



Lipofilling after breast conserving surgery: a comprehensive literature review investigating its oncologic safety

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Abstract: Lipofilling has regenerative properties used to improve deformities after breast conserving surgery. Our hypothesis is that there is inadequate data to ensure that lipofilling does not increase locoregional cancer recurrence after breast conserving surgery. A PRISMA comprehensive literature review was conducted of articles published prior to October 2019 investigating recurrence in patients who underwent lipofilling after breast conserving surgery. All forms of breast conserving surgery, fat grafting, and injection intervals were included. Patients undergoing mastectomy were excluded. Requirements to define lipofilling as “safe” included (I) a defined interval between resection and lipofilling; (II) a minimum follow-up period of 6 years from tumor resection; (III) a minimum follow-up period of 3 years from lipofilling; (IV) presence of a control group; (V) controls matched for ER/PR/Her-2; (VI) a sub-group analysis focusing on ER/PR/Her-2; (VII) adequate powering. Nineteen studies met inclusion criteria. The range in time from breast conserving surgery to fat injection was 0–76 months. The average time to follow-up after lipofilling was 23 days–60 months. Two studies had a sufficient follow-up time from both primary resection and from lipofilling. Seventeen of the nineteen studies specified the interval between resection and lipofilling, but there is currently no consensus regarding how soon lipofilling can be performed following BCS. Eight studies performed a subgroup analysis in cases of recurrence and found recurrence after lipofilling was associated with number of positive axillary nodes, intraepithelial neoplasia, high grade histology, Luminal A subtype, age <50, Ki-67 expression, and lipofilling within 3 months of primary resection. Of the eleven studies that included a comparison group, one matched patient for Her-2 and there was a statistically significant difference in Her-2 positive cancers in the study arms of two articles. Several studies deemed lipofilling “safe,” two showed association of lipofilling and local recurrence, and most studies concluded that further research was needed. Insufficient and contradictory data exists to demonstrate the safety of lipofilling after breast conserving surgery. A multicentered, well designed study is needed to verify the safety of this practice.

Keywords: Breast conserving surgery; lipofilling; recurrence

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Introduction

Breast conservation surgery (BCS) continues to be the most popular form of breast cancer surgery (1). As the indications for BCS continue to expand, there has been increased interest in personalized techniques of breast reconstruction (2). First introduced by Bircoll *et al.* in 1987, lipofilling, or autologous fat grafting, is a technique in which a patient's fat is harvested and centrifuged to obtain a concentrate rich in stem cells which is then transferred to the breast (3). With its advantages that include improved aesthetics in the area of the partial mastectomy, this technique is gaining increased use in BCS without clear consensus in this technique's oncologic safety. Multiple *in vitro* studies have conjectured that adipocytes, preadipocytes, and their products may play a role in tumor recurrence as they are involved in the tumor cell cycle through autocrine, paracrine, and exocrine/endocrine secretions (4,5). Moreover, a review article published by Lohsiriwat *et al.* proposed that a "tumor-stroma interaction" can potentially induce cancer reappearance by "fueling" dormant breast cancer cells in the tumor bed (6). This would be particularly concerning if it were to occur at a positive tumor margin after BCS.

In 2009, the American Society of Plastic Surgeons (ASPS) established a task force to assess the indications, safety and efficacy of lipofilling and concluded that, due to the limited data, they could not suggest evidence based recommendations concerning cancer recurrence (7). Few studies have focused on the oncological safety of lipofilling after BCS (8-10). Petit *et al.* reported the first case-matched retrospective series, which found no significant difference in local events (local relapse, locoregional relapse, or local relapse with synchronous metastases) between patients who underwent lipofilling after BCS and those who underwent BCS alone (10). Similarly, Gale *et al.* conducted a case-matched retrospective series comparing oncological outcomes between 211 patients who underwent lipofilling after BCS with control patients matched for five variables and found no significant association between lipofilling and disease recurrence, both locoregional and distant (11). However, in 2013, Krastev *et al.* performed a systematic review and found marked increase in locoregional recurrence in patients who underwent lipofilling after BCS when compared to a large series of women treated with BCS (12). Despite the merits of these and other studies found in the literature, the lack of stratification of recurrence rate by tumor subtype, tumor stage, receptor

status, and time to follow-up potentially limit their utility and applicability. The purpose of this project is to conduct a literature review utilizing PRISMA guidelines to investigate whether sufficient data exists to determine whether lipofilling following BCS increases the rate of locoregional tumor recurrence (LRR).

Methods

A systematic, online literature search was conducted following PRISMA guidelines (*Figure 1*). PubMed and MEDLINE were utilized to identify articles that investigated or commented on the oncological safety of lipofilling following BCS up until October 2019. Keywords included: "breast conserving surgery," "lumpectomy," "partial mastectomy," "lipofilling," "fat transfer," "fat grafting," "recurrence," and "safety". Oncoplastic surgery is a form of BCS (13,14) and was included in our definition of BCS. Ninety-three articles were initially identified. The citations of the 7 review articles/meta-analyses acquired from our search were screened to identify 6 additional articles. Fifty-four unique articles remained after removing duplicates. Articles met inclusion criteria if (I) the study participants underwent lipofilling following BCS and (II) the authors reported the recurrence rate. Exclusion criteria included (I) mastectomy or other types of surgery without any patients undergoing BCS prior to lipofilling; (II) non-cancer related reconstruction; (III) *in vitro* and animal studies; (IV) review articles and meta-analyses; (V) correspondence/commentary; (VI) full text unavailable; (VII) languages other than English without an available translation. Nineteen articles satisfied inclusion and exclusion criteria.

After excluding ineligible publications, nineteen articles underwent full-text analysis by two independent reviewers (SMC, YS) to extract information regarding the number of patients that specifically underwent BCS, average time to follow-up from lipofilling, the interval between primary resection and lipofilling, presence of a subgroup analysis for ER/PR/HER-2 status to determine if there was an association with recurrence, if the study design included a control, if the control was matched for ER/PR/Her-2, commentary on adequate powering, recurrence rates, statement of oncologic safety, and call for additional studies/trials. Lipofilling was considered "safe" if there was (I) a description of the interval between cancer resection and lipofilling; (II) a minimum follow-up period of 6 years after primary cancer resection; (III) a minimum follow-up period of 3 years after lipofilling; (IV) an analysis of breast

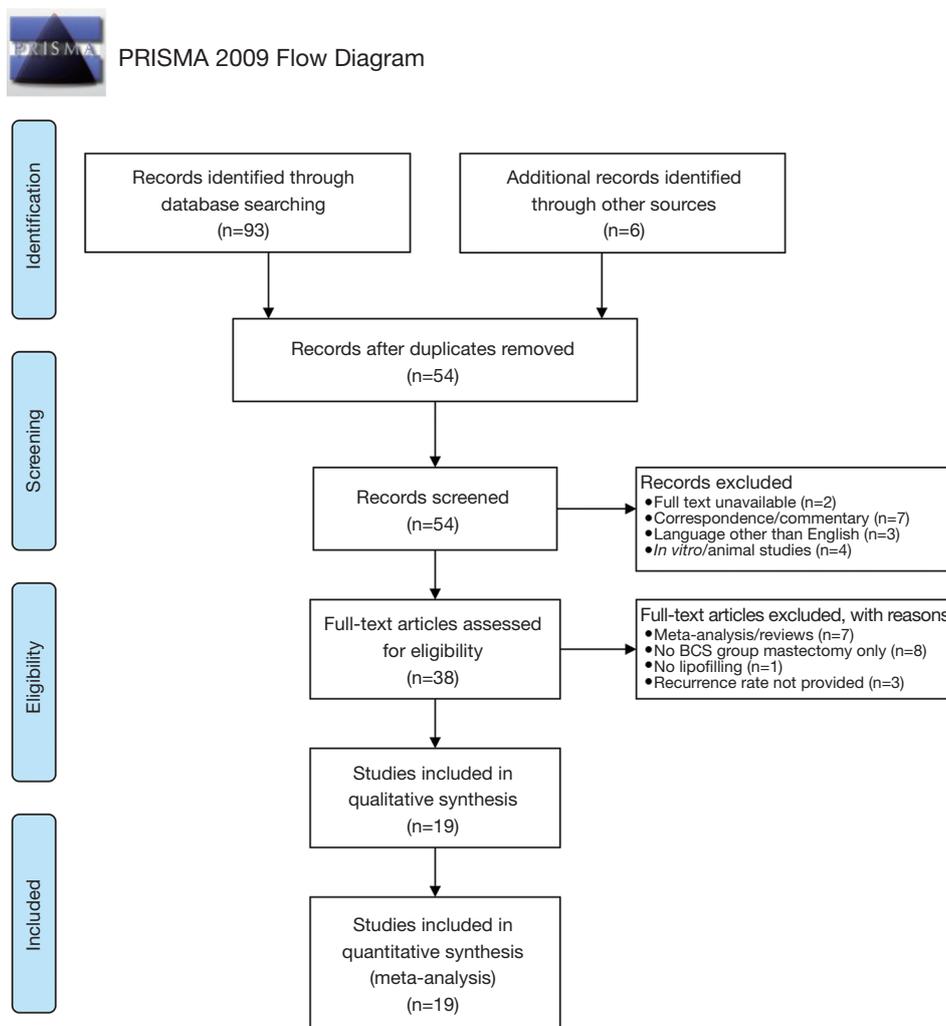


Figure 1 PRISMA methodology schematic.

cancer sub-groups specifically focusing on ER/PR/Her2; (V) a defined cohort comparison group; (VI) controls matched for receptor status; (VII) adequate powering.

The interval between the primary oncologic surgery and lipofilling needed to be defined, as immediate lipofilling poses the risk of having positive margins prior to transferring stem cells, and adequate time may be required to ensure there is no recurrence before introduction of these autologous cells. A follow-up time of 6 years from primary resection and 3 years from lipofilling was requisite to conclude whether lipofilling is safe since most locoregional recurrences occur between 3–6 years following BCS (15,16). In addition, the ACOSOG Z0011 trial, which dramatically impacted the management of patients with

axillary metastases, required a median time to follow-up of 6 years (17). It is critical to match for receptor status in a cohort study design. A sub-group analysis of receptor status and outcome after lipofilling is needed as specific types of cancers have different tendencies to recur (18).

Results

Study selection

Nineteen studies satisfied inclusion and exclusion criteria (Figure 1). Of the nineteen, none of the studies satisfied all 7 criteria required to conclude that fat grafting after BCS is safe (Figure 2).

	Description of interval to fat injection	Time to follow-up from BCS	Time to follow-up from lipofilling	Subgroup analysis	Comparison group	Appropriately matched controls	Powering
Biasio <i>et al.</i>	Green	Red	Green	Green	Green	Red	Red
Biazus <i>et al.</i>	Green	Red	Green	Red	Red	Red	Red
Brenelli <i>et al.</i>	Green	Green	Red	Green	Red	Red	Red
Debald <i>et al.</i>	Green	Green	Red	Red	Red	Red	Red
Gale <i>et al.</i>	Green	Green	Red	Red	Green	Red	Red
Garcia <i>et al.</i>	Green	Red	Red	Red	Red	Red	Red
Kahn <i>et al.</i>	Green	Red	Green	Red	Green	Red	Red
Krastev <i>et al.</i>	Green	Green	Green	Red	Red	Red	Red
Mazur <i>et al.</i>	Red	Red	Green	Red	Red	Red	Red
Mestack <i>et al.</i>	Green	Green	Red	Red	Green	Red	Red
Perez-Cano <i>et al.</i>	Red	Red	Red	Red	Red	Red	Red
Petit, Botteri <i>et al.</i>	Green	Red	Red	Red	Green	Red	Red
Petit, Lohsiriwat <i>et al.</i>	Green	Red	Red	Red	Red	Red	Red
Petit, Rietjens <i>et al.</i>	Green	Red	Green	Green	Red	Red	Red
Reitjens <i>et al.</i>	Green	Red	Red	Red	Red	Red	Red
Silva <i>et al.</i>	Green	Red	Green	Green	Red	Red	Red
Sorrentino <i>et al.</i>	Green	Green	Green	Red	Red	Green	Red
Silva <i>et al.</i>	Green	Red	Red	Red	Red	Red	Red
Stumpf <i>et al.</i>	Green	Red	Red	Green	Green	Red	Red

Figure 2 Graphic representation of required criteria to establish safety of lipofilling following BCS. Criteria to determine safety of lipofilling following BCS included: (I) description of the interval between BCS and lipofilling; (II) time to follow-up from BCS of 6 years; (III) time to follow-up from lipofilling of 3 years; (IV) subgroup analysis focusing on ER, PR, Her-2; (V) presence of any comparison group at all; (VI) comparison group matched controls specifically for ER, PR, and Her-2; (VII) adequate powering. BCS, breast conservation surgery.

Participants

The number of patients who underwent lipofilling following BCS ranged from 7–143 patients (*Table 1*). Krastev *et al.* found that 13 patients were diagnosed with a second primary tumor in the contralateral breast during oncologic follow-up and underwent additional lipofilling following tumor resection. Ipsilateral recurrence between primary resection and lipofilling was intended to be a contraindication to lipofill in groups not investigating the role of “immediate” lipofilling, however, but one patient in the study performed by Brenelli *et al.* experienced a locoregional recurrence and underwent subsequent lipofilling (19).

Study characteristics

Four retrospective case series, six prospective case series, six retrospective case control studies, and three prospective case control studies were included (*Table 1*).

Comparison group

Eleven studies included a comparison group (*Table 2*). Eight of the eleven studies were case control studies and three were retrospective case series in which patients who underwent BCS without lipofilling during the same time period at the same institution were selected as the comparison group without matching for any patient characteristics (*Table 3*). Three studies matched patients for ER receptor status alone (10,11,20), two studies matched patients for both ER and PR (21,22), and one study by Sorrentino *et al.* matched patients for Luminal A subtype, Luminal B subtype, and Triple Negative disease (23).

Sorrentino *et al.* performed a sub-analysis examining fat grafting and locoregional recurrence and distant metastases showed no increase in rate of recurrence during follow-up. However, their predictive model demonstrates that after 80 months, there would be a statistically significant greater recurrence rate in patients with Luminal A cancers that

Table 1 Study design and rates of locoregional recurrence (LRR)

Study	Design	BCS + lipofilling (n)	BCS alone (n)	LRR BCS + lipofilling (%)	LRR BCS alone (%)
Biasio <i>et al.</i>	RCS	37	88	0	n/a
Biazus <i>et al.</i>	PCS	65	0	7.86	n/a
Brenelli <i>et al.</i>	PCS	59 patients (75 cases)	0	5.1*	n/a
Debald <i>et al.</i>	RCS	17	0	0	n/a
Gale <i>et al.</i>	RCC	35	64	5.7	3.1
Garcia <i>et al.</i>	PCS	37	0	0	n/a
Kahn <i>et al.</i>	PCS	32	39	0	0
Krastev <i>et al.</i>	RCC	139	150	0.72	4.7
Mazur <i>et al.</i>	PCC	7	28	3.7**	4.1**
Mestack <i>et al.</i>	RCC	32	45	0	4.4
Perez-Cano <i>et al.</i>	PCS	67	0	0	n/a
Petit, Botteri <i>et al.</i>	RCC	125	250	1.0	4.0
Petit, Lohsiriwat <i>et al.</i>	RCS	143 patients (170 cases)	0	0.8	n/a
Petit, Rietjens <i>et al.</i>	RCC	59	118	0.18	0.3
Rietjens <i>et al.</i>	PCS	77	0	0.01	n/a
Silva <i>et al.</i>	RCS	63	0	3.2	n/a
Silva <i>et al.</i>	PCC	58	124	1.7	2.4
Sorrentino <i>et al.</i>	PCC	54	444	6.4**	5.0**
Stumpf <i>et al.</i>	RCC	27	167	3.7	4.2

*, reported as % recurrence per patient enrolled; **, overall LRR, not stratified for only BCS (includes mastectomy). BCS, breast conservation surgery; RCS, retrospective case series; PCS, prospective case series; RCC, retrospective case control; PCC, prospective case control.

underwent lipofilling compared to the matched control Luminal A cancers that did not undergo lipofilling (23).

There was a statistically significant difference in Her-2 expression between study arms in two studies: Silva *et al.* 2017 included 19.5% Her-2 positive in the lipofilling group *vs.* 28% in the control group ($P=0.022$) (20); Gale *et al.* included 15% Her-2 positive in the lipofilling group *vs.* 7.3% in the control group ($P=0.013$), but 37% of patients in the lipofilling group and 52.4% of patients in the control group had an unknown Her-2 status (11). There was equal representation of triple negative disease, ER, PR, and HER-2 expression in the experimental arms inclusive of both BCS and mastectomy without stratification for BCS alone in the study performed by Krastev *et al.* (24).

Time intervals

Seventeen of the nineteen studies specified the interval between BCS and lipofilling. Five studies evaluated safety after immediate lipofilling, lipofilling performed during the same operative time as the primary resection (Table 2). There were two articles that mandated that patients were cancer free for 12 months after primary cancer surgery as a part of their inclusion criteria, but they did not specify the actual interval between surgery and fat injection (25,26).

The overall average range in time from primary surgery to fat injection ranged from 0–76 months. The average time to follow-up after lipofilling to assess for recurrence ranged from 23 days–60 months.

Eight studies out of nineteen had a three year time-

Table 2 Studies included and criteria to conclude lipofilling is safe

Study	Interval between resection and lipofilling	Time to follow-up after lipofilling	Comparison group	Subgroup analysis of ER/PR/HER-2 in cases of recurrence	Matched for ER/PR/Her2	Adequate powering
Biasio <i>et al.</i>	Immediate	36 months	Institutional database	Meets criteria	**	Not quantified
Biazus <i>et al.</i>	Immediate	40.8 months				Not quantified
Brenelli <i>et al.</i>	76±30.9 months	34.4±15.3 months		Meets criteria		Not quantified
Debald <i>et al.</i>	71.6 months (7–291.3 months)	23 days				Not quantified
Gale <i>et al.</i>	54 months	32 months	Matched controls		ER***	Not quantified
Garcia <i>et al.</i>	Immediate	12 months				Not quantified
Kahn <i>et al.</i>	Immediate	36 months	Institutional database		**	Not quantified
Krastev <i>et al.</i>	51.6 months	60 months	Matched controls	Meets criteria	****	Not quantified
Mazur <i>et al.</i>	Minimum of 12 months	36 months	Matched controls			Not quantified
Mestack <i>et al.</i>	50 months	27 months	Matched controls		ER and PR****	Not quantified
Perez-Cano <i>et al.</i>	Minimum of 12 months	12 months				Not quantified
Petit, Botteri <i>et al.</i>	56 months (8–155 months)	26 months (1–128 months)	Matched controls		ER*****	Not quantified
Petit, Lohsirwat <i>et al.</i>	39.7 months (0–216 months)*	19.2 months				Not quantified
Petit, Rietjens <i>et al.</i>	32% <1 year	38 months lipofilling	Matched controls	Meets criteria	ER and PR****	Not quantified
	22% 1–2 years	42 months control				
	10% 2–3 years					
	36% >3 years					
Rietjens <i>et al.</i>	35.2 months	6 months				Not quantified
Silva <i>et al.</i>	36 months (4–324 months)	31 months		Meets criteria		Not quantified
Silva <i>et al.</i>	48.3 (0–269 months)	40.4 months	Matched controls	Meets criteria	ER***	Not quantified
Sorrentino <i>et al.</i>	24.2% <1 year	51.2 (±35 months)	Matched controls	Meets criteria	Luminal A	Not quantified
	45.1% 1–2 years				Luminal B	
	30.7% >3 years				Triple negative	
Stumpf <i>et al.</i>	Immediate	34 months	Institutional database	Meets criteria	**	Not quantified

*, did not distinguish interval for BCS group, study included both mastectomy and BCS; **, unmatched control, comparison group of BCS performed during the same time period at the same institution without comment on ER/PR/HER-2; ***, statistically significant difference in Her-2+ status between fat grafting and control groups without stratifying for type of surgery (BCS vs. mastectomy), PR and triple negative unmatched but equally represented without stratifying for type of surgery; ****, unmatched but equal representation of ER/PR/Her2 positive and Triple Negative disease in study arms in all surgical groups without stratifying for type of surgery; *****, no comment on HER-2 status or triple negative distribution between groups; *****, unmatched but equal representation of Her-2 and PR in study arms in all surgical groups without stratifying for type of surgery, no comment on representation of triple negative disease. BCS, breast conservation surgery.

Table 3 Matched variables in studies including a comparison group

Reference	Matching criteria
Biasio <i>et al.</i>	Unmatched controls
Gale <i>et al.</i>	Date of primary surgery (within 2 years) Age (within 5 years) Type of surgery (BCS vs. mastectomy) Histology ER status Disease free interval before fat grafting
Kahn <i>et al.</i>	Unmatched controls
Krastev <i>et al.</i>	Age Type of surgery (BCS vs. mastectomy) Tumor invasiveness Disease stage Disease free interval before fat grafting
Mazur <i>et al.</i>	Year of admission to a single institution Age Histology
Mestack <i>et al.</i>	Date of primary surgery Date of fat grafting Histology ER status PR status Adjuvant hormone therapy Disease free interval after primary surgery Disease free interval after fat grafting
Petit, Botteri <i>et al.</i>	Age (within 5 years) Year of surgery (within 2 years) Type of surgery (BCS vs. mastectomy) Histology Tumor size (T1/2/3) ER status

Table 3 (continued)

to-follow-up after lipofilling (22-25,27-30), seven studies satisfied an average time to follow-up after BCS of at least six years (11,19-21,23,24,31). Krastev *et al.* and Sorrentino *et al.* satisfied both the time to follow-up from BCS and from

Table 3 (continued)

Reference	Matching criteria
Petit, Rietjens <i>et al.</i>	Age (within 5 years) Year of surgery (within 2 years) Type of surgery (BCS vs. mastectomy) histology ER status PR status margin status Hormonal therapy Radiotherapy Disease free interval after primary surgery
Silva <i>et al.</i> 2017	Age (within 5 years) Year of surgery (within 3 years) Type of surgery (BCS vs. mastectomy), Histology Lymphatic involvement ER status
Sorrentino <i>et al.</i>	Age Histopathology Stage Luminal A (ER+ PR+ HER2-) Luminal B (ER+ PR+ HER2-) Triple negative
Stumpf <i>et al.</i>	Unmatched controls

BCS, breast conservation surgery.

lipofilling, Krastev *et al.* followed patients for an average of 9 years from BCS and 4.3 years from lipofilling (23,24). Sorrentino *et al.* followed patients for an average of 6.2 years from BCS and 4.2 years from lipofilling (Figure 2). One of the subgroups within the Petit, Rietjens *et al.* study may also satisfy both criteria, as 36% of their study participants underwent lipofilling >36 months after primary cancer resection and the average time to follow-up after lipofilling was 38 months (22).

None of the “immediate” lipofilling studies satisfied our required time to follow-up after primary cancer resection since there was no waiting period between resection and lipofilling. However, all of the immediate lipofilling studies with the exception of Garcia *et al.*, satisfied a requisite 3-year follow-up time following fat grafting (32). Of the other

immediate lipofilling studies, Biasio, Biazus *et al.*, Kahn *et al.*, and Stumpf *et al.* had a time to follow-up from the BCS and immediate lipofilling of 36, 40, 36 and 34 months respectively (27-29,33).

Sub-group analysis for receptor status

Eight studies reported the ER/PR/Her-2 status of cases of locoregional recurrence as a part of their subgroup analysis (Figure 2). Only one looked at Her-2 enriched and triple negative disease (23). Sorrentino *et al.* did not find a statistically significant difference in LRR upon subgroup analysis for Luminal A, Luminal B, Her-2 enriched, or Triple Negative disease in lipofilling compared to control groups. However, their logistic regression model found a statistically significant difference in locoregional recurrence after 80 months for Luminal-A subtype. This analysis was not restricted to BCS and included patients undergoing mastectomy.

Recurrence

Petit, Rietjens *et al.* demonstrated a significant difference in the locoregional recurrence rates between patients undergoing lipofilling after BCS compared to BCS alone, 0.18% and 0.03% respectively (Table 1). Five studies reported a locoregional recurrence rate of 0% in the fat grafting group. Krastev *et al.* and Sorrentino *et al.* found that there was a higher rate of locoregional recurrence in the control group than the fat grafting group after BCS (Table 1), but that the difference was not significant. Krastev *et al.* found a statically significant difference in overall mortality in the control group compared lipofilling group in all forms of surgery (both mastectomy and BCS) of 11.0% in the control group compared to 2.6% in the lipofilling group ($P < 0.001$). This difference persisted when the analysis was restricted to breast cancer-specific mortality (24).

Statement of oncological safety

Fifteen papers determined that further investigation is required to determine if there is an association between lipofilling after BCS and recurrence. Five articles stated that it is unclear whether or not lipofilling is safe. There were seven studies that simultaneously declared that there was a need for further investigation but endorsed that lipofilling is “safe” (20,21,25,26,30,31,33). Four utilized ambiguous verbiage such as “seems to be safe,” or “interpret with

other similar case-controlled studies” (10,11,27,28). Petit, Rietjens and Botteri concluded that there is an increased risk in certain groups and that lipofilling may be unsafe for those patients (22).

Statistical power

None of the studies quantified the statistical power of their analyses.

Risk factors for recurrence

Biazus, Stumpf, Melo *et al.* performed a subgroup analysis that demonstrated that the number of metastatic axillary lymph nodes was associated with increased recurrence after lipofilling (28). Petit, Botteri, Lohsiriwat *et al.* found a higher risk of recurrence in patients with intraepithelial neoplasia and not invasive disease (10). Petit, Rietjens, and Botteri found that Ki-67 expression, age < 50 , and high-grade neoplasia were associated with increased rates of recurrence (22). Silva-Vergara, Fontdevila *et al.* found that there was an increased risk of recurrence if lipofilling was performed within 3 months of primary resection (20). Krastev *et al.* found no significant difference in local recurrence rates based on receptor subtype or if the injection interval was < 5 years from primary resection to lipofilling (24).

Sorrentino *et al.* did not find that there was a statistically significant increase in LRR based on tumor subtype during their time to follow-up but their logistic regression model found a statistically significant difference in locoregional recurrence after 80 months for patients with Luminal A type cancer.

Discussion

The importance of this study cannot be understated. Lipofilling in the setting of breast conservation is presently being done and the data presented here shows, at best, that the oncologic safety supporting this technique in this population of patients is unclear. Surgeons and their patients performing this type of reconstruction need to know the potential unclear implications of injecting stem cells into a breast defect that has had a history of cancer present. Several studies have attempted to address the safety of lipofilling, with some confusingly concluding that lipofilling is safe yet still proceeding to recommend for future studies to investigate for safety (20,21,23,25,26,29,30). Our criteria

for safety was adopted from past studies that addressed oncologic safety based on interventions performed. With regards to our first criteria, seventeen of the nineteen studies specified the average time interval between resection and lipofilling. Average values reflect a range of time intervals, raising the possibility that some study participants had adequate time (>6 years) to follow-up from primary surgery while others did not. The wide ranges in injection intervals between studies demonstrates a lack of consensus for a “safe” time of injection. It can be argued that the time to injection may affect the response of local cells to the stem cell effect of fat being injected. Silva-Vergara *et al.* demonstrated that there was an increased risk of recurrence if lipofilling occurred within three months after partial mastectomy (30). On the other hand, Krastev *et al.* found that there was not an increased risk of recurrence when injection intervals were <5 years (24) and Sorrentino *et al.* found early fat grafting was not associated statistically significant increased rates of recurrence despite finding that there was a higher proportion of early fat grafting among recurrent patients (23). Brenelli *et al.* reported a locoregional recurrence risk of 5.1% and only included 3 patients of the 59 that underwent lipofilling following BCS in their locoregional recurrence calculation rather than the 4 that experienced a recurrence since one patient actually had a histologically confirmed tumor recurrence in the interval prior to lipofilling (24).

Immediately injecting fat into a partial mastectomy cavity without proven negative margins could be dangerous if a positive margin would receive stem cells from injected fat. There have been retrospective studies that have injected fat into partial mastectomy defects at the same time of oncologic resection which is not recommended by the authors without clear future prospective randomized data and patient-informed consent proving safety (28,29,32,33). Krastev *et al.* and Sorrentino *et al.* were the only groups that employed an experimental design with an adequate time to follow-up from BCS and from lipofilling, but their methodology and results were still imperfect and plagued with design flaws that shall be discussed (23,24).

Locoregional recurrence was studied in all included articles, but a majority of studies underpowered their comparison groups, especially since the number of subjects became too few if breast cancers were separated into their molecular subtypes (based on the ER, PR and Her2 status). Of the 11 studies that had a comparison group, only 3 studies matched patients based on both ER and PR status (21,22). Krastev *et al.* did attempt to investigate the role

of hormone receptor status and triple negative disease and found no significant difference in locoregional recurrence between lipofilling and control groups (24). However, this study mixed mastectomy patients with breast conservation patients when looking at molecular subtypes between the lipofilling and control groups. Sorrentino *et al.* matched study participants by breast cancer subtype: Luminal A, Luminal B, Her-2 enriched, and Triple Negative disease. However, they did not match patients for the type of surgery performed. In fact, mastectomy accounted for 76.8% of lipofilling arm whereas only 25.6% of the controls underwent mastectomy and the remainder underwent BCS. Given this mixture of mastectomy and BCS patient sampling, even though they did perform a sub-group analysis, one cannot say with statistical certainty that receptor status does not impact recurrence after BCS when cancerous cells may still persist in the tumor cavity.

Without adequate powering for the different molecular subtype presentations between the lipofilling and control groups specifically undergoing BCS, a Type II statistical error is possible showing no statistical difference between the lipofilling and no lipofilling arms when in fact there may be, as chance plays a large role in the conclusion. To date, there is no study with confirmed, adequate powering looking at lipofilling after breast conservation when separating breast cancers into their molecular subtypes.

Although Krastev *et al.* did not find a difference in locoregional recurrence in the cases of lipofilling after BCS, the overall mortality for patients undergoing both BCS and mastectomy without lipofilling was 11.0% while the overall mortality in lipofilling group was 2.6%. This recurrence rate is high considering they did not enroll any patients with stage IV disease, and the majority of their patients had either stage 0 or early stage disease. The 5-year breast cancer specific survival for stage 1 disease has been noted to be between 98–100% according to the literature (34). Thus, it is highly unlikely that fat grafting lead to a more favorable prognosis and further investigation into pre-selection biases or confounding variables is critical. In contradiction, Petit *et al.* found that lipofilling was associated with an increase of local recurrence when intraepithelial neoplasia (e.g., DCIS) was present as opposed to invasive disease (10).

There have been transitional studies utilizing animal models to explore the safety of lipofilling which also have had mixed conclusions (35,36). Tsuji *et al.* and Silva *et al.* both utilized “immortal” cell lines injected into rats to simulate a tumor bed prior to fat transfer. They found that autologous fat transfer did not encourage tumor

growth, and may actually suppress tumor cell proliferation. However, clonal cell lines do not reproduce the tumor heterogeneity that is present *in vivo*, and surgery was not performed in either study. In fact, Silva *et al.* suggested that mechanical pressure of the adipose cells injected adjacent to the tumors may have impaired tumor cell proliferation.

In vitro models have associated fat grafting with increased tumor growth. Almarzougi *et al.* examined the role of lipoaspirates and resected abdominal fat on tumor cells and found that adipose increases the proliferation of MCF-7 (ER/PR positive, luminal type) cells, contrary to the findings in the Tsuji *et al.* animal model (37). Moreover, Massa *et al.* demonstrated that adipose fat grafts could accelerate development a subclinical tumor or support locoregional recurrence of a previous tumor (38).

Historically, past surgical interventions were studied using strict experimental design requirements (17,39,40) that are absent from the studies so far that have investigated lipofilling. The authors submit that the same rigor of experimental design that would include appropriate molecular subtype analysis with adequate powering, an established follow-up period, and an ethical, informed consent process given prospectively to the patient should be required before declaring lipofilling as safe in breast conservation. Fat grafting may be useful in certain clinical scenarios, but if it was found to be harmful in partial mastectomy defect corrections, it is possible that there could be subsequent reactionary regulations limiting the ability to fat graft in all facets of reconstruction.

The data supporting the “safety” of lipofilling in breast conservation so far are incomplete; thus, one cannot state that lipofilling in breast conservation is safe. At best, these results show that the safety of lipofilling in breast conservation is unclear with contradictory data present in the literature. Surgeons with interest in fat grafting and lipofilling need to be cautious and inform their patients requesting these interventions of these uncertainties regarding loco-regional recurrences. Central to our Hippocratic Oath is to do no harm and with this, regardless of how nicely lipofilling corrects poor aesthetics after partial mastectomy, form can never trump oncologic safety. In a perfect world, there is a need for prospective studies with adequately powered cohort control groups looking at molecular subtypes and initiating lipofilling treatments at appropriate time intervals after margins are clear with appropriate post-operative follow-up in order to prioritize patient safety.

Conclusions

Present studies looking at lipofilling in the setting of breast conservation have several design limitations and do not prove oncologic safety. A well designed, ethical, appropriately powered, prospective study with comparison groups looking at molecular subtypes needs to be performed to ensure patient safety before surgeons consider treating breast conservation defects with lipofilling.

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Footnote

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