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Review

Systematic review: The oncological safety of adipose fat transfer after breast cancer surgery

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ABSTRACT

Objectives: Oncological concerns have risen around the safety of adipose fat transfer (AFT) after breast cancer surgery. In this article, we present the clinical and molecular evidences, and discuss the current contradiction between them.

Materials and methods: Every clinical trial and experimental study on AFT and its oncological influences was screened. Between September 2014 and September 2016, 856 articles from four databases were found. 105 core articles were selected.

Results: A total of 18 clinical studies have been published. The loco-regional recurrence (LRR) incidence rates range between 0 and 3.90% per year. For the mastectomy and breast conservative therapy group separately, a LRR per year between 0 and 1.62% and 0–3.90 has been reported, respectively. Some studies included a matched control group and found no significant difference between cases and controls, with the exception of a subgroup of patients with intraepithelial breast carcinoma.

Adipose derived mesenchymal stem cells have a potential oncogenic effect on residual cancer cells after breast cancer surgery. Numerous signalling proteins and pathways have been described that can stimulate tumour initiation and growth.

Conclusion: There is a contradiction between experimental and clinical findings. Numerous adipokines have been discovered that could potentially promote tumour initiation and growth, but clinical studies fail to point out a significant increase in LRR in patients who receive AFT after breast cancer surgery. More prospective studies are needed with a sufficient follow-up time and analysis of some critical factors, such as adjuvant radiotherapy and hormonal therapy, the origin and volume of the injected fat, and genetic influences.

Contents

Abbreviations: AFT, autologous fat grafting; BCT, breast conservative therapy; MST, mastectomy; ADMSC, adipose derived mesenchymal stem cells; LRR, loco-regional recurrence rate; CAF, cancer-associated fibroblasts; OSM, Oncostatin M.

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1. Introduction

Adipose fat transfer (AFT) has been described in the literature for decades. The first reports of fat transfer date back to 1893 by Neuber et al. [1,2] Two years later, Czerny et al. reported the first use of a lipoma from the dorsal flank to perform partial breast reconstruction [3,4]. Initially, surgeons were confronted with complications such as graft resorption, fat necrosis, and the formation of micro-calcifications, that can interfere with the mammographic detection of breast cancer.

AFT only gained mainstream access in 1997, when Coleman et al. described a new refined technique of AFT [5]. Through liposuction, purification, and fat injection, the rate of complications diminished significantly and fat graft survival improved. Since then, AFT has found important clinical application in numerous fields, both cosmetic and reconstructive, and has been proven to be superior over conventional methods of breast reconstruction [4,6–13]. Adipose tissue (AT) is particularly useful in the correction of small defects of the breast after breast conservative therapy (BCT) or mastectomy (MST) followed by breast reconstruction using a flap, when irregularities or asymmetry remain.

However, oncological concerns have risen since the use of AFT for breast reconstruction. Numerous studies have reported interactions between adipocytes, adipokines, and stroma as potential actors in breast cancer tumorgenesis [14–23]. Moreover, several studies have mentioned their concerns regarding the link between these adipokine secretions, breast cancer recurrence and metastasis [24–26]. Other concerns focus on adipose derived mesenchymal stem cells (ADMSC) within the transferred fat and their interaction with primary breast cancer cells [27,28]. Through a process of adipogenesis and angiogenesis, these cells play the leading role in the restorative and reconstructive functions of AFT and are the main reason why AFT is so successful for breast reconstruction [29–32]. Moreover, they possess several pro-regenerative features (anti-apoptotic, pro-proliferative, and paracrine immunomodulatory effects), which makes them very attractive candidates for regenerative therapy approaches [33–35]. Following some case reports, questions started to raise regarding AFT - the intentional placement of regenerative tissue at the site of a previous tumour bed - and the potential risk of breast cancer recurrence [7,24,27,28,36–43]. ADMSCs secrete certain cytokines, chemokines, and growth factors, that help develop and maintain an inflammatory state, in which tissue regeneration is stimulated. However, the wound and tumour micro-environments share a lot of similarities, and it was found that an inflammatory response also contributes to the process of tumour genesis, as well as metastasis [44–47]. In 2009, the American Society of Plastic Surgeons set up a task force to assess the indications, safety and efficacy of AFT [48]. They concluded that most of what was known came from expert's opinions and case series and that the knowledge back then was mostly based on a low grade of scientific evidence. Therefore, they declared that they could not provide specific recommendations regarding the use of AFT due to the lack of a standardized technique and randomized, controlled trials.

In this article, we present both the clinical and molecular evidences on the oncological risk of AFT after breast cancer surgery, and discuss the current contradiction that exists between them.

2. Materials and methods

Every clinical trial that involved AFT for breast reconstruction in female patients after breast cancer surgery - MST or BCT - was considered. Additionally, every relevant experimental study around AFT and its oncological influences was screened. An electronic search was performed in four medical databases to identify all published studies: PubMed, Web of Science, Embase, and the Cochrane Library. The search was focused on “breast” and “autologous fat transfer”. As there are a number of different terms describing AFT, and to maintain a systematic approach, available synonyms were also used as search terms. The used Mesh-terms were: lipofilling, adipose fat transfer, lipotransfer, adipose tissue, breast cancer, fat grafting, and cancer recurrence. This review was performed according to the criteria of the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement [49]. Between September 2014 and September 2016, 856 articles were found after removing duplicates between the four databases. The number of found articles were manually narrowed to 105 by three individual researchers through screening of title and abstract and were included in this review. The Jadad scale was used to assess the quality of found RCT's. RCT's that scored less than 2 points were withdrawn from this study. Finally, 18 clinical trials were included in this study, as seen in Table 1. The following data was extracted from 18 articles: study period, number of patients, mean age, type of surgery before AFT, percentage of invasive carcinomas, percentage of carcinomas in situ (CIS), percentage of patients receiving radiotherapy (RT) before AFT, mean time between surgery and AFT, mean follow-up period after AFT, and the number of patients with local recurrence. We considered the LRR to be the most important outcome to validate the effect of local treatment with AFT. We considered all women undergoing AFT procedure after MST or BCT. No focus on patient age, publication language or publication date was set.

To make sure that other relevant publications were not missed, the references in all found publications were additionally screened. The function ‘Related articles’ was also used on a regular basis.

Few studies have been conducted around AFT and the possible effect on the recurrence of breast cancer. Moreover, studies that did not provide any follow-up data were excluded from this article.

3. Results

3.1. Clinical studies

Table 1 shows an overview of the clinical studies on the oncological risk of AFT after breast cancer surgery. The largest study ever conducted is a retrospective study by Kronowitz et al. which included 719 patients, who received AFT after breast cancer surgery (MST or BCT) [50]. An equal loco-regional recurrence (LRR) incidence rate of 0.25% per year was reported for all patients, the MST-, and BCT-group. A comparison with 670 matched controls showed no significant difference in LRR (1.3% vs. 2.4%, $p = 0.455$). However, in the subgroup treated with hormonal therapy, AFT was associated