Journal of Plastic, Reconstructive & Aesthetic Surgery (2018) 71, 1392–1409

JPRAS
An International Journal of Surgical Reconstruction
www.JPRASurg.com

Review

Efficacy of autologous fat transfer for the correction of contour deformities in the breast: A systematic review and meta-analysis

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Received 27 September 2017; accepted 27 May 2018

KEYWORDS
Autologous fat transfer;
Breast reconstruction;
Mastectomy;
Lumpectomy;
Congenital breast deformity;
Breast cancer

SUMMARY *Background:* Autologous fat transfer (AFT), also known as fat grafting or lipofilling, has already become a part of clinical practice for treating contour deformities of the breast, even though evidence regarding its efficacy is still lacking. This is the first meta-analysis on this subject, aimed to facilitate intuitive interpretation of the available data by clinicians, guideline committees and policy makers.
Methods: A literature search was performed on 1 September 2017 in PubMed, EMBASE and the Cochrane Library to identify all relevant studies. A rigorous data extraction and standardisation process allowed pooling of clinical outcome data into a meta-analysis.
Results: Eighty-nine studies consisting of 5350 unique patients were included. The mean follow-up was 1.9 years. Meta-analysis revealed a very high overall patient and surgeon satisfaction rate of 94.3% and 95.7%, respectively, which was also confirmed by high satisfaction scores and Breast-Q scores. Overall, only 1.5 sessions were needed to achieve the desired result. Though evidence on the long-term volume retention is lacking, based on the current data it was calculated to be 52.4% at one year. Only 5.0% of procedures resulted in clinical complications and 8.6% of breasts required biopsy due to abnormal clinical or radiological findings.

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https://doi.org/10.1016/j.bjps.2018.05.021

Conclusions: AFT seems to be an effective procedure in breast reconstruction, reflected by the high patient and surgeon satisfaction and low incidence of clinical and radiological complications. Future research should focus on evaluating the technical and patient factors influencing the rate of fat resorption as well as its oncological safety.

Contents

Introduction 1393
Research objectives 1394
Patients and methods 1394
Search strategy 1394
Data collection 1394
Statistical analysis 1394
Results 1394
Study selection 1394
Study characteristics 1395
Population 1395
Intervention 1395
Control group 1395
Outcome measures 1395
Meta-analysis 1395
Patient and surgeon satisfaction – categorical data 1395
Patient and surgeon satisfaction – continuous data 1395
Quality of life 1398
Volume measurements 1398
Number of AFT sessions 1398
Complications 1398
Abnormal findings after AFT requiring biopsy 1398
Discussion 1398
Synthesis of results 1398
Clinical relevance 1402
Limitations 1405
Future recommendations 1406
Conclusion 1406
Financial disclosure statement 1406
Conflict of interests 1406
Supplementary materials 1406
References 1407

Introduction

More than two decades have passed since pioneers such as Coleman helped transform autologous fat transfer (AFT), also known as fat grafting or lipofilling, into a relatively simple and effective procedure for treating soft-tissue deficiencies. Its application in the breast has been of particular interest to plastic surgeons, as the prospect of achieving an autologous reconstruction by a minimally-invasive procedure offers numerous advantages to conventional techniques. AFT has been shown to excel primarily in the restoration of *contour deformities* in the breast, which can essentially involve any primary breast defects of congenital (e.g. Poland syndrome) or acquired origin (e.g. lumpectomy), as well as residual local volume deficiencies after breast reconstruction.

The high demand for AFT among patients and plastic surgeons alike has resulted in a widespread application over the years as reflected by the large number of published studies. Unfortunately, despite the predominance of encouraging findings in the literature, the evidence is still severely limited due to the lack of reliable data from randomised controlled trials (RCTs). Currently, our understanding of AFT is based on the individual findings of primarily case-series and cohort studies differing in indications, surgical technique and outcome measures, which has resulted in a body of knowledge that is highly fragmented and difficult to interpret. In addition, inconsistent findings related to the rate of fat resorption have engendered divergent and even polarised views among many plastic surgeons on whether AFT is a reliable solution for correcting contour deformities of the breast. This has inspired many systematic reviews in the past that reached the unanimous conclusion that results of AFT are encouraging but unconvincing due to the low level-of-evidence.[1-11] Unfortunately, as most of these papers relied on summarising results from individual studies, they have not been able to provide more definite answers on key questions, such as:

1. How satisfied are patients and surgeons with AFT?
2. What is the expected volume retention of grafted fat in the long-term?
3. What are the risks with AFT?

Without the prospect of the acquisition of high-quality data from randomised trials in the near future, there is an urgent need for a thorough examination of the published literature on AFT in the form of a meta-analysis. Ultimately, it would also facilitate a more straightforward interpretation by clinicians, guideline committees and policy-makers and help reach consensus regarding efficacy of AFT in correcting contour deformities of the breast.

Research objectives

To identify, evaluate and synthesise the evidence examining the overall *efficacy* of AFT for the correction of contour deformities of the breast. Efficacy is defined as the performance of AFT with respect to relevant outcome measures such as the rate of patient and surgeon satisfaction, quality of life, volume retention, the need to repeat the procedure as well as the associated clinical and radiological complications.

Patients and methods

Search strategy

This systematic review adhered to the standards of the *Cochrane Handbook for Systematic Reviews of Interventions*[12] and was written in the format provided by the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)* statement[13] (*Online supplement 1 - eTable 1*). A comprehensive, reproducible electronic search was conducted in *PubMed, EMBASE* and the *Cochrane Library* to identify all published studies with human subjects receiving the intervention AFT for volume correction of contour deformities of the breast (*Online supplement 2 - e*Table 2 *and 3*). The search was performed on 1 September 2017. Eligibility assessment was performed in a standardised manner. The retrieved hits were screened and reviewed by two independent reviewers (T.K and G.A.) based on the title and abstract using predefined inclusion and exclusion criteria. Disagreements were solved through discussion until consensus was reached. An additional assessment was performed based on the full-text versions of all selected papers and those with insufficient information in the title and abstract. Finally, if studies from the same author or institution conducted in the same time period and reporting the same outcomes were suspected for overlap of more than 25% of the sample size, only the largest or most relevant study was included. All references were stored in *Endnote Reference Management Tool, (version X7.3.1, Thomson Reuters)*.

Data collection

To conduct a meta-analysis, a thorough extraction of all relevant data was performed (*Online supplement 2 - eTable 4*). In some occasions, authors were contacted to send additional data. In cases when key data were reported only in graphs or figures, the data were extracted using the WebPlotDigitizer software.[14] Whenever necessary, units were transformed to a standard format to ensure comparability and allow pooling of data. Continuous variables reported in the form of median $\pm$ range were transformed into mean $\pm$ standard deviations (SD) using the standard estimating equations used for meta-analyses.[15] To standardise scoring systems or scales consisting of different ranges of values, these were arithmetically converted into a 0–10 point scale, resembling a standard Visual Analogue Scale (VAS). Similarly, categorical outcomes reported as Likert scales (e.g. degree of satisfaction), were dichotomised to allow analysing as proportions. In addition, this also acted as a means of standardisation of scores from different scales by taking the lowest common denominator.

Statistical analysis

Meta-analyses were performed using the *RStudio software (Version 1.0.136 - © 2009-2016 RStudio, Inc., package 'metafor')*.[16,17] Summary measures were pooled in a standard random-effects model and presented as forest plots. All categorical outcomes were pooled and analysed as proportions, before converting them into percentages to allow more intuitive interpretation. Continuous variables were analysed without additional transformations. To reduce heterogeneity between studies, subgroup meta-analyses were performed for most outcomes by segregating studies based on known or presumed confounders (e.g. indications).

Results

Study selection

The electronic search yielded a total of 776 unique hits (Figure 1). Screening of the title and abstract lead to the inclusion of 160 records for further evaluation. A total of 85 studies were selected through further screening of the full-text. Exclusion criteria included unavailability of the full-text, secondary sources (reviews, commentaries), the use of AFT for breast augmentation, the use of supplements (such as platelet rich plasma, PRP or stromal-vascular fraction, SVF) and pre-expansion devices (such as BRAVA). In addition, studies investigating the efficacy of AFT for total breast reconstruction as opposed to contour deformities, were also excluded. Case reports (defined as reports of five cases or less) were also not considered for inclusion. Seven articles that were only available in French were translated to aid the data extraction. Screening of the citations, references and related articles of the 85 selected records yielded four additional hits, leading to the definite selection of 89 studies.

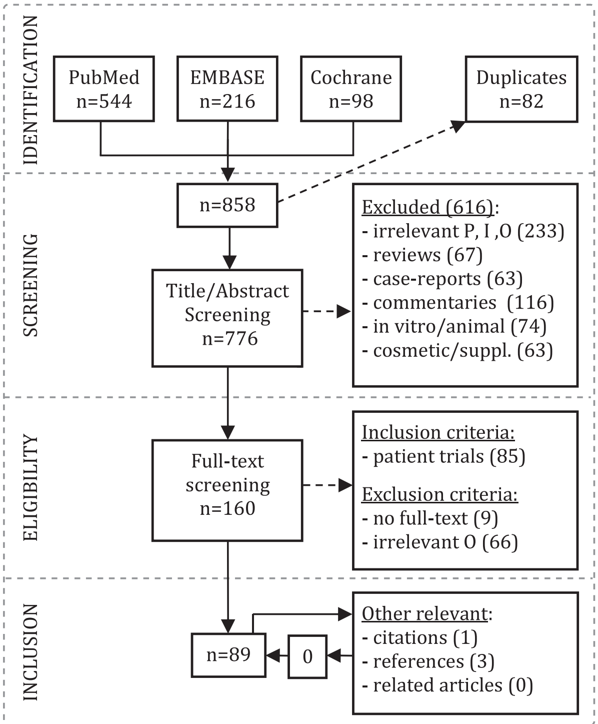

Figure 1 Flowchart of the search strategy. Legend: n = number of studies, P = population, I = intervention, O = outcome, suppl. = supplements (e.g. PRP, stromal-vascular fraction enrichment).

Study characteristics

Eighty-nine clinical studies were identified for inclusion[18-106] (Table 1). These studies consisted of 60 case-series, 27 cohort studies and two RCTs. Of these, the vast majority of the studies were retrospective ($n = 71$) and were conducted between 1983 and 2016. Of the 89 included studies (7434 patients), 23 were suspected of the risk of significant overlap in patient populations, resulting in 66 studies comprising of 5350 unique patients. Although most of the trials were retrospective analyses, the vast majority (79.8%) of the trials specified to have included only consecutive patients treated with AFT, which reduces the risk of selection bias (*Online supplement 3 - eTable 5*).

Population

An overview of the patient populations in the included studies is presented in Figure 2. Each individual study would typically evaluate the effect of AFT treatment in a specific patient population or indication. Most commonly, it would involve a series of oncological (breast cancer) patients with disfiguring contour deformity after mastectomy (MST), breast conserving therapy (BCT) or both (*any oncological deformity*). Less frequently, studies would evaluate the efficacy of AFT for a heterogeneous group consisting of both oncological and congenital patients (*any deformity*). Only a few studies, with a combined total of less than 100 patients investigated the role of AFT in the correction of congenital deformities. The overall age of patients receiving AFT to the breast was 46.7 years (95% CI 44.4–48.9), but this was significantly lower in the subgroup of congenital patients - 21.8 years (95% CI 19.0–24.5). The mean body mass index (BMI) of all included patients was 25.3 kg/m^2 (95% CI 24.6-26.0).

Intervention

Of the included trials, consisting of 5350 patients undergoing 8088 procedures, the vast majority of trials adhered to the principles of AFT as described by Coleman,[107] though some variations have been described for each step of AFT. For more information, see *Online supplement 4*.

Control group

Only 14 studies provided relevant control groups to allow comparison of the results of AFT treatment with a control treatment. In six studies, one of the treatment arms involved the use of supplements in addition to AFT (excluded from the analysis), treating the remaining AFT arms as case-series. As most of the studies did not have a control group, no direct comparison between AFT and controls could be made in the meta-analyses.

Outcome measures

As almost every study reported the number and type of adverse events observed after AFT, the complication rate was the most common outcome in the literature (57 studies). It was followed by the patient satisfaction obtained from questionnaires (27 studies) and the surgeon satisfaction based on pre- and post-operative photographs (26 studies). Twelve studies reported the biopsy rates in treated breasts due to suspicious clinical (e.g. palpable mass) or radiological findings (e.g. fat necrosis) resulting from the procedure. Furthermore, eight studies reported high-precision, serial volume measurements to determine the volume retention of grafted fat over time. Another one of the less commonly reported outcomes is the satisfaction with the outcome/breasts and the breast-related quality of life, measured by the Breast-Q (seven studies). Lastly, four studies assessed the role of AFT in post-mastectomy pain syndrome, whilst another three evaluated its cost-efficiency, but the data were insufficient to allow pooling into meta-analyses. More detailed descriptive statistics on the outcome measures can be found in *Online supplement 5*.

Meta-analysis

Patient and surgeon satisfaction - categorical data

Meta-analysis of categorical data revealed an overall patient satisfaction of 94.3% (95% CI 89.9–96.9), after a mean follow-up of 1.9 years (Figure 3). It varied between 93–98% among subgroups, but the differences were not significant. Similarly, a very high percentage of the plastic surgeons were satisfied with the result – 95.7% (95% CI 90.5–98.1), after a mean follow-up of 1.8 years.

Patient and surgeon satisfaction - continuous data

Meta-analysis of reported mean patient satisfaction scores resulted in an average score of 7.4 (95% CI 6.8–8.1), without significant differences between MST and BCT subgroups

Table 1 Baseline table of all studies [19#x2013;105].

	Study characteristics			Demographics				Intervention			Reported outcomes										
											Patient satisfaction		Surgeon satisfactrion								
	Study	Study design	Overlap (with study ...)	n. subjects	Indication	age	BMI	Treatment group	n. AFT sessions	Length of follow-up	Likert	VAS	Likert	VAS	Volume retention	Breast-Q	Pain reduction	Cost-efficiency	Radiological abnorm.[1]	Complications	**Level of evidence[109]**
1	Amar (2008)[18]	CS	no	15	BCT	53	-	AFT	1.0	0.8		✓		✓		✓			✓	✓	4
2	Beck (2012)[19]	CS	no	10	BCT	49	-	AFT	1.0	3.0	✓	✓				✓			✓	✓	4
3	Bennett (2017)[20]	CH	no	165	MST	48	27	AFT	-	1.0		✓			✓						2b
				1883	MST	50	27	C	-	1.0		✓			✓						
4	Betal (2011)[21]	CS	6	28	ONC	-	-	AFT	-	-										✓	4
5	Biazus (2015)[22]	CS	no	20	BCT	55	27	AFT	1.0	-		✓		✓					✓	✓	4
6	Bonomi (2013)[23]	CS	4	31	MST	55	-	AFT	1.3	1.8	✓									✓	4
7	Brault (2017)[24]	CH	no	15	cong.	21	-	AFT	1.5	0.5		✓			✓					✓	2b
				22	cong.	25	-	C	-	0.5		✓			✓						
8	Brenelli (2010)[26]	CS	9,65,71	158	ONC	-	-	AFT	1.2	1.5										✓	4
9	Brenelli (2014)[25]	CS	8,65,71	59	BCT	50	-	AFT	1.3	2.9									✓	✓	4
10	Brown (2017)[27]	CS	no	88	ONC	47	25	AFT	1.8	1.3		✓			✓					✓	4
11	Brzezienski (2017)[28]	CH	no	13	any	-	-	AFT	-	-								✓			2b
				24	any	-	-	AFT	-	-								✓			
12	Caviggioli (2016)[29]	CH	54	131	ONC	-	-	AFT	1.0	1.0							✓				2b
				78	ONC	-	-	C	-	1.0							✓				
13	Chirappapha (2015)[30]	CS	65	137	ONC	65	-	AFT	1.6	1.3									✓	✓	4
14	Choi (2013)[31]	CS	no	90	ONC	50	-	AFT	1.0	0.4						✓					4
15	Cigna (2012)[32]	CS	70	20	MST	65	-	AFT	1.0	1.0		✓		✓						✓	4
16	Cogliandro (2017)[33]	CH	no	46	MST	41	-	AFT	2.2	2.5					✓						2b
				24	MST	41	-	C	-	2.5					✓						
17	Cohen (2017)[34]	CH	14	248	MST	53	25	AFT	1.23	-										✓	2b
				581	MST	48	26	C	-	-										✓	
18	Coleman (2007)[35]	CS	no	17*	any	38	-	AFT	1.2	-	✓								✓		4
19	Constantini (2013)[36]	CS	73,74	24	ONC	51	-	AFT	2.2	1.0									✓	✓	4
20	Cuomo (2014)[37]	CH	no	22	MST	45	-	AFT	1.0	0.3							✓			✓	2b
				18	MST	45	-	C	-	0.3							✓				
21	De Blacam (2011)[38]	CS	no	49	MST	111	-	AFT	1.6	1.4				✓						✓	4
22	Debald (2017)[39]	CS	no	40	ONC	-	-	AFT	1.7	0.8								✓		✓	4
23	Delay (2008)[41]	CS	24,34,65	42	BCT	51	22	AFT	1.3	1.7	✓		✓							✓	4
24	Delay (2009)[40]	CS	23,25,34, 65,66,81	303	any	-	-	AFT	2.9	1.0			✓							✓	4
25	Delay (2013)[42]	CS	24	31	cong.	23	22	AFT	1.5	6.5	✓		✓						✓	✓	4
26	Derder (2014)[43]	CS	no	10	cong.	18	-	AFT	1.7	5.7	✓								✓	✓	4
27	Doren (2012)[44]	CS	64	278	MST	51	27	AFT	1.4	2.3	✓									✓	4
28	Gabriel (2016)[45]	CH	no	98	ONC	52	27	AFT	1.4	0.5								✓		✓	2b
				96	ONC	50	27	AFT	1.7	0.5								✓		✓	
29	Gentile (2012)[47]	CS	30	10	any	-	-	AFT	1.0	1.0				✓						✓	4
30	Gentile (2013)[46]	CS	29	50	any	-	-	AFT	1.0	1.0	✓									✓	4
31	Gentile (2015)[48]	CS	no	10	any	-	-	AFT	2.0	1.0	✓									✓	4
32	Hammond (2015)[49]	CS	no	22	MST	47	-	AFT	1.4	0.9										✓	4
33	Helme (2014)[50]	CS	no	29	BCT	-	-	AFT	1.7	3.1										✓	4
34	Hitier (2014)[51]	CS	23,24,65	150	ONC	51	22	AFT	1.1	1.9	✓		✓							✓	4
35	Ho Quoc (2013)[52]	CS	37	19	cong.	20	28	AFT	1.6	1.0	✓		✓							✓	4
36	Ho Quoc (2013) (2)[53]	CS	36,38	1000	any	39	-	AFT	-	4.5										✓	4
37	Ho Quoc (2015)[54]	CS	36	27	MST	52	25	AFT	1.0	0.3						✓					4
38	Hogan (2015)[55]	CS	no	13	cong.	25	26	AFT	2	-										✓	4
39	Ihrai (2013)[56]	CS	no	64	ONC	-	-	AFT	1.6	3.9									✓	✓	4
40	Irani (2012)[57]	CS	no	25	MST	52	-	AFT	1.1	2.0	✓	✓	✓	✓						✓	4
41	Jones (2015)[58]	CS	no	100	ONC	-	-	AFT	1.4	-										✓	4

(*continued on next page*)

Table 1 (*continued*)

42	Juhl (2016)[59]	RCT	no	8	MST	60	26	AFT	1.1	0.5							✓		✓	2b
				7	MST	59	24	C	-	-							✓			
43	Kanchwala (2009)[60]	CS	no	110	MST	-	-	AFT	1.5	-	✓		✓						✓	4
44	Kaoutzanis (2014)[61]	CS	45	108	MST	48	-	AFT	-	1.3									✓	4
45	Kaoutzanis (2016)[62]	CS	44	108	MST	48	-	AFT	1.3	1.7								✓	✓	4
46	Khan (2017)[63]	CH	no	35	BCT	49	-	AFT	1.3	3.0	✓									2b
				39	BCT	54	-	C	1.3	3.0	✓									
47	Kim (2014)[64]	CS	no	102	MST	46	-	AFT	1.3	2.4						✓		✓	✓	4
48	Komorowska (2017)[65]	CH	no	26	MST	49	25	AFT	1.3	2.6									✓	2b
				59	MST	51	26	AFT	1.4	2.6									✓	
49	Kristenstein (2015)[66]	CS	no	176	any	53	-	AFT	2.0	-									✓	4
50	Lakhiani (2014)[67]	CH	no	3	MST	52	26	AFT	1.3	0.5				✓					✓	2b
				16	MST	52	27	AFT	1.9	0.5				✓					✓	
				4	MST	52	25	C	-	0.5				✓						
51	Laporta (2015)[68]	CH	no	20	MST	45	23	AFT	1.1	1.9		✓		✓					✓	2b
				20	MST	45	29	C	-	2.1		✓		✓						
52	Le Brun (2013)[69]	CS	no	42	MST	-	-	AFT	1.6	2.0	✓								✓	4
53	Losken (2011)[70]	CS	67	107	MST	52	-	AFT	1.3	0.7	✓								✓	4
54	Maione (2014)[71]	CH	12	59	BCT	51	30	AFT	1.0	0.8							✓		✓	2b
				37	BCT	54	30	C	-	0.9							✓			
55	Mestak (2014)[72]	RCT	no	15	BCT	38	-	AFT	1.0	1.8		✓		✓	✓			✓	✓	2b
				15	BCT	38	-	AFT	1.0	1.8		✓		✓	✓			✓	✓	
56	Missana (2007)[73]	CS	no	69	ONC	51	-	AFT	1.2	1.0			✓					✓	✓	4
57	Molto Garcia (2014)[74]	CS	no	37	BCT	55	-	AFT	1.0	1.0	✓							✓	✓	4
58	Momoh (2012)[75]	CS	no	33	MST	42	-	AFT	1.3	0.5			✓						✓	4
59	Murphy (2011)[76]	CS	no	100	any	-	-	AFT	1.6	-									✓	4
60	Murthy (2016)[77]	CS	no	33	MST	-	-	AFT	1.5	-	✓								✓	4
61	Nelissen (2015)[78]	CS	no	23	MST	52	23	AFT	1.0	0.4						✓				4
62	Niddam (2016)[79]	CS	no	20	MST	55	26	AFT	1.1	1.1									✓	4
63	Panettierre (2009)[80]	CH	no	20	MST	48	-	AFT	3.4	1.5				✓					✓	2b
				41	MST	49	-	C	-	1.5				✓						
64	Parikh (2012)[81]	CS	27	286	MST	-	-	AFT	-	1.0								✓	✓	4
65	Petit (2011)[82]	CS	8-10, 23-24,66, 71,75-76,81	513	ONC	52	-	AFT	1.3	1.6								✓	✓	4
66	Pierrefeu (2006)[83]	CS	24,65,81	30	MST	51	-	AFT	1.3	1.0								✓		4
67	Pinell (2015)[84]	CS	53	46	MST	50	-	AFT	1.2	4.2								✓		4
68	Pinsolle (2008)[85]	CS	no	8	cong.	25	-	AFT	2.1	-									✓	4
69	Qureshi (2017)[86]	CH	no	9	MST	44	24	AFT	-	1.3		✓			✓					2b
				6	MST	44	24	C	-	1.3		✓			✓					
70	Ribuffo (2013)[87]	CH	15	16	MST	50	-	AFT	1.4	1.5	✓								✓	2b
				16	MST	49	-	C	-	1.5	✓								✓	
71	Rietjens (2011)[88]	CS	8,5,65	158	MST	48	-	AFT	1.2	1.5								✓	✓	4
72	Russe (2014)[89]	CS	no	155	any	46	-	AFT	1.5	-									✓	4
73	Salgarello (2011)[91]	CS	19	25	any	47	-	AFT	1.9	0.8			✓	✓				✓	✓	4
74	Salgarello (2012)[90]	CS	19	16	MST	41	-	AFT	2.4	1.2		✓	✓	✓	✓				✓	4
75	Sarfati (2011)[93]	CS	65,76	28	MST	45	-	AFT	1.8	1.4			✓	✓					✓	4
76	Sarfati (2013)[92]	CS	65,75	68	MST	46	-	AFT	2.3	1.9			✓	✓					✓	4
77	Schultz (2012)[94]	CS	no	44	MST	53	24	AFT	1.5	0.5		✓							✓	4
78	Serra-Renom (2010)[95]	CS	no	65	MST	48	-	AFT	2.1	1.0		✓		✓					✓	4
79	Seth (2012)[96]	CS	no	69	MST	49	25	AFT	1.1	2.1									✓	4
80	Silva (2016)[97]	CS	no	195	ONC	52	24	AFT	1.6	2.6									✓	4
81	Sinna (2010)[98]	CS	24,65,66	200	MST	49	23	AFT	1.2	1.2	✓		✓						✓	4
82	Small (2014)[99]	CH	no	27	MST	49	-	AFT	1.0	0.4						✓				2b
				46	MST	49	-	AFT	1.0	0.4						✓				
83	Sommeling (2017)[100]	CS	no	15	MST	46	-	AFT	3.2	2.8						✓			✓	4
84	Spear (2005)[101]	CS	no	37	MST	-	-	AFT	1.1	1.3			✓						✓	4
85	Thekkinkattil (2015)[102]	CS	no	10	MST	56	-	AFT	3.0	3.3		✓							✓	4
86	Tissiani (2016)[103]	CS	no	8	MST	50	26	AFT	1.0	1.4						✓			✓	4
87	Turnhout (2017)[104]	CS	no	109	BCT	55	26	AFT	2.0	2.2				✓					✓	4
88	Veber (2012)[105]	CS	65,81	20	MST	45	22	AFT	1.2	1.0	✓		✓						✓	4
89	Weichmann (2013)[106]	CS	no	61	MST	49	25	AFT	1.1	1.5									✓	4

Legend: RCT = randomised controlled trial, CH = cohort, CS = case-series, '-'. = data not available/reported, mix = mixed population, ONC = oncological population, MST = mastectomy patients, BCT = breast conserving therapy population, cong. = patients with congenital breast deformities, AFT = autologous fat transfer, C = control treatment group.*Only 4/17 patients met the inclusion criteria and were included in the meta-analysis.

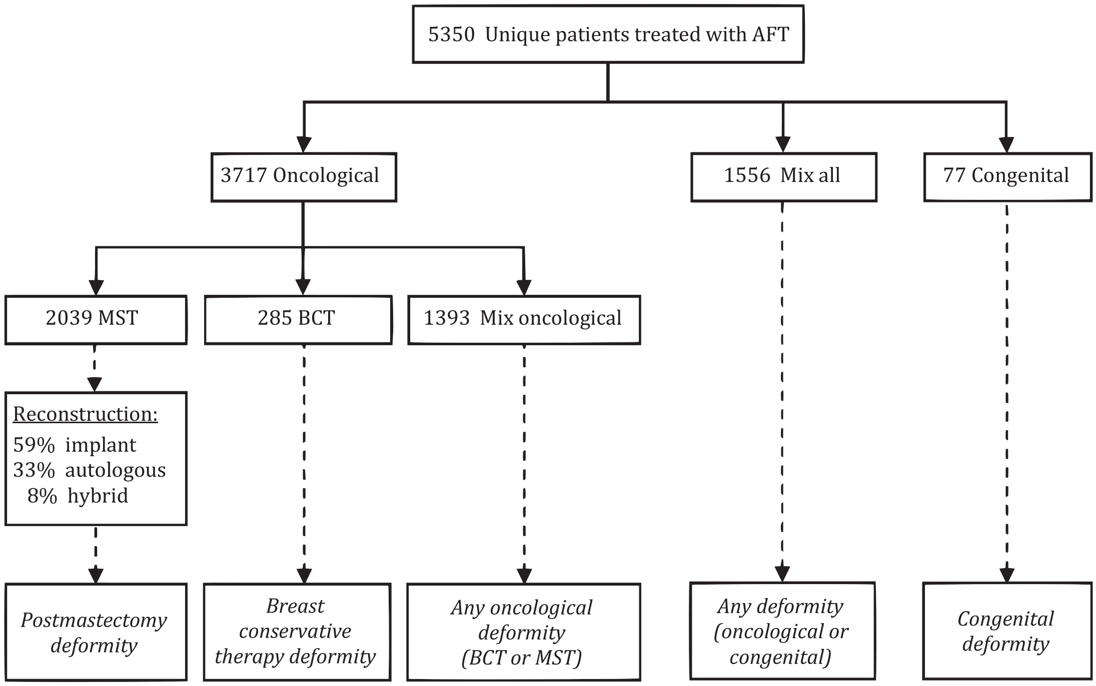

Figure 2 Flowchart depicting the patient population in the included (non-overlapping) studies. Legend: BCT = breast conserving treatment, MST = mastectomy, implant = implant-based breast reconstruction, autologous = breast reconstruction using pedicled/free flap transfer, hybrid = breast reconstruction with a flap (e.g. latissimus dorsi) and implant.

($p = 0.802$), see Figure 4. Only the congenital and oncological subgroups, represented by a single study each, measured significantly lower scores ($p < 0.001$). The surgeons confirmed results reported by patients as they scored their satisfaction as 7.5 (95% CI 6.9-8.0), with a slightly lower score in the BCT subgroup (Figure 4). However, this difference was not statistically significant ($p = 0.323$).

Quality of life

Meta-analysis of reported Breast-Q scores revealed an overall score of 73.0 (95% CI 67.7-78.4), demonstrating moderate to good satisfaction with outcome/breasts and the breast-related quality of life. In addition, no significant differences were seen in subgroups reflecting the patient satisfaction ('Satisfaction with breasts' and 'Satisfaction with outcome', $p = 0.341$), as well as the physical, psychosocial and sexual well-being components ($p = 0.142$), see Figure 5.

Volume measurements

Eight studies provided data on volume retention, which was plotted against time in a meta-regression model (Figure 6). The volume showed a gradual decrease of initially grafted volume to 52.4% (95% CI 45.0-59.8) at one year follow-up and reaching a plateau at approximately 50% when extrapolated to the long term. All studies involved either MST or BCT patients and performed AFT according to the principles of Coleman, with the exception of the harvesting method. Between 30-100% of the breasts within each study had previously received radiotherapy.

Number of AFT sessions

Meta-analysis of data from 6169 patients in 65 studies provided an overall mean number of AFT sessions of 1.5 (95%CI 1.4-1.6), with a mean injected volume of approximately 100 ml (Figure 7). Subgroup analysis revealed a significantly lower number of AFT sessions performed for BCT deformities (1.2, 95% CI 1.0-1.5) compared to congenital deformities ($p = 0.007$) and any deformity ($p = 0.047$). No significant differences were noted between the remaining groups.

Complications

The incidence of AFT-related clinical complications based on our meta-analysis was low - 5.0% (95% CI 3.7-6.9) (Figure 8). Although the BCT group displayed noticeably higher rate of complications (10.7%) compared to the remaining populations (2.6-5.4%), it was significantly increased only with respect to studies with mixed populations (2.6%, $p = 0.002$).

Abnormal findings after AFT requiring biopsy

The final meta-analysis revealed that 8.6% (95%CI 5.8-12.4) of breasts treated with AFT, had to eventually undergo additional histopathological examination due to the presence of abnormal radiological images or clinically detected palpable mass (Figure 9).

Discussion

Synthesis of results

This meta-analysis represents the most thorough evaluation of more than two decades of accumulated data from published literature investigating AFT for the correction of

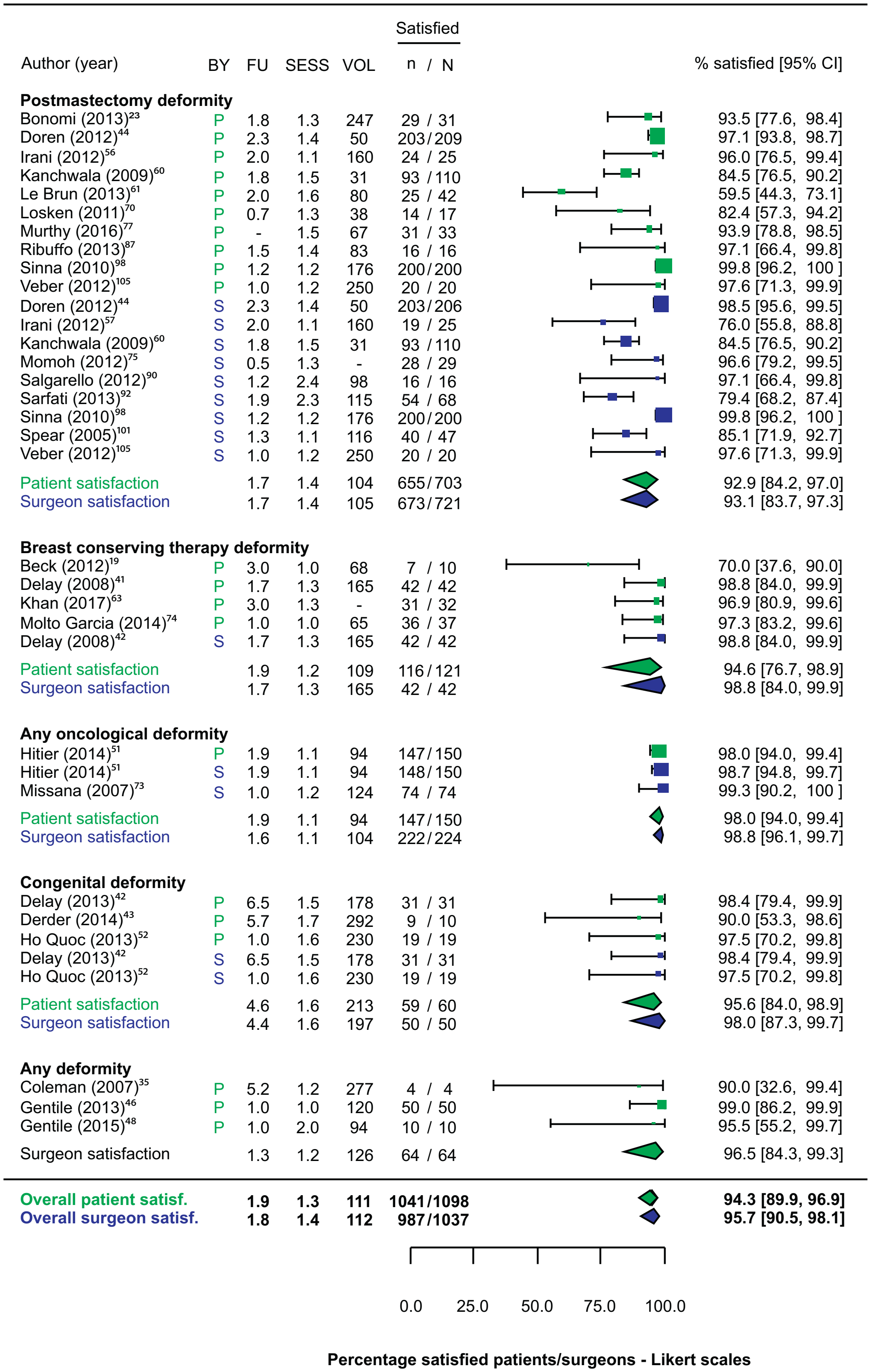

Figure 3 Meta-analysis of patient and surgeon satisfaction - categorical data. Legend: BY = 'outcome assessed by', P = patient, S = surgeon, FU = follow-up, SESS = number of AFT sessions, VOL = mean injected volume, n = number of satisfied patients/surgeons, N = total number of patients, satisf. = satisfaction.

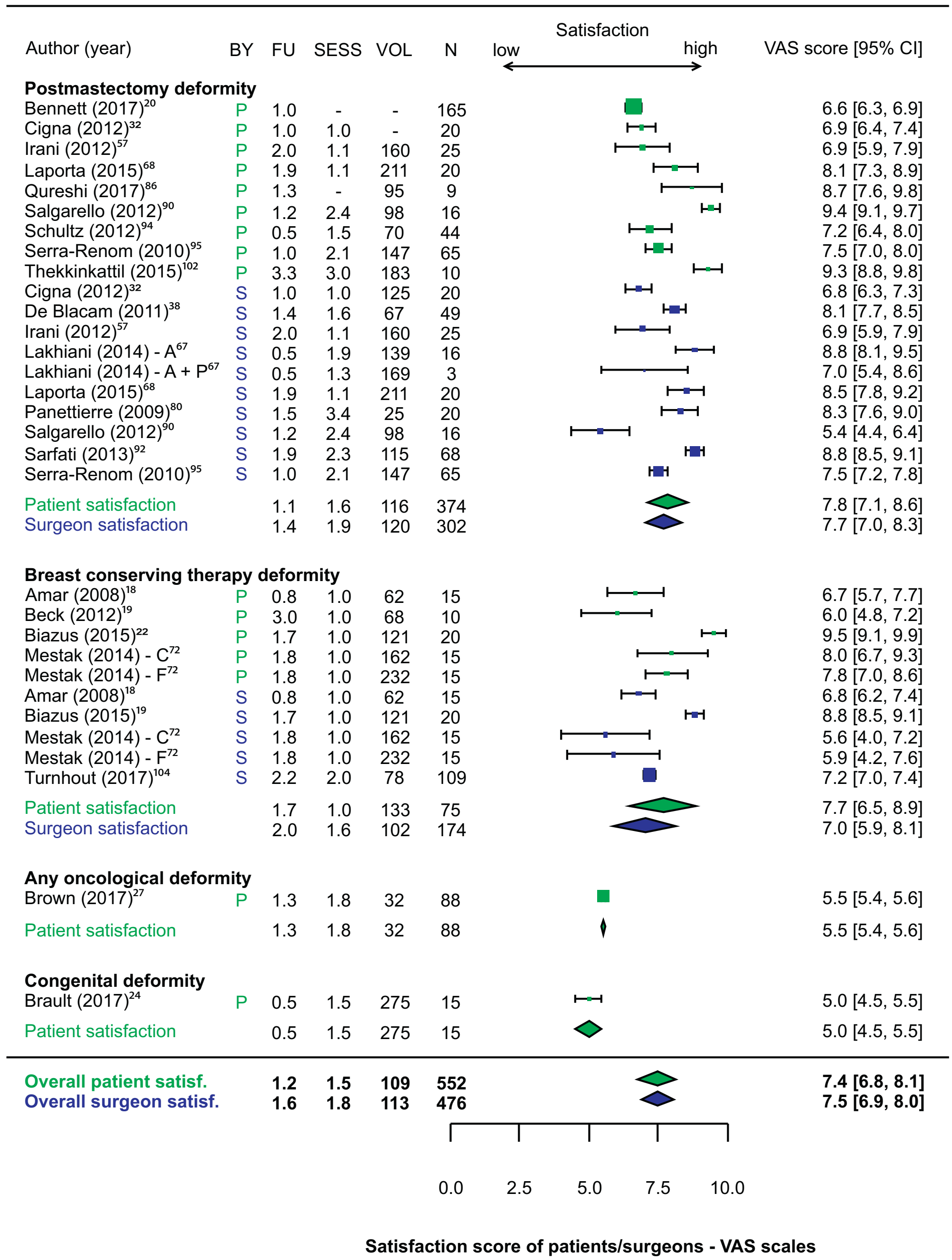

Figure 4 Meta-analysis of patient and surgeon satisfaction - continuous data. Legend: BY = 'outcome assessed by', P = patient, S = surgeon, FU = follow-up, SESS = number of AFT sessions, VOL = mean injected volume, N = total number of patients, A = AFT, A + P = AFT in addition to breast implant, C = centrifugation, F = filtration, VAS = visual analogue scale, satisf. = satisfaction.

contour deformities in the breast. A total of 89 records reporting one or more relevant outcomes reflecting AFT's efficacy were selected for analysis. The patient satisfaction was the most commonly reported outcome, measured in 1640 unique patients. It displayed an overall satisfaction rate of 94.3% that was consistently high among all relevant subgroups. This was confirmed by a satisfaction score of 7.4/10 from the continuous data, signifying a high degree of contentment among patients. Similarly, 95.7% of plastic surgeons were pleased with the result based on pre- and post-operative photographs and gave a high overall score of 7.5/10 in a combined total of 1404 patients. A much smaller number of studies employed the Breast-Q to investigate patient satisfaction and breast-related quality of life (248 patients) and these were similar to the satisfaction scores measured by other VAS scales (73.0/100).

The volume retention was evaluated in 259 patients from eight studies by performing serial measurements using 3D imaging, magnetic resonance imaging (MRI) or computed tomography (CT)-scan. The results were highly variable between studies but the meta-regression model against time showed 52.4% volume retention at one year, possibly

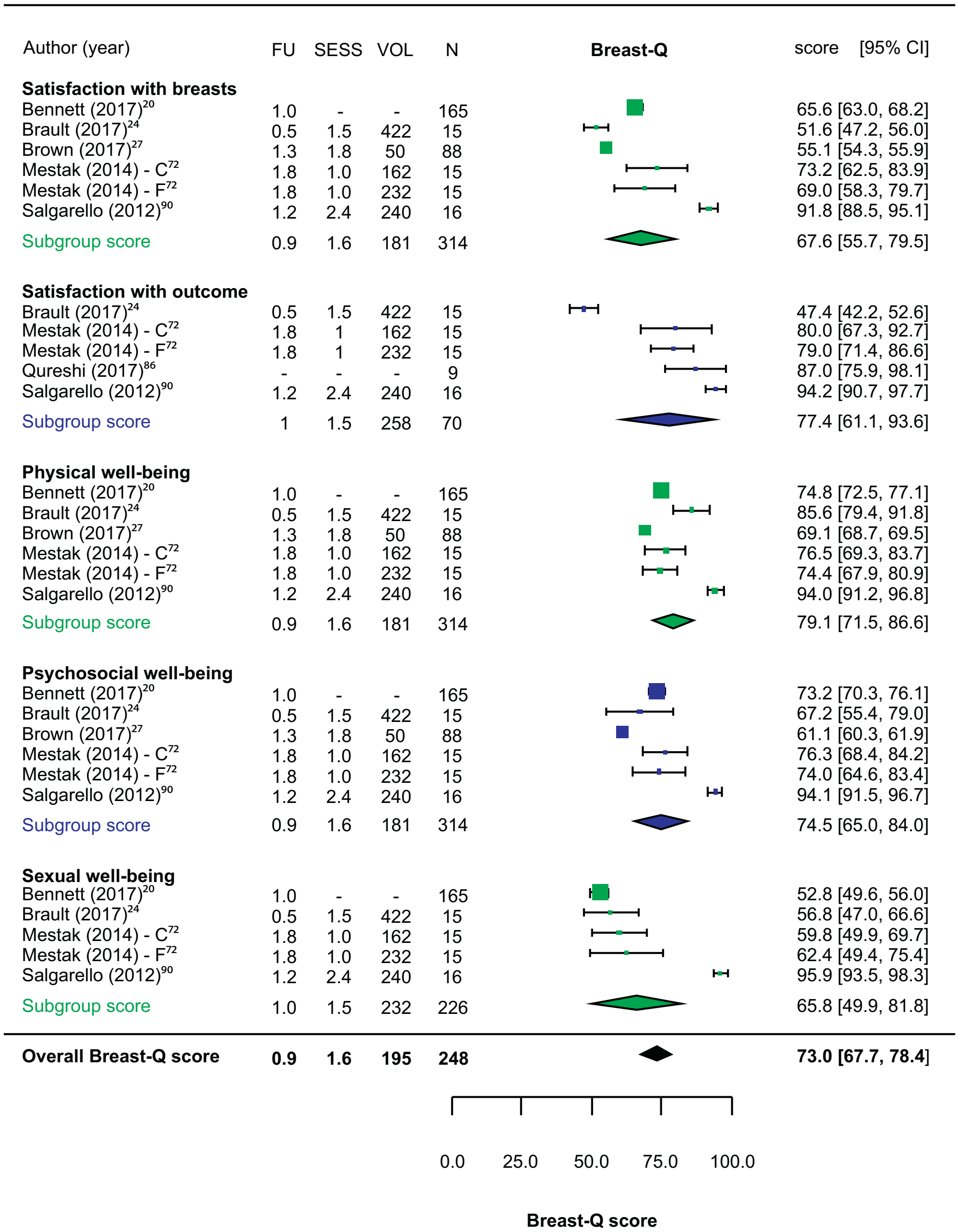

Figure 5 Meta-analysis of Breast-Q scores. Legend: FU = follow-up, SESS = number of AFT sessions, VOL = mean injected volume, N = total number of patients, C = centrifugation, F = filtration.

converging towards 50% in the long run. Unfortunately, the data are severely limited as measurements beyond six and 12 months were provided for only 96 and 18 patients, respectively. In addition, studies differed in the type of indication, exposure to radiotherapy and the surgical technique. Interestingly, studies performing fat harvesting with a liposuction machine, displayed a tendency towards a higher resorption than those using a syringe. However, the possible effects of other important confounders such as radiotherapy could not be demonstrated due to the mixed patient populations containing between 30% and 100% of irradiated breasts. As no definite conclusions can be drawn based on the available data, whether such associations exist should be investigated in future studies.

Surprisingly, the overall number of sessions required to correct a contour deformity of the breast was relatively low - 1.5. Though it can be argued that this number would become higher if excessive fat resorption would result in patients demanding extra AFT sessions, the mean follow-up length of 1.9 years would be sufficient to accommodate for this. Moreover, the rate of clinical complications per procedure was only 5.0%, and these were predominantly minor. Finally, the risk that a breast treated with AFT would result in clinical or radiological abnormalities that would require histopathological examination (biopsy) was 8.6%. Of these,

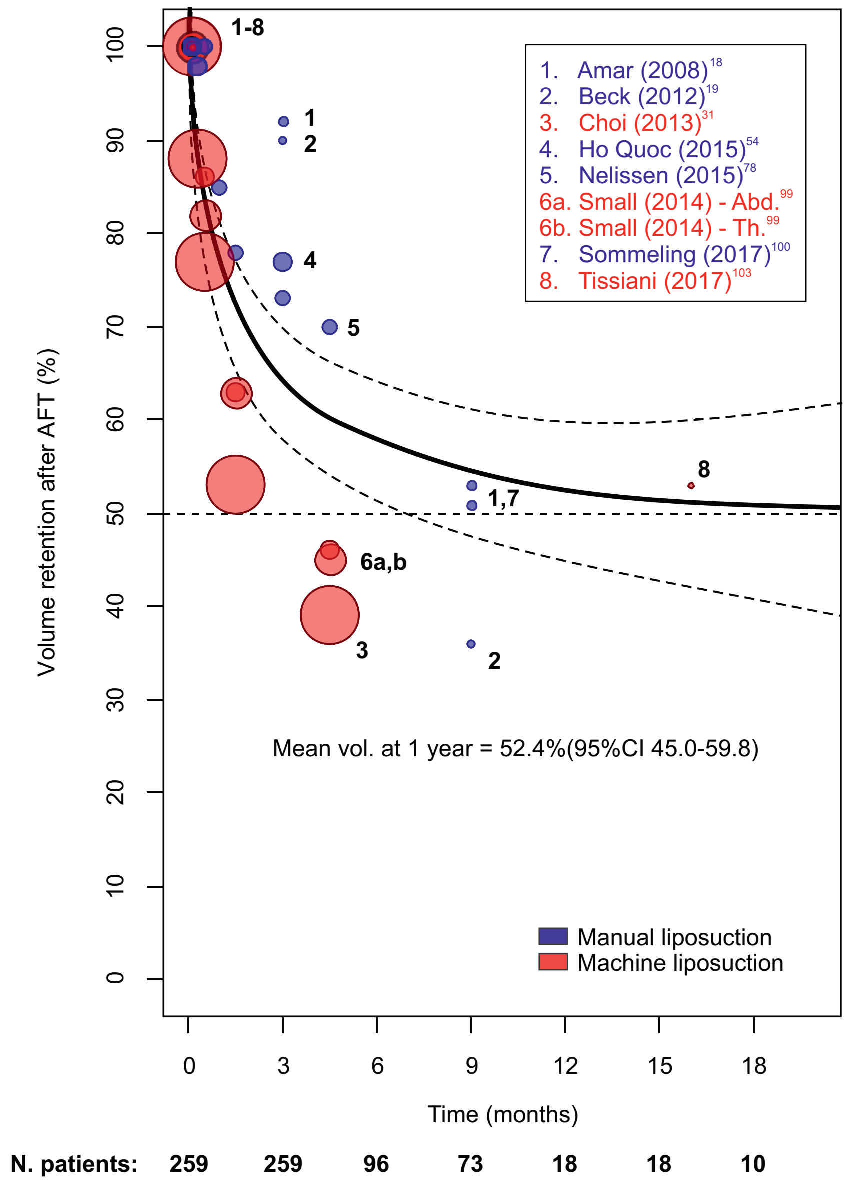

Figure 6 Meta-analysis of graft retention over time. Meta-regression model was applied to estimate the trends in graft survival over time. Each circle represents a particular study, the diameter corresponding to its sample size. The meta-regression model trendline and respective 95% CI estimate the volume retention over time. Differences in harvesting technique used were colour coded. The number of patients with volume measurements at each time point is shown below. Abd. = fat harvested from the abdomen, Th. = fat harvested from the thighs. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the vast majority involved benign lesions due to fat necrosis and only 0.6% were diagnosed as cancer relapse. Whether a direct correlation exists between AFT and the development of locoregional recurrence is outside the scope of this paper as such a task would involve a whole different set of studies and statistics.

Clinical relevance

This meta-analysis set out to deliver the first quantifiable evidence of pooled data from published studies to evaluate the overall efficacy of the procedure based on patient- and surgeon-reported outcome measures, volume retention data and associated complications. This was possible by the identification of 67-88% more relevant studies compared to past systematic reviews[1,4,5] and standardisation of outcomes. In this way, it aims to facilitate a more sophisticated and balanced interpretation of study evidence on AFT in order to allow healthcare providers to make evidence-based recommendations on the efficacy of the technique.

The choice of an appropriate outcome measure is one of the key elements of achieving an unbiased evaluation of the effectiveness of any treatment. In the case of AFT, it has been a challenge to find a suitable method of quantifying the magnitude of its effect. This is largely due to its

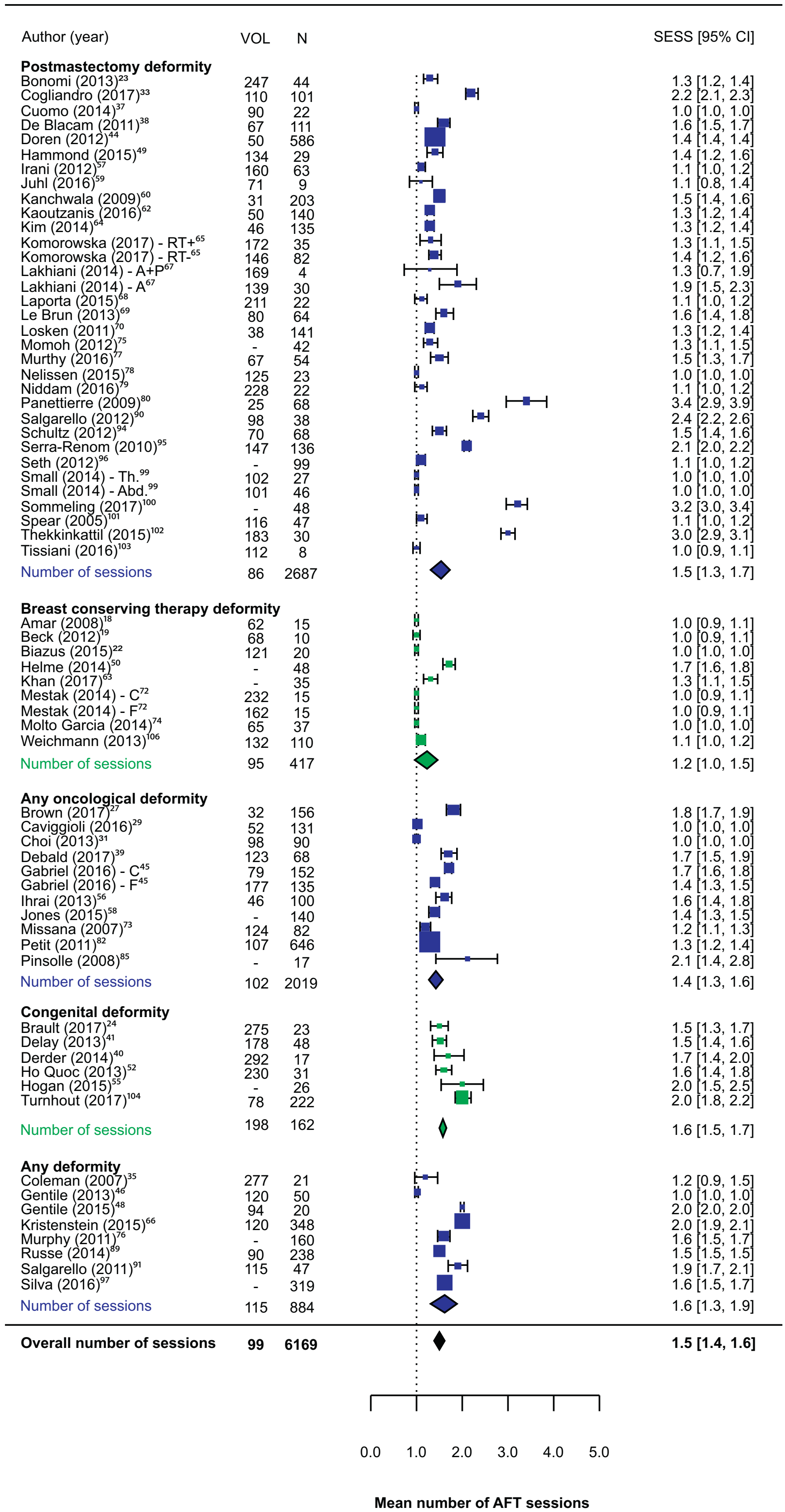

Figure 7 Meta-analysis of the mean number of AFT sessions. Legend: VOL = mean injected volume, N = total number of patients, RT + = with radiotherapy, RT- = without radiotherapy, A = AFT, A + P = AFT in addition to breast implant, C = centrifugation, F = filtration.

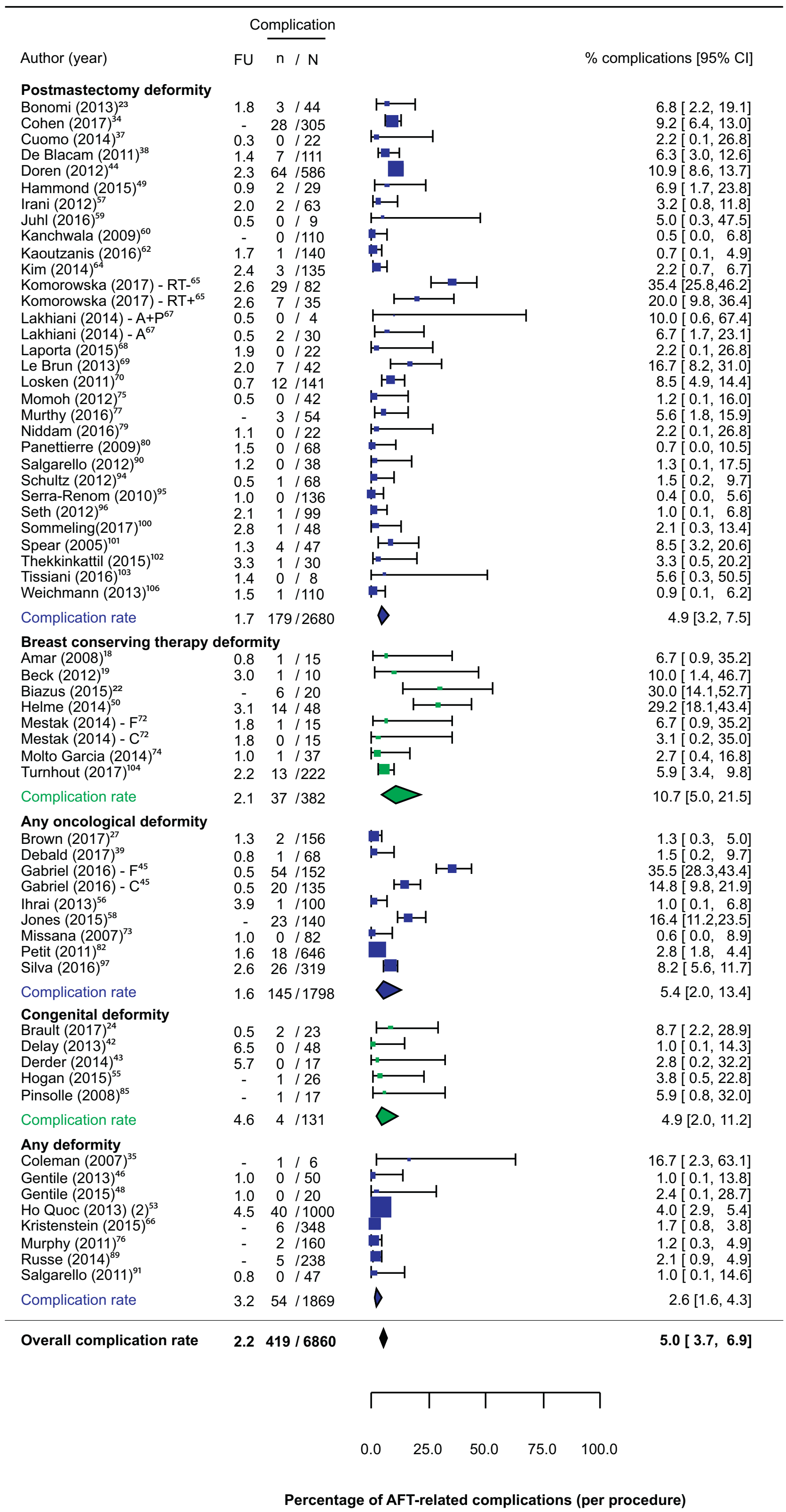

Figure 8 Meta-analysis of the AFT-related complication rate. Legend: FU = follow-up, N = total number of procedures, RT + = with radiotherapy, RT- = without radiotherapy, A = AFT, A + P = AFT in addition to breast implant, C = centrifugation, F = filtration.

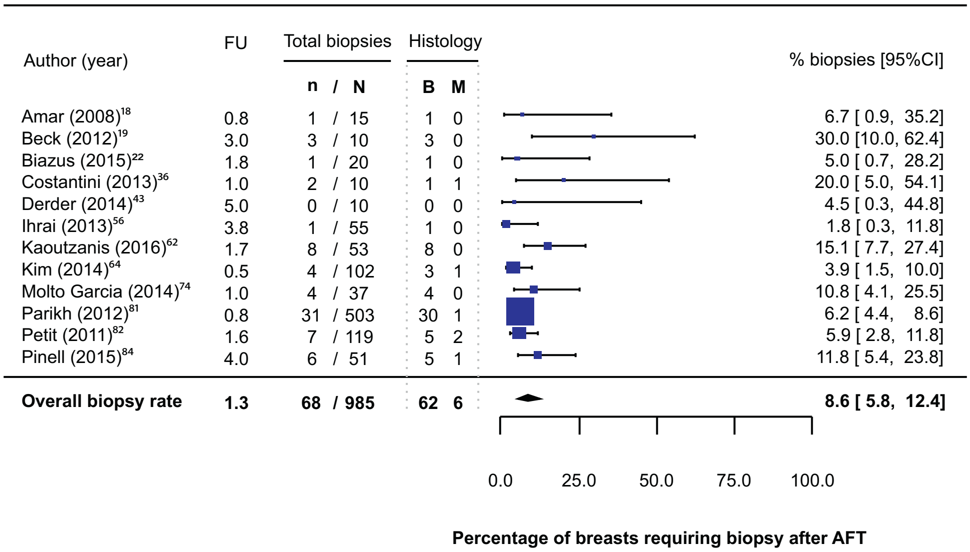

Figure 9 Meta-analysis of the AFT-related biopsy rates. Legend: FU = follow-up, n = total number of biopsies, N = total number of breasts, B = number of benign findings (fat necrosis), M = number of malignant findings (cancer relapse).

inherent properties, which make it fundamentally different from conventional reconstructive techniques. The survival of adipocytes relies heavily upon the injection of fat in a fan-like fashion, with the intent to obtain an optimal spread of aliquots in multiple directions and planes. Inevitably, this makes it virtually impossible to distinguish grafted tissue from its surroundings. Therefore, the only way to quantify its volume correction capability would be a direct measure of the change in the surrounding tissue volume. In the past, this was only possible with MRI or CT-scans but their use has been limited due to the high-costs and exposure to radiation. Only more recently, the development of 3D-image capturing devices has made such measurements more practical and these have been implemented in approximately a dozen studies so far.

Still, the majority of the literature on AFT is based on more traditional evaluation by a wide array of patient-reported outcome measures (PROMs) and scoring of photographs. Both the objective (volume) and more subjective (PROMs, scores) outcomes have their unique advantages and drawbacks. Whilst volume assessment provides the most reliable measure of the performance of AFT in the correction of volume deficiency, it remains an outcome from the viewpoint of the investigator. Such measurements are therefore best suited for investigating the more technical aspects of the AFT procedure, rather than the overall success of the treatment, which is best reflected by the evaluation performed by the patient herself. In addition, the reliability of evaluating fat survival through serial volume measurements is dubious. Measuring the change in breast volume with respect to the total injected volume is subject to several limitations. First, it is difficult to accurately determine the exact volume of injected fat as lipoaspirates can contain between 5% and 25% fluid,[108] depending on the amount of infiltration before harvesting and the processing technique used. Therefore, volume measurements would be influenced not only by the rate of fat resorption, but also by the initial fluid content of injected fat. Secondly, fluctuations in breast tissue volume due to oedema (inflammation), haematoma as well as fluctuations in the BMI can also influence post-operative measurements. The use of PROMs, on the other hand, focuses on assessing how the result is perceived by the patient, which is becoming increasingly popular in recent years, considering that the main goal of breast reconstruction is to improve the quality of life and not the score of certain investigations or tests.[109] This can then be confirmed by surgeon's satisfaction, which can also help identify possible discrepancies between the perception of the outcome from the viewpoint of the patient and clinician.

Other methods of assessment involve indirect measures that are somewhat less specific, standard parameters related to its burden and morbidity, such as operating time, hospitalisation, number of revision procedures, complications as well as the need for additional imaging or tests.

Unfortunately, perioperative data specific to AFT are scarce as it is often performed in combination with other procedures, but short operating time and fast recovery are believed to be key benefits of AFT. The need for re-intervention can also provide an indication of the overall burden and costs of the AFT treatment. Although it can imply excessive resorption, the mean number of sessions required to achieve the desired result is heavily influenced by the patient's characteristics, the operator's experience and the size of the defect. Therefore, it cannot provide anything more than a rough estimate on the expected number of procedures that are generally performed for specific indications. Lastly, the rate of clinical complications and abnormal radiological images that require additional histopathological examination, could reflect on the morbidity and extra costs associated with AFT.

Limitations

One of the main limitations with this meta-analysis is the relatively low level-of-evidence due to the scarcity of RCTs. As AFT has already become part of clinical practice,

Table 2 Recommendations for future research.

Research question	Proposed study design
1. Oncological safety of AFT in the breast reconstruction after cancer	Retrospective matched-cohort studies
2. Factors determining the (long-term) volume retention	Prospective 3D imaging studies
3. Added value of supplements (PRP, SVF) or devices (BRAVA)	RCTs, prospective cohort studies
4. Optimisation of the AFT technique (speed, volume, ↑ survival)	RCTs, prospective cohort studies
5. Effect of AFT on function, fibrosis, pain	RCTs, prospective cohort studies

setting-up a randomised trial with it would likely be viewed as unnecessary or unethical, because investigators would have to withhold a part of their patients from a treatment that they would have otherwise received in the absence of the trial. Currently, there are no indications that such studies will become common in the near future. In addition, because of the lack of a suitable and safe alternative to AFT, few studies have managed to include a control group. Ultimately, this prevents applying standard summary measures such as odds ratios or relative risks when analysing the outcomes. Therefore, our second-best chance of understanding the fragmented data gathered over the past two decades is such a meta-analysis, which focuses on providing pooled effect estimates of a large number of observational studies, by determining the magnitude, direction and confidence intervals for each outcome.

Another obstacle is the rare implementation of standard, validated outcome instruments (e.g. Breast-Q) to increase the validity as well as enable comparability of different studies. For many years, investigators have relied on a wide variety of non-validated, custom-made scales and questionnaires or the use of pre- and post-operative photographs. In addition, outcomes have been often presented as either continuous (means ± SD) or categorical variables (frequencies), each having its own (dis)advantages. The main issue with continuous data is their limited utility without a direct comparison to a baseline value or control group, which are uncommon in the case of AFT. Even if such data would be available, it would be difficult to assess the data as the same change in scores from different baseline values could be perceived very differently. On the other hand, the categorical approach (e.g. dichotomisation) often oversimplifies outcomes by assigning subjects to a particular category (dissatisfied vs satisfied). However, as it does not rely on baseline values, it can more accurately reflect the absolute effect of AFT, though it lacks the precision of continuous data.

As with all meta-analyses, heterogeneity between studies can have an important effect on the results. The included studies consist of a variable number of patients with different diagnoses and indications. However, as this paper aims to evaluate the overall efficacy of AFT for the correction of *contour deformities* in the breast, it can be argued that the patient populations closely resemble the group we wish to draw conclusions about. In addition, a random-effects model was applied to all analyses and different indications were analysed in subgroups to account for the inter-study heterogeneity.

Future recommendations

This meta-analysis delivers convincing evidence concerning the overall efficacy of AFT and also lays the foundation for further research in this area. To allow for more nuanced recommendations for specific subgroups or indications, it is crucial to improve the methodological quality of future studies. Ideally, this can be achieved by adopting a prospective study design, including suitable control groups and using validated outcome measurement instruments. Based on the current data, several research questions should be addressed by the plastic surgery community worldwide within the next five years (see Table 2). Considering that the vast majority of breast deformities involve breast cancer patients, it is of paramount importance that definite answers are provided regarding its oncological safety. In addition, future studies should also focus on evaluating other positive effects of AFT such as improvement of function, fibrosis and pain in the breast region. Last but not least, the search for the optimal AFT technique should involve determining the long-term volume retention, the effect of nuances in the technique and radiotherapy, as well as the added value of supplements or devices.

Conclusion

AFT was found to be highly effective in correcting contour deformities in breast reconstruction, as reflected by the high patient satisfaction (94.3%) and surgeon satisfaction (95.7%), achieved after a mean of 1.5 procedures. Volume retention was 52.4% after one year but needs further investigation. With only 5.0% of procedures resulting in minor complications and 8.6% leading to additional biopsy, it can be considered as a safe procedure.

Financial disclosure statement

This research was funded by the Dutch Society of Plastic Surgeons for the purpose of autologous fat transfer guideline development in the Netherlands.

Conflict of interests

None of the authors has a financial interest in any of the products, devices, or drugs mentioned in this manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjps.2018.05.021.

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