if grafting immediately after mastectomy could probably be an interesting option. Poor donor tissues are other possible limits. The main advantage of breast reconstruction using free fat grafts is the absence of significant contraindications, as it can be performed in almost all patients under local anaesthesia. The technique is undoubtedly easier and extremely less expensive than any other reconstructive option. It can also offer an autologous reconstruction option without major surgeries when other procedures failed.

6. Conclusion

Free fat grafts proved to be a remarkable alternative in irradiated breast reconstruction. Some doubts still remain about the risk of reactivation of dormant cancer cells and further studies should assess chemotherapy, hormone suppression and monoclonal antibodies effects on the regenerated tissues. Advances in adipocyte cryoconservation techniques could further improve the effectiveness by reducing the number of harvesting procedures.

7. References

Agris, J. (1987). Autologous fat transplantation: A 3-year study. *Am J Cosmet Surg,* Vol.4, No.2, (June 1987), pp. 95-102, ISSN 0748-8068

Alexander, R.W. (2010). Fat Transfer with Platelet-Rich Plasma for Breast Augmentation, In: *Autologous Fat Transfer*, Shiffman, M.A. (Ed.), pp. 243-259, Springer-Verlag, ISBN 978-3-642-00472-8, Berlin Heidelberg

Alexander, R.W. (2010). Autologous Fat Grafting: A Study of Residual Intracellular Adipocyte Lidocaine, In: *Autologous Fat Transfer*, Shiffman, M.A. (Ed.), pp. 445-450, Springer-Verlag, ISBN 978-3-642-00472-8, Berlin Heidelberg

Amar, O.; Bruant,-Rodier C.; Lehmann, S.; Bollecker, V. & Wilk A. (2008). Greffe de tissu adipeux: restauration du volume mammaire après traitement conservateur des cancers du sein, aspect clinique et radiologique. *Ann Chir Plast Esthet*, Vol.53, No.2, (April 2008), pp. 169-177, ISSN 0294-1260

Amar, R. (1999). Microinfiltration adipocytaire (MIA) au niveau de la face, ou restructuration tissulaire par greffe de tissu adipeux. *Ann Chir Plast Esthet,* Vol.44, No.6, (December 1999), pp. 593-608, ISSN 0294-1260

Andreassen, C.N.; Alsner, J.; Overgaard, J.; Herskind, C.; Haviland, J.; Owen, R.; Homewood, J.; Bliss, J. & Yarnold, J. (2005). TGFB1 polymorphisms are associated

with risk of late normal tissue complications in the breast after radiotherapy for early breast cancer. *Radiother Oncol*, Vol.75, No.1, (April 2005), pp. 18-21, ISSN 0167-8140

Asaadi, M. & Haramis, H.T. (1993). Successful autologous fat injection at 5-year follow-up. *Plast Reconstr Surg*, Vol.91, No.4, (December 1993), pp. 755-756, ISSN 0032-1052

Asken, S. (1988). Facial liposuction and microlipoinjection. *J Dermatol Surg Oncol*, Vol.14, No.3, (March 1988), pp. 297-305, ISSN 0148-0812

Autio, P.; Saarto, T.; Tenhunen, M.; Elomaa, I.; Risteli, J. & Lahtinen, T. (1998). Demonstration of increased collagen synthesis in irradiated human skin in vivo. *Br J Cancer*, Vol.77, No.12 (June 1998), pp. 2331-2335, ISSN 0007-0920

Baran, C.N.; Celebioglu, S.; Sensoz, O.; Ulusoy, G.; Civelek, B. & Ortak, T. (2002). The behavior of fat grafts in recipient areas with enhanced vascularity. *Plast Reconstr Surg*, Vol.109, No.5, (April 2002), pp. 1646-1651, ISSN 0032-1052

Barcellos-Hoff, M.H.; Park, C. & Wright, E.G. (2005). Radiation and the microenvironment-tumorigenesis and therapy. *Nat Rev Cancer,* Vol.5, No.11, (November 2005), pp. 867-875, ISSN 1474-175X

Bentzen, S.M. (2006). Preventing or reducing late side effects of radiation therapy: radiobiology meets molecular pathology. *Nat Rev Cancer*, Vol.6, No.9, (September 2006), pp. 702-713, ISSN 1474-175X

Berdeguer, P. (1995). Five years of experience using fat for leg contouring. *Am J Cosmet Surg*, Vol.12, No.3, (n.d.), pp. 221-229, ISSN 0748-8068

Bircoll, M. & Novack, B.H. (1987). Autologous fat transplantation employing liposuction techniques. *Ann Plast Surg*, Vol.18, No.4, (April 1987), pp. 327-329, ISSN 0148-7043

Boschert, M.T.; Beckert, B.W.; Puckett, C.L. & Concannon, M.J. (2002). Analysis of lipocyte viability after liposuction. *Plast Reconstr Surg*, Vol.109, No.2, (February 2002), pp. 761-765, ISSN 0032-1052

Bruning, P. (1914). Cited by Broeckaert, TJ & Steinhaus, J. Contribution a l'etude des greffes adipueses. *Bull Acad Roy Med Belgique*, Vol.28, (n.d.), pp. 440

Brush, J.; Lipnick, S.L.; Phillips, T.; Sitko, J.; McDonald, J.T. & McBride, W.H. (2007). Molecular mechanisms of late normal tissue injury. *Semin Radiat Oncol*, Vol.17, No.2, (April 2007), pp. 121-130, ISSN 1053-4296

Caplan, A.I. & Dennis, J.E. (2006). Mesenchymal stem cells as trophic mediators. *J Cell Biochem*, Vol.98, No.5, (August 2006), pp. 1076-1084, ISSN 1097-4644

Carpaneda, C.A. & Ribeiro, M.T. (1993). Study of the histologic alterations and viability of the adipose graft in humans. *Aesthetic Plast Surg*, Vol.17, No.1, (Winter 1993), pp. 43-47, ISSN 0364-216X

Casteilla, L.; Planat-Bénard, V.; Cousin, B.; Silvestre, J.S.; Laharrague, P.; Charrière, G.; Carrière, A. & Pénicaud, L. (2005). Plasticity of adipose tissue: a promising therapeutic avenue in the treatment of cardiovascular and blood diseases? *Arch Mal Coeur Vaiss*, Vol.98, No.9, (September 2005), pp. 922-926, ISSN 0003-9683

Casteilla, L.; Planat-Benard, V.; Laharrague, P. & Cousin, B. (2011) Adipose-derived stromal cells: Their identity and uses in clinical trials, an update. *World J Stem Cells*, Vol.3, No.4, (April 2011), pp. 25-33, ISSN 1948-0210

Cavarretta, I.T.; Altanerova, V.; Matuskova, M.; Kucerova, L.; Culig, Z. & Altaner, C. (2010). Adipose tissue-derived mesenchymal stem cells expressing prodrug-converting

enzyme inhibit human prostate tumor growth. *Mol Ther*, Vol.18, No.1, (January 2010), pp. 223-231, ISSN 1525-0016

Chajchir, A. & Benzaquen, I. (1986). Liposuction fat grafts in face wrinkles and hemifacial atrophy. *Aesth Plast Surg*, Vol.10, No.2 (February 1986), pp. 115-117, ISSN 1432-5241

Coleman, S.R. (1995). Long-term survival of fat transplants: Controlled demonstrations. *Aesthetic Plast Surg*, Vol.19, No.5, (September-October 1995), pp. 421-425, ISSN 0364-216X

Coleman, S.R. (1997). Facial recontouring with lipostructure. *Clin Plast Surg*, Vol.24, No.2, (April 1997), pp. 347-367, ISSN 0094-1298

Coleman, S.R. (2001). Structural fat grafts: The ideal filler? *Clin Plast Surg*, Vol.28, No.1, (January 2001), pp. 111-119, ISSN 0094-1298

Constantin, G.; Marconi, S.; Rossi, B.; Angiari, S.; Calderan, L.; Anghileri, E.; Gini, B.; Bach, S.D.; Martinello, M.; Bifari, F.; Galiè, M.; Turano, E.; Budui, S.; Sbarbati, A.; Krampera, M. & Bonetti, B. (2009). Adipose-derived mesenchymal stem cells ameliorate chronic experimental autoimmune encephalomyelitis. *Stem Cells*, Vol.27, No.10 , (October 2009), pp. 2624-2635, ISSN 1549-4918

Cousin, B.; Andre, M.; Arnaud, E.; Penicaud, L. & Casteilla, L. (2003). Reconstitution of lethally irradiated mice by cells isolated from adipose tissue. *Biochem Biophys Res Commun*, Vol.301, No.4, (February 2003), pp. 1016-1022, ISSN 0006-291X

Cousin, B.; Ravet, E.; Poglio, S.; De Toni, F.; Bertuzzi, M.; Lulka, H.; Touil, I.; André, M.; Grolleau, JL.; Péron, JM.; Chavoin, JP.; Bourin, P.; Pénicaud, L.; Casteilla, L.; Buscail, L. & Cordelier, P. (2009). Adult stromal cells derived from human adipose tissue provoke pancreatic cancer cell death both in vitro and in vivo. *PLoS One* Vol.4, No.7, (July 2009), pp. e6278, ISSN 1932-6203

Cowan, C.M.; Shi, Y.Y.; Aalami, O.O.; Chou, Y.F.; Mari, C.; Thomas, R.; Quarto, N.; Contag, C.H.; Wu, B. & Longaker, M.T. (2004). Adipose-derived adult stromal cells heal critical-size mouse calvarial defects. *Nat Biotechnol*, Vol.22, No.5, (May 2004), pp. 560-567, ISSN 1087-0156

Delaporte, T.; Delay, E.; Toussoun, G.; Delbaere, M. & Sinna, R. (2009). Reconstruction mammaire par transfert graisseux exclusif: à propos de 15 cas consécutifs. *Ann Chir Plast Esthet*, Vol.54, No.4, (August 2009), pp. 303-316, ISSN 0294-1260

Del Vecchio, D. (2009). Breast reconstruction for breast asymmetry using recipient site pre-expansion and autologous fat grafting: a case report. *Ann Plast Surg*, Vol.62, No.5, (May 2009), pp. 523-527, ISSN 0148-7043

Delay, E.; Garson, S.; Tousson, G. & Sinna, R. (2009). Fat injection to the breast: technique, results, and indications based on 880 procedures over 10 years. *Aesthet Surg J*, Vol.29, No.5 (September-October 2009), pp. 360-376, ISSN: 1090-820X

Dessy, L.A.; Mazzocchi, M.; Fioramonti, P. & Scuderi N. (2006). Conservative management of local Mycobacterium chelonae infection after combined liposuction and lipofilling. *Aesthetic Plast Surg*, Vol.30, No.6, (November-December 2006), pp. 717-722, ISSN 0364-216X

Donnenberg, V.S.; Zimmerlin, L.; Rubin, J.P. & Donnenberg, A.D. (2010). Regenerative therapy after cancer: what are the risks? *Tissue Eng Part B Rev*, Vol.16, No.6, (December 2010), pp. 567-575, ISSN 1937-3376

Ebrahimian, T.G.; Pouzoulet, F.; Squiban, C.; Buard, V.; André, M.; Cousin, B.; Gourmelon, P.; Benderitter, M.; Casteilla, L. & Tamarat, R. (2009). Cell therapy based on adipose

tissue-derived stromal cells promotes physiological and pathological wound healing. *Arterioscler Thromb Vasc Biol*, Vol.29, No.4, (April 2009), pp. 503-510, ISSN 1524-4636

Efimenko, A.; Starostina, E.; Kalinina, N & Stolzing, A. (2011). Angiogenic properties of aged adipose derived mesenchymal stem cells after hypoxic conditioning. *J Transl Med*, Vol.18, No.9, (January 2011), pp. 10-24, ISSN 1479-5876

Eppley, B.L.; Sidner, R.A.; Platis, J.M. & Sadove, A.M. (1992). Bioactivation of free-fat transfers: A potential new approach to improving graft survival. *Plast Reconstr Surg,* Vol.90, No.6, (December 1992), pp. 1022-1030, ISSN 0032-1052

Erdim, M.; Tezel, E.; Numanoglu, A. & Sav, A. (2009). The effects of the size of liposuction cannula on adipocyte survival and the optimum temperature for fat graft storage: an experimental study. *J Plast Reconstr Aesthet Surg*, Vol.62, No.9, (September 2009), pp. 1210-1214, ISSN 1748-6815

Faghahati, S.; Delaporte, T.; Toussoun, G.; Gleizal, A.; Morel, F.; Delay, E. (2010). Traitement par transfert graisseux des séquelles postradiques de tumeur faciale maligne de l'enfance. *Ann Chir Plast Esthet*, Vol.55, No.3, (June 2010), pp. 169-178, ISSN 0294-1260

Fagrell, D.; Enestrom, S.; Berggren, A. & Kniola, B. (1996). Fat cylinder transplantation: An experimental comparative study of three different kinds of fat transplants. *Plast Reconstr Surg*, Vol.98, No.1, (July 1996), pp. 90-96, ISSN 0032-1052

Favaro, E.; Amadori, A. & Indraccolo, S. (2008). Cellular interactions in the vascular niche: implications in the regulation of tumor dormancy. *Acta Pathologica Microbiologica et Immunologica Scandinavica*, Vol.116, No. 7-8, (July-August 2008), pp. 648-659, ISSN 1600-0463

Fournier, P.F. (1988). Who should do syringe liposculpturing? *J Dermatol Surg Oncol*, Vol.14, No.10, (October 1988), pp. 1055-1056, ISSN 0148-0812

Fournier, P.F. (1988). Why the syringe and not the suction machine? *J Dermatol Surg Oncol,* Vol.14, No.10, (October 1988), pp. 1062-1107, ISSN 0148-0812

Fournier, P.F. (1990). Facial recontouring with fat grafting. *Dermatol Clin*, Vol.8, No.3, (July 1990), pp. 523-537, ISSN 0733-8635

Fournier, P.F. (1990). Reduction syringe liposculpturing. *Dermatol Clin*, Vol.8, No.3, (July 1990), pp. 539-551, ISSN 0733-8635

Fournier, P.F. (1996). A simplified procedure for locking the plunger during syringe-assisted liposculpturing. *Plast Reconstr Surg*, Vol.98, No.3, (September 1996), pp. 569-570, ISSN 0032-1052

Fournier, P.F. (2000). Fat grafting: My technique. *Dermatol Surg*, Vol.26, No.12, (December 2000), pp. 1117-1128, ISSN 1076-0512

Fox, J.M.; Chamberlain, G.; Ashton, B.A. & Middleton, J. (2007). Recent advances into the understanding of mesenchymal stem cell trafficking. *Br J Haematol*, Vol.137, No.6, (June 2007), pp. 491-502, ISSN 0007-1048

Erickson, G.R.; Gimble, J.M.; Franklin, D.M.; Rice, H.E.; Awad, H. & Guilak, F. (2002). Chondrogenic potential of fat derived stromal cells. *Biochem Biophys Res Comm*, Vol.290, No.2, (January 2002), pp. 763-769, ISSN 0006-291X

Fulton, J.E.; Suarez, M.; Silverton, K. & Bames, T. (1998). Small volume fat transfer. *Dermatol Surg*, Vol.24, No.8, (August 1998), pp. 857-865, ISSN 1076-0512

Garcia-Olmo, D.; Garcia-Arranz, M. & Herreros, D. (2008). Expanded adipose-derived stem cells for the treatment of complex perianal fistula including Crohn's disease. *Expert Opin Biol Ther*, Vol.8, No.9, (September 2008), pp. 1417-1423, ISSN 1744-7682

Garcia-Olmo, D.; Herreros, D.; Pascual, I.; Pascual, JA.; Del-Valle, E.; Zorrilla, J.; De-La-Quintana, P.; Garcia-Arranz, M. & Pascual, M. (2009). Expanded adipose-derived stem cells for the treatment of complex perianal fistula: a phase II clinical trial. *Dis Colon Rectum*, Vol.52, No.1, (January 2009), pp. 79-86, ISSN 1530-0358

Gehmert, S.; Gehmert, S.; Prantl, L.; Vykoukal, J.; Alt, E. & Song, Y.H. (2010). Breast cancer cells attract the migration of adipose tissue-derived stem cells via the PDGF-BB/PDGFR-beta signaling pathway. *Biochem Biophys Res Commun*, Vol.398, No.3, (July 2010), pp. 601-605, ISSN 1090-2104

Gimble, J. & Guilak, F. (2003). Adipose-derived adult stem cells: Isolation, characterization, and differentiation potential. *Cytotherapy*, Vol.5, No.5, (n.d.), pp. 362-369, ISSN 1465-3249

Gimble, J.M.; Katz, A.J. & Bunnell, B.A. (2007). Adipose-derived stem cells for regenerative medicine. *Circ Res*, Vol.100, No.9, (May 2007), pp. 1249-1260, ISSN 1524-4571

Giotopoulos, G.; Symonds, R.P.; Foweraker, K.; Griffin, M.; Peat, I.; Osman, A. & Plumb, M. (2007). The late radiotherapy normal tissue injury phenotypes of telangiectasia, fibrosis and atrophy in breast cancer patients have distinct genotype-dependent causes. *Br J Cancer*, Vol.96, No.6, (March 2007), pp. 1001-1007, ISSN 0007-0920

González, M.A.; Gonzalez-Rey, E.; Rico, L.; Büscher, D. & Delgado, M. (2009). Treatment of experimental arthritis by inducing immune tolerance with human adipose-derived mesenchymal stem cells. *Arthritis Rheum*, Vol.60, No.4, (April 2009), pp. 1006-1019, ISSN 0004-3591

Har-Shai, Y.; Lindenhaum, E.S.; Gamliel-Lazarovich, A.; Beach, D. & Hirshowitz, B. (1999). An integrated approach for increasing the survival of autologous fat grafts in the treatment of contour defects. *Plast Reconstr Surg*, Vol.104, No.4, (September 1999), pp. 945-954, ISSN 0032-1052

Hiragun, A.; Sato, M. & Mitsui, H. (1980). Establishment of a clonal cell line that differentiates into adipose cells in vitro. *In Vitro*, Vol.16, No.8, (August 1980), pp. 685-693, ISSN 0073-5655

Horl, H.W.; Feller, A.M. & Biemer, E. (1991). Technique for liposuction fat reimplantation and long-term volume evaluation by magnetic resonance imaging. *Ann Plast Surg*, Vol.26, No.3, (March 1991), pp. 248-258, ISSN 0148-7043

Hoeller, U.; Tribius, S.; Kuhlmey, A.; Grader, K.; Fehlauer, F. & Alberti, W. (2003). Increasing the rate of late toxicity by changing the score? A comparison of RTOG/EORTC and LENT/SOMA scores. *Int J Radiat Oncol Biol Phys*, Vol.55, No.4, (March 2003), pp. 1013-1018, ISSN 0360-3016

Illouz, Y.G. (1985). De l'utilisation de la graisse aspire pour combler les défets cutanés. *Rev Chir Esth Langue Franc*, Vol.10, No.40, (n.d.), pp. 13

Illouz, Y.G. (1986). The fat cell "graft". A new technique to fill depressions. *Plast Reconstr Surg*, Vol.78, No.1, (July 1986), pp. 122-123, ISSN 0032-1052

Illouz, Y.G. & Pflug, M.E. (1986). Die selektive lipektomie oder lipolyse nach IIIouz. *Handchir Mikrochir Plast Chir*, Vol.18, No.3, (May 1986), pp. 118-121, ISSN 0722-1819

Indraccolo, S.; Favaro, E. & Amadori, A. (2006). Dormant tumors awaken by a short-term angiogenic burst: the spike hypothesis. *Cell Cycle*, Vol.5, No.16, (August 2006), pp. 1751-1755, ISSN 1538-4101

Jones, B.J. & McTaggart, S.J. (2008). Immunosuppression by mesenchymal stromal cells: from culture to clinic. *Exp Hematol*, Vol.36, No.6, (June 2008), pp. 733-741, ISSN 0301-472X

Kang, S.K.; Jun, E.S.; Bae, Y.C. & Jung, J.S. (2003). Interactions between human adipose stromal cells and mouse neural stem cells in vitro. *Brain Res Dev Brain Res*, Vol.145, No.1, (October 2003), pp. 141-149, ISSN 0165-3806

Kaufman, M.R.; Bradley J.P.; Dickinson B.; Heller J.B.; Wasson K. O'Hara C.; Huang C.; Gabbay J.; Ghadjar K.; Miller T.A. & Jarrahy R. (2010). Autologous Fat Transfer National Consensus Survey: Trends in Techniques and Results for Harvest, Preparation, and Application, In: *Autologous Fat Transfer*, Shiffman, M.A. (Ed.), 451-458, Springer-Verlag, ISBN 978-3-642-00472-8, Berlin Heidelberg

Mojallal, A.; Lequeux, C.; Shipkov, C.; Rifkin, L.; Rohrich, R.; Duclos, A.; Brown, S. & Damour, O. (2011). Stem Cells, Mature Adipocytes, and Extracellular Scaffold: What Does Each Contribute to Fat Graft Survival? *Aesthetic Plastic Surgery*, DOI: 10.1007/s00266-011-9734-8, (May 2011), pp. 1-12, ISSN 1432-5241

Khouri, R. & Del Vecchio, D. (2009). Breast reconstruction and augmentation using pre-expansion and autologous fat transplantation. *Clin Plast Surg*, Vol.36, No.2, (April 2009), pp. 269-280, ISSN 1558-0504

Kim, J.M.; Lee, S.T.; Chu, K.; Jung, K.H.; Song, E.C.; Kim, S.J.; Sinn, D.I.; Kim, J.H.; Park, D.K.; Kang, K.M.; Hyung Hong, N.; Park, H.K.; Won, C.H.; Kim, K.H.; Kim, M.; Kun Lee, S. & Roh, J.K. (2007). Systemic transplantation of human adipose stem cells attenuated cerebral inflammation and degeneration in a hemorrhagic stroke model. *Brain Res*, Vol.1183, (December 2007), pp. 43-50, ISSN 0006-8993

Kim, U.; Shin, D.G.; Park, J.S.; Kim, Y.J.; Park, S.I.; Moon, Y.M. & Jeong, K.S. (2011). Homing of adipose-derived stem cells to radiofrequency catheter ablated canine atrium and differentiation into cardio-myocyte-like cells. *Int J Cardiol*, Vol.146, No.3, (February 2011), pp. 371-378, ISSN 1874-1754

Kim, Y.; Kim, H.; Cho, H.; Bae, Y.; Suh, K. & Jung, J. (2007). Direct comparison of human mesenchymal stem cells derived from adipose tissues and bone marrow in mediating neovascularization in response to vascular ischemia. *Cell Physiol Biochem*, Vol.20, No.6, (n.d.), pp. 867-876, ISSN 1015-8987

Klein, J.A. (1993). Tumescent technique for local anesthesia improves safety in large-volume liposuction. *Plast Reconstr Surg*, Vol.92, No.6, (November 1993), pp. 1085-1098, ISSN 0032-1052

Kubis, N.; Tomita, Y.; Tran-Dinh, A.; Planat-Benard, V.; Andre, M.; Karaszewski, B.; Waeckel, L.; Penicaud, L.; Silvestre, J.S.; Casteilla, L.; Seylaz, J. & Pinard, E. (2007). Vascular fate of adipose tissue-derived adult stromal cells in the ischemic murine brain: A combined imaging-histological study. *Neuroimage*, Vol.34, No.1, (January 2007), pp. 1-11, ISSN 1053-8119

Lamfers, M.; Idema, S.; van Milligen, F.; Schouten, T.; van der Valk, P.; Vandertop, P.; Dirven, C. & Noske, D. (2009). Homing properties of adipose-derived stem cells to intracerebral glioma and the effects of adenovirus infection. *Cancer Lett*, Vol.274, No.1, (February 2009), pp. 78-87, ISSN 1872-7980

Lee, D.H.; Ahn, Y.; Kim, S.U.; Wang, K.C.; Cho, B.K.; Phi, J.H.; Park, I.H.; Black, P.M.; Carroll, R.S.; Lee, J. & Kim, S.K. (2009). Targeting rat brainstem glioma using human neural stem cells and human mesenchymal stem cells. *Clin Cancer Res*, Vol.15, No.15, (August 2009), pp. 4925-4934, ISSN 1078-0432

Lin, G.; Yang, R.; Banie, L.; Wang, G.; Ning, H.; Li, L.C.; Lue, T.F. & Lin, C.S. (2010). Effects of transplantation of adipose tissue-derived stem cells on prostate tumor. *Prostate*, Vol.70, No.10, (July 2010), pp. 1066-1073, ISSN 1097-0045

Locke, M.B. & de Chalain, T.M. (2008). Current practice in autologous fat transplantation: Suggested clinical guidelines based on a review of recent literature. *Ann Plast Surg*, Vol.60, No.1, (January 2008), pp. 98-102, ISSN 0148-7043

Mazo, M.; Planat-Bénard, V.; Abizanda, G.; Pelacho, B.; Léobon, B.; Gavira, J.J.; Peñuelas, I.; Cemborain, A.; Pénicaud, L.; Laharrague, P.; Joffre, C.; Boisson, M.; Ecay, M.; Collantes, M.; Barba, J.; Casteilla, L. & Prósper, F. (2008). Transplantation of adipose derived stromal cells is associated with functional improvement in a rat model of chronic myocardial infarction. *Eur J Heart Fail*, Vol.10, No.5, (May 2008), pp. 454-462, ISSN 1388-9842

Missana, M.C.; Laurent, I.; Barreau, L. & Balleyguier, C. (2007). Autologous fat transfer in reconstructive breast surgery: indications, technique and results. *Eur J Surg Oncol*, Vol.33, No.6, (August 2007), pp. 685-690, ISSN 0748-7983

Moore, J.H.Jr.; Kolaczynski, J.W.; Morales, L.M.; Considine, R.V.; Pietrzkowski, Z.; Noto, P.F. & Caro, J.F. (1995). Viability of fat obtained by syringe suction lipectomy: Effects of local anesthesia with lidocaine. *Aesthetic Plast Surg*, Vol.19, No.4, (July-August 1995), pp. 335-339, ISSN 0364-216X

Moseley, T.A.; Zhu, M. & Hedrick, M.H. (2006). Adipose-derived stem and progenitor cells as fillers in plastic and reconstructive surgery. *Plast Reconstr Surg*, Vol.118, No.3 supp, (September 2006), pp. 121S-128S, ISSN 0032-1052

Murohara, T.; Shintani, S. & Kondo, K. (2009). Autologous adipose-derived regenerative cells for therapeutic angiogenesis. *Curr Pharm Des*, Vol.15, No.24, (n.d.), pp. 2784-2790, ISSN 1873-4286

Nakamura, S.; Ishihara, M.; Takikawa, M.; Murakami, K.; Kishimoto, S.; Nakamura, S.; Yanagibayashi, S.; Kubo, S.; Yamamoto, N. & Kiyosawa, T. (2010). Platelet-rich plasma (PRP) promotes survival of fat-grafts in rats. *Ann Plast Surg*, Vol.65, No.1 (July 2010), pp. 101-106, ISSN 0148-7043

Naumov, G.N.; Akslen, L.A. & Folkman J. (2006). Role of angiogenesis in human tumor dormancy: animal models of the angiogenic switch. *Cell Cycle*, Vol.5, No.16, (August 2006), pp. 1779-1787, ISSN 1538-4101

Neuber F. (1893). Fettransplantation. *Chir Kongr Verhandl Deutsche Gesellsch Chir,* Vol.22, (n.d.), pp. 66

Newman, J. & Levin, J. (1987). Facial lipo-transplant surgery. *Am J Cosmet Surg*, Vol.4, No.2, (n.d.), pp. 131-140, ISSN 0748-8068

Niamtu, J. (2002). Fat transfer gun used as a precision injection device for injectable soft tissue fillers. *J Oral Maxillofac Surg*, Vol.60, No.7, (July 2002), pp. 838-839, ISSN 0278-2391

Niamtu, J. (2010). Injection Gun Used as a Precision Device for Fat Transfer, In: *Autologous Fat Transfer*, Shiffman, M.A. (Ed.), 397-401, Springer-Verlag, ISBN 978-3-642-00472-8, Berlin Heidelberg

Niechajev, I. (1992). Autologous transplantation of fat (lipofilling) for the improvement of the cheek contour, long-term results. In *Plastic Surgery*, Hinderer, V.T. (Ed.), Vol. II, 747-748, Excerpta Medica, Amsterdam

Niechajev, I. & Sevcuk, O. (1994). Long-term results of fat transplantation: Clinical and histologic studies. *Plast Reconstr Surg*, Vol.94, No.3, (September 1994), pp. 496-506, ISSN 0032-1052

Nomoto-Kojima, N.; Aoki, S.; Uchihashi, K.; Matsunobu, A.; Koike, E.; Ootani, A.; Yonemitsu, N.; Fujimoto, K. & Toda, S. (2011). Interaction between adipose tissue stromal cells and gastric cancer cells in vitro. *Cell Tissue Res*, Vol.344, No.2, (May 2011), pp. 287-298, ISSN 0302-766X

Panettiere, P.; Marchetti, L. & Accorsi, D. (2009). The serial free fat transfer in irradiated prosthetic breast reconstructions. *Aesthetic Plast Surg*, Vol.33, No.5, (September 2009), pp. 695-700, ISSN 0364-216X

Panettiere, P.; Accorsi, D.; Marchetti, L.; Sgrò, F. & Sbarbati, A. (2011) Large-Breast Reconstruction Using Fat Graft Only after Prosthetic Reconstruction Failure. *Aesthetic Plast Surg*, Vol.128, No.5, (October 2011), pp. 703-708, ISSN 0364-216X

Pavy, J.J.; Denekamp, J.; Letschert, J.; Littbrand, B.; Mornex, F.; Bernier, J.; Gonzales-Gonzales, D.; Horiot, J.C.; Bolla, M. & Bartelink, H. (1995). EORTC Late Effects Working Group. Late effects toxicity scoring: the SOMA scale. *Radiother Oncol,* Vol.35, No.1 (April 1995), pp. 11-15, ISSN 0167-8140

Percec, I. & Bucky, L.P. (2008). Successful prosthetic breast reconstruction after radiation therapy. *Ann Plast Surg*, Vol.60, No.5, (May 2008), pp. 527-531, ISSN 0148-7043

Perrot, P.; Rousseau, J.; Bouffaut, A.L.; Rédini, F.; Cassagnau, E.; Deschaseaux, F.; Heymann, M.F.; Heymann, D.; Duteille, F.; Trichet, V. & Gouin, F. (2010) Safety concern between autologous fat graft, mesenchymal stem cell and osteosarcoma recurrence. *PLoS One*, Vol.5, No.6, (June 2010), pp. e10999, ISSN 1932-6203

Petit, J.Y.; Botteri, E.; Lohsiriwat, V.; Rietjens, M.; De Lorenzi, F.; Garusi, C.; Rossetto, F.; Martella, S.; Manconi, A.; Bertolini, F.; Curigliano, G.; Veronesi, P.; Santillo, B. & Rotmensz, N. (2011), Locoregional recurrence risk after lipofilling in breast cancer patients. *Ann Oncol*, doi: 10.1093/annonc/mdr158, (May 2011), ISSN 1569-8041

Phinney, D.G. & Prockop, D.J. (2007). Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair - current views. *Stem Cells*, Vol.25, No.11, (November 2007), pp. 2896-2902, ISSN 1549-4918

Phulpin, B.; Gangloff, P.; Tran, N.; Bravetti, P.; Merlin, J.L. & Dolivet G. (2009). Rehabilitation of irradiated head and neck tissues by autologous fat transplantation. *Plast Reconstr Surg*, Vol.123, No.4, (April 2009), pp. 1187-1197, ISSN 0364-216X

Pires Fraga, M.F.; Nishio, R.T.; Ishikawa, R.S.; Perin, L.F.; Helene, A.Jr. & Malheiros, C.A. (2010). Increased survival of free fat grafts with platelet-rich plasma in rabbits. *J Plast Reconstr Aesthet Surg*, Vol.63, No.12 (December 2010), pp. e818-822, ISSN 1748-6815

Planat-Benard, V.; Silvestre, J.S.; Cousin, B.; André, M.; Nibbelink, M.; Tamarat, R.; Clergue, M.; Manneville, C.; Saillan-Barreau, C.; Duriez, M.; Tedgui, A.; Levy, B.; Pénicaud, L. & Casteilla, L. (2004). Plasticity of human adipose lineage cells toward endothelial cells: physiological and therapeutic perspectives. *Circulation*, Vol.109, No.5, (February 2004), pp. 656-663, ISSN 1524-4539

Poglio, S.; Galvani, S.; Bour, S.; André, M.; Prunet-Marcassus, B.; Pénicaud, L.; Casteilla, L. & Cousin, B. (2009). Adipose tissue sensitivity to radiation exposure. *Am J Pathol*, Vol.174, No.1, (January 2009), pp. 44-53, ISSN 1525-2191

Por, Y.C.; Yeow, V.K.; Louri, N.; Lim, T.K.; Kee, I. & Song, I.C. (2009). Platelet-rich plasma has no effect on increasing free fat graft survival in the nude mouse. *J Plast Reconstr Aesthet Surg*, Vol.62, No.8, (August 2009), pp. 1030-1034, ISSN 1748-6815

Prantl, L.; Muehlberg, F.; Navone, N.M.; Song, Y.H.; Vykoukal, J.; Logothetis, C.J. & Alt, E.U. (2010). Adipose tissue-derived stem cells promote prostate tumor growth. *Prostate*, Vol.70, No.15, (November 2010), pp. 1709-1715, ISSN 1097-0045

Prunet-Marcassus, B.; Cousin, B.; Caton, D.; André, M.; Pénicaud, L. & Casteilla, L. (2006). From heterogeneity to plasticity in adipose tissues: site-specific differences. *Exp Cell Res*, Vol.312, No.6, (April 2006), pp. 727-736, ISSN 0014-4827

Puissant, B.; Barreau, C.; Bourin, P.; Clavel, C.; Corre, J.; Bousquet, C.; Taureau, C.; Cousin, B.; Abbal, M.; Laharrague, P.; Penicaud, L.; Casteilla, L. & Blancher, A. (2005). Immunomodulatory effect of human adipose tissue-derived adult stem cells: comparison with bone marrow mesenchymal stem cells. *Br J Haematol*, Vol.129, No.1, (April 2005), pp. 118-129, ISSN 0007-1048

Quarmby, S.; Fakhoury, H.; Levine, E.; Barber, J.; Wylie, J.; Hajeer, A.H.; West, C.; Stewart, A.; Magee, B. & Kumar, S. (2003). Association of transforming growth factor beta-1 single nucleotide polymorphisms with radiation-induced damage to normal tissues in breast cancer patients. *Int J Radiat Biol*, Vol.79, No.2, (February 2003), pp. 137-143, ISSN 0955-3002

Ramon, Y.; Shoshani, O.; Peled, I.J.; Gilhar, A.; Carmi, N.; Fodor, L.; Risin, Y. & Ulmann, Y. (2005). Enhancing the take of injected adipose tissue by a simple method for concentrating fat cells. *Plast Reconstr Surg*, Vol.115, No.1, (January 2005), pp. 197-201, ISSN 0032-1052

Rehman, J.; Traktuev, D.; Li, J.; Merfeld-Clauss, S.; Temm-Grove C.J.; Bovenkerk, J.E.; Pell C.L.; Johnstone, B.H.; Considine, R.V. & March, K.L. (2004). Secretion of angiogenic and antiapoptotic factors by human adipose stromal cells. *Circulation*, Vol.109, No.10, (March 2004), pp. 1292-1298, ISSN 1524-4539

Riekki, R.; Parikka, M.; Jukkola, A.; Salo, T.; Risteli, J. & Oikarinen, A. (2002). Increased expression of collagen types I and III in human skin as a consequence of radiotherapy. *Arch Dermatol Res*, Vol.294, No.4, (July 2002), pp. 178-184, ISSN 0340-3696

Rigotti, G.; Marchi, A.; Galiè, M.; Baroni, G.; Benati, D.; Krampera, M.; Pasini, A. & Sbarbati, A. (2007). Clinical treatment of radiotherapy tissue damage by lipoaspirate transplant: a healing process mediated by adipose-derived adult stem cells. *Plast Reconstr Surg*, Vol.119, No.5, (April 2007), pp. 1409-1422, ISSN 0032-1052

Rigotti, G.; Marchi, A.; Stringhini, P.; Baroni, G.; Galiè, M.; Molino, AM.; Mercanti, A.; Micciolo, R. & Sbarbati, A. (2010). Determining the oncological risk of autologous lipoaspirate grafting for post-mastectomy breast reconstruction. *Aesthetic Plast Surg*, Vol.34, No.4, (August 2010), pp. 475-480, ISSN 0364-216X

Roberts, D.L.; Dive, C. & Renehan, A.G. (2010). Biological mechanisms linking obesity and cancer risk: new perspectives. *Annu Rev Med*, Vol.61, (n.d.), pp. 301-316, ISSN 1545-326X

Rodemann, H.P. & Blaese, M.A. (2007). Responses of normal cells to ionizing radiation. *Semin Radiat Oncol*, Vol.17, No.2, (April 2007), pp. 81-88, ISSN 1053-4296

Rohrich, R.J.; Sorokin, E.S. & Brown, S.A. (2004). In search of improved fat transfer viability: A quantitative analysis of the role of centrifugations and harvest site. *Plast Reconstr Surg*, Vol.114, No.1, (January 2004), pp. 391-395, ISSN 0032-1052

Rose, J.G.Jr.; Lucarelli, M.J.; Lemke, B.N.; Dortzbach, R.K.; Boxrud, C.A.; Obagi, S. & Patel, S. (2006). Histologic comparison of autologous fat processing methods. *Ophthal Plast Reconstr Surg*, Vol.22, No.3, (May-June 2006), pp. 195-200, ISSN 0032-1052

Rubin, A. & Hoefflin, S. (2002). Fat purification: Survival of the fittest. *Plast Reconstr Surg*, Vol.109, No.4, (April 2002), pp. 1463-1464, ISSN 0032-1052

Salgarello, M.; Visconti, G. & Farallo, E. (2010). Autologous fat graft in radiated tissue prior to alloplastic reconstruction of the breast: report of two cases. *Aesthetic Plast Surg*, Vol.34, No.1, (February 2010), pp. 5-10, ISSN 0364-216X

Salgarello, M.; Visconti, G. & Rusciani A. (2011) Breast fat grafting with platelet-rich plasma: a comparative clinical study and current state of the art. *Plast Reconstr Surg*, Vol.127, No.6, (June 2011), pp 2176-2185, ISSN 0032-1052

Sarfati, I.; Ihrai, T.; Kaufman, G.; Nos, C. & Clough, K.B. (2001). Adipose-tissue grafting to the post-mastectomy irradiated chest wall: Preparing the ground for implant reconstruction. *J Plast Reconstr Aesthet Surg*, Vol.64, No.9, (September 2011)

Sbarbati, A.; Accorsi, D.; Benati, D.; Marchetti, L.; Orsini, G.; Rigotti, G. & Panettiere P. (2010). Subcutaneous adipose tissue classification. *European Journal of Histochemistry* Vol.54, No.4, (November 2010), pp. e48, ISSN 2038-8306

Shiffman, M.A. (2010) Editor's commentary, In: *Autologous Fat Transfer*, Shiffman, M.A. (Ed.), 463-465, Springer-Verlag, ISBN 978-3-642-00472-8, Berlin Heidelberg

Shoshani, O.; Berger, J.; Fodor, L.; Ramon, Y.; Shupak, A.; Kehat, I.; Gilhar, A. & Ullmann, Y. (2005). The effect of lidocaine and adrenaline on the viability of injected adipose tissue - an experimental study in nude mice. *J Drugs Dermatol*, Vol.4, No.3, (May-June 2005), pp. 311-316, ISSN 1545-9616

Shoshani, O.; Livne, E.; Armoni, M.; Shupak, A.; Berger, J.; Ramon, Y.; Fodor, L.; Gilhar, A.; Peled, I.J. & Ulmann, Y. (2005). The effect of interleukin-8 on the viability of injected adipose tissue in nude mice. *Plast Reconstr Surg*, Vol.115, No.3, (March 2005), pp. 853-859, ISSN 0032-1052

Sommer, B. & Sattler, G. (2000). Current concepts of fat graft survival: Histology of aspirated adipose tissue and review of the literature. *Dermatol Surg*, Vol.26, No.12, (December 2000), pp. 1159-1166, ISSN 1076-0512

Son, D.; Oh, J.; Choi, T.; Kim, J.; Han, K.; Ha, S. & Lee, K. (2010). Viability of fat cells over time after syringe suction lipectomy: the effects of cryopreservation. *Ann Plast Surg*, Vol.65, No.3, (September 2010), pp. 354-360, ISSN 0148-7043

Talbot, S.G.; Parrett, B.M. & Yaremchuk, M.J. (2010) Sepsis after autologous fat grafting. *Plast Reconstr Surg*, Vol.126, No.4 (October 2010), pp. 162e-164e, ISSN 1529-4242

Tholen, R.H.; Jackson, I.T.; Simman, R. & Di Nick, V.D. (2010). Recontouring Postradiation Thigh Defect with Autologous Fat Grafting In: *Autologous Fat Transfer*, Shiffman, M.A. (Ed.), 341-346, Springer-Verlag, ISBN 978-3-642-00472-8, Berlin Heidelberg

Toledo, L.S. (1991). Syringe liposculpture: A two-year experience. *Aesthetic Plast Surg*, Vol.15, No.4, (Fall 1991), pp. 321-326, ISSN 0364-216X

Uccelli, A.; Moretta, L & Pistoia, V. (2008). Mesenchymal stem cells in health and disease. *Nat Rev Immunol*, Vol.8, No.9, (September 2008), pp. 726-736, ISSN 1474-1733

Ullmann, Y.; Shoshani, O.; Fodor, A.; Ramon, Y.; Carmi, N.; Eldor, L. & Gilhar, A. (2005). Searching for the favorable donor site for fat injection: in vivo study using the nude mice model. *Dermatol Surg*, Vol.31, No.10, (October 2005), pp. 1304-1307, ISSN 1076-0512

Valdatta, L.; Thione, A.; Buoro, M. & Tuinder S. (2001). A case of life-threatening sepsis after breast augmentation by fat injection. *Aesthetic Plast Surg*, Vol.25, No.5 (September-October 2001), pp. 347-349, ISSN 0364-216X

Vessella, R.L.; Pantel, K. & Mohla, S. (2007). Tumor cell dormancy: an NCI workshop report. *Cancer Biol Ther,* Vol.6, No.9, (September 2007), pp. 1496-1504, ISSN 1555-8576

Von Heimburg, D.; Hemmerich, K.; Haydarlioglu, S.; Staiger, H. & Pallua, N. (2004). Comparison of viable cell yield from excised versus aspirated adipose tissue. *Cells Tissues Organs*, Vol.178, No.2, (2004), pp. 87-92, ISSN 1422-6405

Wang, P.; Mariman, E.; Renes, J. & Keijer, J. (2008). The secretory function of adipocytes in the physiology of white adipose tissue. *J Cell Physiol*, Vol.216No.1, (July 2008), pp. 3-13, ISSN 1097-4652

Weil, B.R.; Markel, T.A.; Herrmann, J.L.; Abarbanell, A.M. & Meldrum, D.R. (2009). Mesenchymal stem cells enhance the viability and proliferation of human fetal intestinal epithelial cells following hypoxic injury via paracrine mechanisms. *Surgery*, Vol.146, No.2, (August 2009), pp. 190-197, ISSN 1532-7361

Wels, J.; Kaplan, R.N.; Rafii, S. & Lyden, D. (2008). Migratory neighbors and distant invaders: tumor-associated niche cells. *Genes Dev*, Vol.22, No.5, (March 2008), pp. 559-574, ISSN 0890-9369

Wickham, M.Q.; Erickson, G.; Gimble, J.; Vail, T. & Guilak, F. (2003). Multipotent stromal cells derived from infrapatellar fat pat of the knee. *Clin Orthop*, Vol.412, (July 2003), pp. 196-212, ISSN 0009-921X

Yañez, R.; Lamana, M.L.; García-Castro, J.; Colmenero, I.; Ramírez, M. & Bueren, J.A. (2006). Adipose tissue-derived mesenchymal stem cells have in vivo immunosuppressive properties applicable for the control of the graft-versus-host disease. *Stem Cells*, Vol.24, No.11, (November 2006), pp. 2582-2591, ISSN 1066-5099

Yang, H.; Lee, H. (2011). Successful use of squeezed-fat grafts to correct a breast affected by Poland syndrome. *Aesthetic Plast Surg*, Vol.35, No.3, (June 2011), pp. 418-425, ISSN 0364-216X

Yuksel, E.; Weinfeld, A.B.; Cleek, R.; Wamsley, S.; Jensen, J.; Boutros, S.; Waugh, J.M.; Shenaq, S.M. & Spira, M. (2000). Increased free fat graft survival with the long-term, local delivery of insulin, insulin-like growth factor-1, and basic fibroblast growth factor by PLGA/PEG microspheres. *Plast Reconstr Surg*, Vol.105, No.5, (April 2000), pp. 1712-1729, ISSN 0032-1052

Zhang, Y.; Daquinag, A.; Traktuev, D.O.; Amaya-Manzanares, F.; Simmons, P.J.; March, K.L.; Pasqualini, R.; Arap, W. & Kolonin, M.G. (2009). White adipose tissue cells are recruited by experimental tumors and promote cancer progression in mouse models. *Cancer Res*, Vol.69, No.12, (June 2009), pp. 5259-5266, ISSN 1538-7445

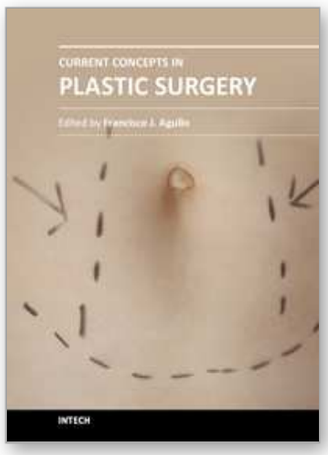
Zhao, B.C.; Zhao, B.; Han, J.G.; Ma, H.C. & Wang, Z.J. (2010). Adipose-derived stem cells promote gastric cancer cell growth, migration and invasion through SDF-1/CXCR4

axis. *Hepatogastroenterology*, Vol.57, No.104, (November-December 2010), pp. 1382-1389, ISSN 0172-6390

Zheng, D.N.; Li, Q.F.; Lei, H.; Zheng, S.W.; Xie, Y.Z.; Xu, Q.H.; Yun, X. & Pu, L.L. (2008) Autologous fat grafting to the breast for cosmetic enhancement: experience in 66 patients with long-term follow up. *J Plast Reconstr Aesthet Surg*, Vol.61, No.7, (July 2008), pp. 792-798, ISSN 1748-6815

Zimmerlin, L.; Donnenberg, A.D.; Rubin, J.P.; Basse, P.; Landreneau, R.J. & Donnenberg, V.S. (2011). Regenerative therapy and cancer: in vitro and in vivo studies of the interaction between adipose-derived stem cells and breast cancer cells from clinical isolates. *Tissue Eng Part A*, Vol.17, No.1-2, (January 2011), pp. 93-106, ISSN 1937-335X

Zuk, P.A.; Zhu, M.; Ashjian, P.; De Ugarte, D.A.; Huang, J.I.; Mizuno, H.; Alfonso, Z.C.; Fraser, J.K.; Benhaim, P. & Hedrick, M.H. (2002). Human adipose tissue is a source of multipotent stem cells. *Mol Biol Cell*, Vol.13, No.12, (December 2002), pp. 4279-4295, ISSN 1059-1524



Current Concepts in Plastic Surgery

Edited by Dr. Frank Agullo

ISBN 978-953-51-0398-1
Hard cover, 264 pages
Publisher InTech
Published online 23, March, 2012
Published in print edition March, 2012

Plastic surgery continues to be a rapidly growing field in medicine. There have been multiple recent advancements in the field. Specifically, there has been a continuously growing interest in fat grafting, body contouring, minimally invasive surgery, and plastic surgery education. At the same time, there have been continued advances and modifications in surgical techniques, which translate into better and improved results for our patients while increasing safety and efficacy. The title of the book is Current Concepts in Plastic Surgery and, as such, it highlights some of the "hot topics" in recent years. We have invited renowned specialists from around the world to share their valued expertise and experience. Most of the chapters will expose the reader to multiple techniques for achieving desired results, with emphasis on the author's preferred methodology.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Pietro Panettiere, Danilo Accorsi and Lucio Marchetti (2012). The Role of Free Fat Graft in Breast Reconstruction After Radiotherapy, Current Concepts in Plastic Surgery, Dr. Frank Agullo (Ed.), ISBN: 978-953-51-0398-1, InTech, Available from: http://www.intechopen.com/books/current-concepts-in-plastic-surgery/the-role-of-free-fat-graft-in-breast-reconstruction-after-radiotherapy

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen