

Oncologic Safety and Viability of Stem Cell-Enriched Autologous Fat Grafting: A Narrative Review of the Preclinical and Clinical Evidence

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ABSTRACT

Autologous fat grafting has become a cornerstone of both reconstructive and aesthetic plastic surgery, yet unpredictable resorption of the transplanted tissue remains its principal technical limitation. This has driven the development of enrichment strategies in which the lipoaspirate is supplemented with the stromal vascular fraction or with culture-expanded adipose-derived stem/stromal cells (ADSCs). Enrichment consistently improves graft retention in most clinical series, but ADSCs are also potent secretors of angiogenic, mitogenic and immunomodulatory mediators, which raises a legitimate concern: could the same biology that keeps a graft alive also awaken or accelerate residual tumor cells in the recipient bed? This narrative review synthesizes the current *in vitro*, animal and clinical evidence on the oncologic safety and technical viability of stem cell-enriched fat transfer, with emphasis on breast reconstruction after oncologic surgery. Laboratory studies remain frankly contradictory, describing both tumor-promoting and tumor-suppressive effects that appear to depend on the donor, the cell subpopulation, the tumor molecular subtype and the experimental model. *In vivo* animal work is similarly divided, although several models suggest that whole fat graft is a less permissive environment for tumor engraftment than the isolated cell fraction. In contrast, clinical series, matched cohorts and multicenter studies including several thousand patients have not demonstrated an increase in locoregional recurrence, systemic recurrence or second primary tumors attributable to either conventional or enriched fat grafting. The available evidence supports the continued use of enriched lipotransfer in patients who have completed oncologic treatment and show no evidence of active disease, provided that informed consent, structured imaging follow-up and prospective data collection are incorporated into routine practice.

KEYWORDS: Autologous fat grafting; adipose-derived stem cells; stromal vascular fraction; cell-assisted lipotransfer; breast reconstruction; oncologic safety; cancer recurrence

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I. INTRODUCTION

The transfer of autologous adipose tissue as a soft-tissue filler is more than a century old, but its modern surgical application began in the 1980s, when the generalization of liposuction made large volumes of donor tissue available through small incisions. Bircoll first described the combination of liposuction with autologous transplantation of the harvested fat into the breast [1,3]. The technique was initially received with skepticism, and in 1987 the American Society of Plastic Surgeons issued a negative position statement, largely because of concerns about radiological interference with cancer detection. The turning point came two decades later, when Coleman and Saboeiro published a structured series of breast augmentation and reconstruction patients followed with serial photography, demonstrating that the procedure was both reproducible and durable when performed with an atraumatic, low-pressure technique [4]. Since then, autologous fat grafting (AFG), also referred to as lipofilling or autologous fat transfer, has been progressively incorporated into the reconstructive armamentarium.

In contemporary practice, AFG is used to correct contour deformities and asymmetry after wide local excision or breast-conserving surgery, with or without radiotherapy; to improve soft-tissue coverage in implant-based reconstruction; to refine the shape and volume of autologous flap reconstructions; and, in staged procedures, to reconstruct the whole breast [1,9]. Beyond the breast, the same principles are applied to facial rejuvenation, correction of post-traumatic and post-oncologic facial deformities, scar release and the management of radiation-induced tissue damage [23]. Fat is an attractive filler because it is autologous, abundant, biologically active and, unlike alloplastic materials, capable of remodeling the recipient bed rather than simply occupying space.

The principal technical limitation of the procedure is the unpredictability of graft take. Reported reductions in transplanted volume range from roughly 20% to 90% over time, and many patients require two or more sessions to achieve the desired result [1,8]. Mature adipocytes are fragile and poorly tolerant of the ischemia that follows transplantation, whereas the progenitor cells contained in the stromal vascular fraction (SVF) survive hypoxia considerably better and can replace the adipocytes that die during the first weeks after grafting [1]. This observation gave rise to the concept of cell-assisted lipotransfer (CAL), in which the graft is supplemented either with freshly isolated SVF or with culture-expanded adipose-derived stem/stromal cells (ADSCs) before injection [18].

Enrichment, however, introduces a biological paradox. The very properties that make ADSCs useful for graft survival, namely their proangiogenic, anti-apoptotic, immunomodulatory and paracrine activity, are also the properties that a residual or dormant tumor cell would require to resume proliferation. A substantial body of preclinical work has therefore examined whether adipocytes and ADSCs can

promote breast cancer growth, invasion and metastasis, with results that remain contradictory and, in several instances, mutually exclusive [1,2]. Because lipofilling is most frequently indicated precisely in patients treated for breast cancer, the question is not academic: it directly conditions the reconstructive options that can be offered.

The present review examines the viability and oncologic safety of stem cell-enriched fat grafting. It summarises the cellular basis of the enriched graft, appraises the clinical evidence for improved retention, analyses the in vitro and animal data on ADSC-tumour crosstalk, reviews the clinical outcomes reported after both conventional and enriched grafting in oncologic patients, and proposes a set of practical recommendations for surgeons who incorporate this technique into their practice.

II. BIOLOGICAL BASIS OF THE ENRICHED FAT GRAFT.

A. Cellular composition of the lipoaspirate

Adipose tissue is not an inert reservoir of lipid but a multicellular endocrine organ. In addition to mature adipocytes, it contains preadipocytes, fibroblasts, endothelial cells, pericytes, resident immune cells and multipotent stromal cells [1]. When lipoaspirate is enzymatically or mechanically digested and centrifuged, the buoyant mature adipocytes separate from a pellet known as the stromal vascular fraction, which concentrates the non-adipocyte populations, including the ADSCs.

Human adipose tissue was first characterized as a source of adult mesenchymal stem cells by Zuk and colleagues in 2001, who demonstrated multilineage differentiation towards adipogenic, osteogenic, chondrogenic and myogenic phenotypes [5]. The International Federation for Adipose Therapeutics and Science and the International Society for Cellular Therapy subsequently standardized the nomenclature and the immunophenotype: ADSCs are plastic-adherent, stable-doubling cells that express CD44, CD73, CD90 and CD105 and lack CD31 and CD45 [6]. Freshly isolated cells express CD34, an antigen progressively lost with successive passages in culture, which explains part of the phenotypic disagreement between laboratories. This detail is not trivial when interpreting oncologic safety data, because the biological behavior of a freshly isolated ADSC and that of an immortalized or extensively passaged cell line are demonstrably different [1].

B. Harvesting, processing and cell isolation

Graft viability begins at the donor site. Mechanical trauma during aspiration compromises adipocyte integrity, and lower negative pressure is associated with better cell viability and graft survival [1]. Blunt, multi-hole cannula of intermediate caliber connected to manual



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syringe aspiration remain the reference technique [7], although power-assisted and ultrasound-assisted devices yield comparable regenerative capacity, whereas laser-assisted liposuction reduces adipocyte yield and viability [1].

Processing may be performed by centrifugation, washing, decantation or filtration. Centrifugation at 3000 revolutions per minute for three minutes separates the lipoaspirate into an oily supernatant derived from disrupted adipocytes, a purified fat layer and an aqueous infranatant containing blood, anesthetic solution and cellular debris [1,23]. When the objective is to obtain SVF, the choice lies between enzymatic digestion, usually with collagenase, and mechanical methods. Comparative work suggests that enzymatic digestion yields the highest number of ADSCs and the best volume maintenance, while filtration is the most efficient of the mechanical alternatives [10]. A randomized three-dimensional volumetric comparison of processing techniques in facial grafting reached a concordant conclusion regarding filtration [11]. In practice, the choice is governed by local regulatory frameworks, since enzymatic digestion and ex vivo expansion are considered advanced therapy manipulations in many jurisdictions.

C. Donor-site and donor-dependent variability

Most experimental and clinical protocols harvest fat from the abdomen. ADSCs obtained from abdominal and breast fat share marker expression and differentiation potential, although breast-derived cells display higher self-renewal capacity and less stable population doubling [2,12]. Donor age, body mass index and metabolic status further modulate cell behavior: stem cells from donors with obesity display an altered secretory profile, with higher leptin production, and have been shown in xenograft models to promote metastasis of triple-negative breast cancer [69]. Donor-to-donor variability is, in fact, one of the most consistent findings in the entire field and a major explanation for the divergent results discussed later in this review [36,70].

D. Why enrichment improves retention

Three complementary mechanisms are usually invoked. First, ADSCs secrete vascular endothelial growth factor, hepatocyte growth factor, fibroblast growth factor and other proangiogenic mediators that accelerate revascularization of the graft, shortening the ischemic window during which adipocytes die. Second, preadipocytes and progenitor cells tolerate hypoxia better than mature adipocytes and can differentiate to replace those lost in the early postoperative period, a phenomenon described as the cellular replacement theory. Third, the immunomodulatory and anti-apoptotic secretum of the SVF attenuates the inflammatory response and the macrophage-mediated phagocytosis of dead adipocytes that dominates the first three months after transfer [1,8,23].

III. CLINICAL EVIDENCE ON EFFICACY OF ENRICHMENT

A. Breast augmentation and reconstruction



The most influential trial in this field remains the randomized, assessor-blinded study by Kolle and colleagues, in which grafts enriched with ex vivo expanded ADSCs achieved a mean volume retention of 80.2% compared with 45.1% for conventional non-enriched grafts, with clinical photographs judged superior by independent experts [13]. The same group later confirmed enhanced retention in a randomized controlled trial of breast augmentation [14]. Yoshimura and colleagues, who introduced the term cell-assisted lipotransfer, reported minimal postoperative atrophy after the second month and a high level of patient satisfaction in a series of forty augmentations, with cyst formation or microcalcification detected in four patients [18].

The evidence is nevertheless not unanimous. A volumetric study using three-dimensional laser scanning found virtually identical twelve-month survival of transplanted fat with and without SVF (67.9% versus 68.7%) and comparable complication rates and did not support routine SVF supplementation for augmentation [16]. A double-blind randomized trial of ADSC-enriched grafting likewise found comparable one-year retention between the enriched and placebo arms, although the sample was small [15]. Conversely, a randomized comparison of cell-assisted and conventional transplantation reported significantly greater postoperative uplift and greater fat retention on magnetic resonance imaging in the cell-assisted group [17], and a prospective study of contour deformities in reconstructed breasts found retention rates of 73.8% versus 62.2% at six months and 65.4% versus 48.4% at twelve months in favor of SVF enrichment, with equivalent complication rates [21]. Volume retention also correlates with the number of SVF cells delivered and with recipient-site characteristics such as skin tension and breast softness [19,20].

A systematic review and meta-analysis comparing stem cell-enriched with conventional grafts in reconstructive surgery found a significant advantage for enrichment in terms of retention, without a significant difference in the incidence of fat necrosis [22]. Taken together, the data support a real but variable benefit, whose magnitude depends on the enrichment protocol, the cell dose and the anatomical site.

B. Facial and non-breast applications

Outside the breast, the evidence is more homogeneous. A phase III double-blind randomized trial in seventy patients undergoing facial rejuvenation compared centrifugation-assisted lipotransfer enriched with adipose-derived stem cells against conventional centrifugation. At twelve months, 94.3%

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of the enriched group retained at least 75% of the injected volume, compared with 8.6% of controls, corresponding to an 86% reduction in the risk of losing graft volume; wrinkle and marionette line scores improved significantly in both groups but more markedly in the enriched arm, and no complications were recorded [23]. Randomized work has also shown that SVF-assisted facial grafting improves skin quality, not only volume, and that patient-reported outcomes measured with validated instruments improve accordingly [24,25]. Enrichment retains its effect in unfavorable recipient beds: in localized scleroderma, ex vivo expanded autologous ADSCs approximately doubled soft-tissue thickness at six months compared with control [29].

C. Platelet-rich plasma and growth factor adjuncts

Platelet-rich plasma has been proposed as a simpler alternative to cell enrichment. In breast reconstruction, the addition of platelet-rich plasma to autologous fat maintained 69% of contour restoration and volume at one year against

39% for centrifuged fat alone [27]. A retrospective comparative analysis, however, found no benefit from a 10% platelet-rich plasma concentration over standard Coleman grafting [28], and a double-blind trial of platelet-derived growth factor supplementation showed no effect whatsoever [26]. The discrepancy underlines that a heterogeneous cell population appears more effective than any single recombinant factor.

D. Interpretation of the efficacy data

Sample sizes are generally small, follow-up rarely exceeds twelve months, volumetric assessment methods differ (ultrasound, magnetic resonance imaging, three-dimensional scanning), and the definition of enrichment ranges from freshly isolated SVF at variable cell doses to several passages of expanded ADSCs. These sources of heterogeneity, summarized in Table I, explain why meta-analytical estimates favor enrichment while individual trials sometimes do not.

TABLE I. SELECTED CLINICAL STUDIES COMPARING ENRICHED AND CONVENTIONAL AUTOLOGOUS FAT GRAFTING

Study (Reference)	Design and Sample	Comparison	Main Retention Outcome
Yoshimura et al., 2008 [18]	Prospective series, n = 40	SVF-enriched grafting (CAL)	Minimal atrophy after 2 months; cyst or microcalcification in 4 patients
Salgarello et al., 2011 [28]	Retrospective, n = 42	10% PRP + fat vs Coleman technique	No advantage of PRP over conventional grafting
Kolle et al., 2013 [13]	Randomised, assessor-blinded, n = 16	Expanded ADSC-enriched vs conventional	80.2% vs 45.1% retention; superior clinical photographs
Gentile et al., 2013 [27]	Comparative, n = 100	Fat + PRP vs centrifuged fat	69% vs 39% maintenance of contour and volume at 1 year
Chiu, 2019 [16]	Comparative volumetric, n = 206	SVF-enriched vs conventional	67.9% vs 68.7% at 12 months; no significant difference
Jeon et al., 2021 [21]	Prospective, n = 20	SVF-enriched vs conventional	65.4% vs 48.4% at 12 months; higher satisfaction
Hu et al., 2022 [17]	Randomised, n = 34	Cell-assisted vs conventional	Greater uplift and greater retention on MRI
Vester-Glowinski et al., 2022 [15]	Double-blind randomised, n = 20	ADSC-enriched vs placebo-enriched	54.0% vs 55.9% at 1 year; comparable retention
Tamayo Carbon et al., 2023 [23]	Phase III double-blind randomised, n = 70	ADSC-assisted vs conventional facial lipotransfer	94.3% vs 8.6% retained 75% or more of volume at 1 year
Karam et al., 2023 [22]	Systematic review and meta-analysis	Enriched vs conventional grafts	Significant advantage in retention; no difference in fat necrosis

IV. IN VITRO CROSSTALK BETWEEN ADSCS AND TUMOUR CELLS

A. Evidence suggesting tumor promotion

A considerable number of co-culture experiments describe pro-tumorigenic effects. Whole lipoaspirate co-cultured with MCF-7 cells increased their proliferation rate and induced expression of matrix metalloproteinase-1 and integrin alpha-2,

markers of matrix degradation and invasive potential [32]. Similar proliferative effects were reported when several breast cancer lines were exposed to whole adipose tissue or to in vitro differentiated adipocytes [31]. ADSC-conditioned medium stimulated migration of triple-negative MDA-MB-231 cells without necessarily increasing their growth, indicating that paracrine factors act preferentially on motility [36].

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Conditioned medium from ADSCs also increased migration, mammosphere formation and the expression of epithelial-to-mesenchymal transition markers in HER2-overexpressing SKBR3 cells, while paradoxically increasing their chemosensitivity to doxorubicin and 5-fluorouracil [33]. Other groups have documented induction of an epithelial-to-mesenchymal transition, mediated at least in part by platelet-derived growth factor-D, with downregulation of E-cadherin and upregulation of Snail, Slug, vimentin and alpha-smooth muscle actin [34]. Autologous experiments combining ADSCs and tumor cells from the same donor showed enhanced migratory capability in a subset of samples and identified higher expression of the proto-oncogene c-Met in the susceptible tumors, together with reciprocal upregulation of hepatocyte growth factor by the ADSCs, suggesting a bidirectional HGF/c-Met loop [35].

B. Evidence suggesting neutrality or inhibition

An equally substantial literature reports the opposite. Conditioned medium from ADSCs reduced the viability of MCF-7, MDA-MB-231 and MDA-MB-468 cells in a dose-dependent manner, activating ATM-Chk2 signaling and caspase-3 cleavage selectively in malignant but not in non-cancerous mammary cells [37]. ADSCs have been shown to inhibit anti-apoptotic protein expression through upregulation of the transcription factor ATF4 [38], and contact co-culture induced retinoblastoma protein-mediated cell cycle arrest in MCF-7 cells [39]. An assay designed specifically to measure the natural tropism of ADSCs towards breast cancer cells found a low oncogenic response [41]. Finally, extracellular vesicles derived from ADSC subpopulations with low CD90 expression suppressed proliferation and migration and induced apoptosis, an effect attributed to their enrichment in the pro-apoptotic microRNA miR-16-5p [42].

C. Dormancy, reactivation and tenascin-C

Because reconstruction is postponed until there is no clinical evidence of active disease, the clinically relevant question is not whether ADSCs stimulate proliferating tumor cells but whether they can awaken dormant ones. Minimal residual disease is a genuine problem, with relapse occurring in approximately one fifth of patients more than five years after primary treatment [30]. Using cobalt chloride to induce reversible quiescence in MCF-7 cells, and validating the model through Ki67, cell-cycle and p21 analysis, Nystrom and colleagues showed that ADSCs from six donors never increased the growth of either active or dormant cancer cells; in four of six co-cultures the dormant state was in fact prolonged [30]. Screening of eighty-four cancer-related proteins in the conditioned medium identified only tenascin-C as differentially expressed, secreted by the ADSCs rather than by the tumor cells and increased further in co-culture. Conditioned medium from the interacting cells significantly increased cancer cell migration, although blocking tenascin-C did not abolish this effect, implying that other mediators are

involved. The authors concluded that ADSCs per se neither promote growth nor migration, but that the products of their interaction with tumor cells may favor invasiveness [30]. A complementary study using metastatic pleural effusion cells reported that ADSCs enhanced the tumorigenicity of active cells while leaving resting cells unaffected [40].

D. Interactions with systemic therapy

ADSCs also modify the pharmacological environment. Combined low-dose paclitaxel and histone deacetylase inhibition induced cytotoxicity in MDA-MB-231 cells while preserving ADSC viability and wound-healing function [44]. ADSCs are able to take up paclitaxel and release it subsequently, a property exploited experimentally to deliver chemotherapy locally [43]. Conversely, exosomes derived from adipocytes reduced early apoptosis in 5-fluorouracil-treated MCF-7 cells, suggesting a protective effect against cytotoxic drugs [2]. These observations point to a dual and dose-dependent relationship rather than to a uniform pro-tumoral influence.

E. Why the in vitro literature disagrees

Several methodological factors account for the contradiction. Donor dependency is the most consistently documented: ADSCs from one donor may markedly stimulate xenograft growth while cells from another do not, and interindividual differences persist even within the same experimental design [36,70]. Tumor heterogeneity is equally decisive, since luminal, HER2-enriched and triple-negative lines respond differently to identical conditioned media [35]. Culture conditions matter as well, because prolonged passaging and immortalization alter the secretory profile, shifting the balance of insulin-like growth factor signaling towards a mitogenic phenotype that freshly isolated cells do not display [1]. Finally, the ADSC-to-tumor cell ratios used in vitro are far higher than any plausible in vivo scenario, and no culture system reproduces the immune surveillance, vascular dynamics and mechanical constraints of the human recipient bed.

V. PRECLINICAL IN VIVO EVIDENCE

Animal models were expected to clarify the picture but have reproduced the same duality. Co-injection of ADSCs with tumor cells has been reported to increase primary tumor growth and pulmonary metastasis compared with controls, an effect attenuated when autologous fat graft was present alongside the isolated cells [45]. Human ADSCs promoted progression and metastatic spread in MCF-7 and MDA-MB-231 rodent models, with the triple-negative line behaving more aggressively [46]. Tumors injected with ADSC-enriched grafts showed higher vascular density and greater growth than those receiving fat graft alone, although Ki-67 staining did not differ between groups, suggesting an angiogenic rather than a directly mitogenic mechanism [47]. Sorted CD34-positive progenitor populations from human adipose tissue increased

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tumor volume and the number of lung metastases in immunodeficient mice, whereas the CD34-negative fraction had no effect [51].

Other models point in the opposite direction. In a humanized model of residual breast cancer, fat grafting performed two weeks after xenografting reduced tumor volume and Ki-67 expression relative to saline injection [49]. When tumor cells were seeded into human lipograft before implantation, a HER2-positive line failed to engraft at any dose and a triple-negative line required a cell dose an order of magnitude higher than in Matrigel, indicating that adipose tissue is a comparatively hostile environment for tumor engraftment; when fat was injected two weeks after tumor engraftment, proliferation indices decreased [50]. A murine model of cell-assisted lipotransfer for reconstruction in the presence of residual breast cancer found comparable tumor weights across groups [48], and ADSC subpopulations with low CD90 expression significantly inhibited tumor progression relative to CD90-high cells or fibroblasts [42]. Dose dependency has also been demonstrated for ADSC-mediated drug delivery: xenografts treated with paclitaxel-loaded ADSCs at 4 micromolar shrank to about half the size of controls, whereas a 2 micromolar dose increased xenograft growth [43].

The most defensible synthesis is that the effect of adipose-derived cells on tumor behavior in vivo is subpopulation-specific, dose-dependent and model-dependent, and that the intact fat graft behaves differently from, and generally more favorably than, the isolated cellular fraction.

VI. CLINICAL EVIDENCE ON ONCOLOGIC SAFETY

A. Conventional non-enriched lipofilling

Clinical data are considerably more reassuring than laboratory data. A matched controlled study of patients undergoing mastectomy for cancer or risk reduction followed by reconstruction with or without lipofilling reported five-year locoregional recurrence rates of 1.6% in the lipofilling group against 4.1% in controls, and systemic recurrence rates of 2.4% against 3.6%, supporting oncologic safety [52]. A case-control study of women previously treated for invasive carcinoma and ductal carcinoma in situ found no significant differences in local, regional or distant recurrence [54]. A matched cohort analysis likewise showed no increase in locoregional recurrence, distant recurrence, disease-free survival or overall survival [53]. The largest dataset to date, a multicenter Italian study of more than six thousand patients, confirmed the non-inferiority of fat grafting for locoregional recurrence-free survival, with consistent findings across luminal-like, HER2-enriched and triple-negative subtypes [55].

Three qualifications deserve emphasis. First, in a monocentric case-control study, lipofilling was not predictive of recurrence, overall survival or distant metastasis in the population as a whole, but emerged as an independent

predictive factor for local recurrence in the subgroup treated for invasive carcinoma [56]. Second, an early and frequently cited series identified a higher risk of local events when the analysis was restricted to intraepithelial neoplasia [58]. Third, timing may matter: fat grafting performed within twelve months of implant-based reconstruction was associated with local recurrence, whereas grafting performed later was not [57]. A long-term exact-matching study also raised the possibility of increased late locoregional recurrence in luminal A tumors, although attrition of the population at prolonged follow-up limits the conclusion [59].

B. Stem cell-enriched and SVF-enriched grafting

Specific data on enriched grafting are fewer but consistent. Cancer recurrence in patients reconstructed with ADSC-enriched fat was 3.7% over three years, compared with 4.13% in patients who did not undergo reconstruction, with no adverse effects attributable to the therapy [60]. A prospective study of SVF-enriched grafting after nipple-sparing mastectomy found loco-regional recurrence rates of 2.4%, 4.7% and 1.6% and systemic recurrence rates of 7.3%, 3.1% and 3.1% in the enriched, non-enriched and control groups respectively, with no variable, including enrichment, emerging as an independent risk factor [61]. Long-term follow-up of patients receiving adipose-derived regenerative cell-enriched grafts after breast-conserving surgery and adjuvant radiotherapy documented no recurrence or metastasis at a mean of almost eight years [62]. The RESTORE-2 prospective trial of enriched grafting for partial mastectomy defects reported no serious adverse events and no local recurrences, with injection-site cysts as the principal complication [63]. Twelve-year institutional experience with fat grafting after breast cancer showed low rates of local recurrence, distant metastasis and tumor-related death together with high patient satisfaction [64], and a multicenter case-cohort study of mastectomy with immediate reconstruction found no association between fat transfer and recurrence [65]. Enriched grafting has additionally shown benefit in breast cancer-related lymphoedema of the upper limb, with significant improvement in arm heaviness, tension and disability scores and an acceptable safety profile at six months [66].

C. Radiological surveillance

Because the original objection to lipofilling was radiological rather than biological, imaging outcomes deserve separate consideration. After breast-conserving surgery, grafting induces frequent imaging changes: oil cysts in up to 85% of patients, calcifications in about one fifth and increased scarring in a small minority [67]. These findings are benign and, in experienced hands, generate few interventions; in a consecutive postmastectomy series the biopsy rate after grafting was 4.8%, all specimens showing fat necrosis, scar or oil cysts without malignancy, and no locoregional recurrences were observed [68]. Ultrasound identifies oil cysts most reliably, whereas magnetic resonance imaging is superior for

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liponecrosis [1]. Structured baseline and follow-up imaging, therefore the practical answer to the detection concern. interpreted by radiologists aware of the surgical history, is

TABLE II. SELECTED CLINICAL STUDIES ADDRESSING ONCOLOGIC SAFETY OF CONVENTIONAL AND ENRICHED FAT GRAFTING

Study (Reference)	Design and Sample	Population	Oncologic Outcome
Perez-Cano et al., 2012 [63]	Prospective trial, n = 71	Partial mastectomy defects, ADRC-enriched graft	No serious adverse events and no local recurrence; injection-site cysts in 10 patients
Gale et al., 2015 [54]	Case-control, n = 211 (2:1 matched)	Invasive carcinoma and ductal carcinoma in situ	No significant difference in local, regional or distant recurrence
Kronowitz et al., 2016 [52]	Matched controlled study, 719 vs 670 breasts	Mastectomy with reconstruction	Locoregional recurrence 1.6% vs 4.1% at 5 years
Myckatyn et al., 2017 [65]	Multicentre case-cohort, n = 1197	Mastectomy with immediate reconstruction	Adjusted hazard ratio for recurrence 0.97 (95% CI 0.54-1.8)
Ito et al., 2017 [62]	Prospective, n = 10	Breast-conserving surgery and radiotherapy, ADRC-enriched graft	No recurrence or metastasis at a mean of 7.8 years
Calabrese et al., 2018 [61]	Prospective, 3 groups, n = 169	Nipple-sparing mastectomy, SVF-enriched vs conventional vs control	Loco-regional recurrence 2.4%, 4.7% and 1.6%; enrichment not an independent risk factor
Mazur et al., 2018 [60]	Comparative cohort, n = 308	ADSC-enriched reconstruction vs no reconstruction	Recurrence 3.7% vs 4.13% over 3 years
Tukiama et al., 2021 [53]	Matched cohort 1:3, n = 168	Breast cancer treated with and without grafting	No increase in locoregional, local or distant recurrence
Berti et al., 2022 [56]	Case-control, n = 412	Reconstruction after mastectomy for cancer	No overall effect; independent predictor of local recurrence in invasive cancer subgroup
Klinger et al., 2022 [55]	Multicentre retrospective, n = 6592	Breast cancer with and without grafting	Locoregional recurrence 3.9% vs 6.1%; non-inferiority confirmed
Kempa et al., 2022 [64]	Monocentric cohort, n = 93	Grafting after breast cancer, 12-year experience	Local recurrence 1.1%, distant metastasis 2.2%, tumor-related death 1.1%
Lee et al., 2023 [57]	Retrospective cohort	Implant-based reconstruction with grafting	Association with recurrence only when grafting performed before 12 months

VII. RECONCILING LABORATORY AND CLINICAL FINDINGS

The discrepancy between alarming in vitro signals and reassuring clinical outcomes is the central intellectual problem of this field, and several explanations converge. The cell ratios and concentrations used in co-culture bear no relation to the physiological situation, in which a small number of putative residual tumor cells would encounter a graft dispersed in microdeposits through a scarred, hypovascular bed. Immunodeficient animals, necessary for xenografting, remove precisely the immune surveillance that

operates in patients. Clinical grafting is by convention performed only after completion of oncologic treatment and documentation of disease-free status, so that the biological target of the supposed stimulus is largely absent [30]. Mechanical factors may also be protective, since the transferred tissue can compress the tumor bed and limit perfusion [1]. Experimental data further indicate that intact adipose tissue is a less permissive substrate for tumor engraftment than either Matrigel or isolated cell suspensions [50], and that the presence of autologous fat attenuates the tumor-promoting effect of isolated ADSCs [45].

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Methodological limitations on the clinical side must also be acknowledged. Most series are retrospective, follow-up is frequently shorter than the interval at which luminal tumors recur, patients selected for reconstruction tend to have more favorable disease biology, and stratification by molecular subtype is generally absent or underpowered [1]. The absence of demonstrated harm is therefore not equivalent to the demonstration of absolute safety, and the appropriate clinical posture is one of documented, monitored use rather than either prohibition or complacency.

VIII. PRACTICAL RECOMMENDATIONS

The following recommendations summarize the position that the available evidence supports for daily practice. They are graded by the strength of the underlying data rather than by tradition.

Perform enriched lipotransfer only after completion of oncologic treatment and documentation of the absence of active disease. There is no consensus on the minimum interval; a period of at least twelve months after reconstruction has been associated with the absence of any recurrence signal, and intervals of up to thirty-six months have been proposed as a conservative minimum [30,57].

Exercise caution, and involve the multidisciplinary team explicitly, in patients treated for invasive carcinoma and in those with intraepithelial neoplasia, the two subgroups in which isolated studies have detected an excess of local events [56,58].

Obtain specific informed consent addressing the state of the evidence, including the existence of contradictory preclinical data and the absence of randomized trials powered for oncologic endpoints.

Establish a baseline imaging study before grafting and a structured follow-up protocol afterwards, combining ultrasound and magnetic resonance imaging as indicated, and inform the reporting radiologist of the procedure and of the volumes injected [1,67,68].

Prefer enzymatic digestion or filtration when SVF enrichment is used, and record the cell dose delivered, since retention correlates with the number of viable cells transferred [10,11,20].

Distribute the graft in multiple small deposits across different planes, using low-pressure harvest and blunt cannula, in order to maximize the surface of contact with vascularized recipient tissue [23].

Document volumes, number of sessions, complications and oncologic outcomes prospectively, ideally within institutional or national registries, since the resolution of the remaining uncertainty depends on the accumulation of standardized long-term data.

IX. LIMITATIONS AND FUTURE DIRECTIONS

This review is narrative rather than systematic, and the primary literature it summarizes is heterogeneous in design,

in the definition of enrichment and in the outcome measures reported. No randomized controlled trial has been designed with cancer recurrence as its primary endpoint, and it is questionable whether such a trial could be conducted ethically and with sufficient power. Priorities for future research are therefore pragmatic: prospective cohorts stratified by molecular subtype and by the interval between oncologic surgery and grafting; standardized characterization and reporting of the transferred cell population, including viability, dose and passage number; longer follow-up, given the propensity of luminal tumors to late recurrence; and translational models that preserve immune competence. In parallel, the capacity of ADSCs to internalize and release cytotoxic agents opens the possibility that the enriched graft could evolve from a passive filler into a local drug delivery platform, an application that will require its own safety evaluation [43,44].

CONCLUSIONS

Enrichment of autologous fat grafts with the stromal vascular fraction or with adipose-derived stem cells is a technically viable procedure that improves graft retention in most, though not all, controlled studies, and that improves tissue quality in addition to volume. The oncologic concern raised by preclinical work is legitimate and should not be dismissed: in vitro and animal studies document that adipose-derived cells can promote proliferation, migration, epithelial-mesenchymal transition and angiogenesis in certain tumor models, while equally rigorous studies document growth inhibition, apoptosis induction and prolongation of tumor dormancy. These effects are donor-dependent, subpopulation-dependent, dose-dependent and tumor subtype-dependent, which explains rather than resolves the contradiction.

Clinical evidence accumulated over more than a decade, including matched cohorts and multicenter series with thousands of patients, has not demonstrated an increase in locoregional recurrence, systemic recurrence or second primary tumors attributable to conventional or enriched fat grafting. Isolated signals in patients treated for invasive carcinoma, in intraepithelial neoplasia and in grafting performed early after reconstruction justify caution in these specific settings rather than a general contraindication. Enriched lipotransfer can therefore be offered to patients who have completed oncologic treatment and are free of active disease, provided that the indication is discussed within a multidisciplinary team, that consent is specific, that imaging follow-up is structured, and that outcomes are recorded prospectively so that the residual uncertainty can be progressively resolved.

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