REVIEW ARTICLE

Research progress on the safety of cell-assisted lipotransfer in breast repairs after breast conserving therapy

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Abstract: With the development of medical technology, more breast cancer patients have the opportunity of receiving breast conserving therapy. Post-operation breast reconstructions have gained more attention nowadays. As a new and important method of breast reconstruction after breast surgery, cell-assisted lipotransfer is being carried out in some clinical works. This paper briefly reviewed the current research progress of adipose-derived stem cell-assisted lipotransfer and the recurrence of breast cancers.

Keywords: breast conserving therapy; breast reconstruction; adipose-derived stem cell; cell-assisted lipotransfer

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Introduction

With the development of medical technology, more breast cancer patients have the opportunity of receiving breast conserving therapy (BCT). Post-operation breast reconstructions have gained more attention nowadays. Societal progress, along with vigorous development of cosmetic surgery, has made autologous fat transplantation one of the hottest areas of research. Autologous fat transplantation is used to fill a variety of congenital or a posteriori tissue defects for breast reconstruction after breast cancer resection and facial atrophy. However, complications of lipotransfer including necrosis, liquidation and infection make it invalid.

As a new and important method of breast reconstruction after breast surgery, cell-assisted lipotransfer (CAL) is being carried out in some clinical works. Many clinical cases claim that it can effectively maintain the survival rate of fat cells transplanted in breasts to achieve the purpose of tissue regeneration and reshaping[1]. However, the recurrence of breast cancer after these reconstructive surgeries still needs further observational studies. This paper briefly reviewed the current research progress of adipose-derived stem cell (ADSC)-assisted lipotransfer and the recurrence of breast cancers.

Recurrence after breast conserving therapy

Breast cancer can be categorized into early or advanced breast cancer according to its range. Early treatment rate of breast cancer can reach more than 90%[2]. As the early detection rate of breast cancer increases and indications of breast conserving therapy (BCT) become more widespread, opportunities for conserving therapy are available to more patients. Breast cancer is a systemic disease during its early stages[3]. Thus, blindly expanding the scope of surgery is not only unhelpful in improving its efficacy but may also result in greater surgical trauma leading to increased postoperative complications[4]. With in-depth understanding of breast cancer and transformation in the modern medical model, treatment of radiotherapy and chemotherapy after BCT has become a new means of early breast cancer treatment.
A comparison study between BCT and radical mastectomy prognosis by Ursaru et al. on a 5-year postoperative follow-up of 248 cases of patients receiving BCT discovered that 38 patients had ipsilateral local recurrences. In another 4-year-study on the efficacy of BCT and quality of life in 56 patients, it was found that 3 patients had local recurrences, 6 had axillary lymph node metastases and 13 had distant metastases. In the analysis on 34 cases of BCT for early breast cancer in 2014, Lin et al. identified that the 5-year recurrence rate of these patients was 12%. In a report by Yang, a 5-year follow-up on 24 patients with BCT for early breast cancer treatment revealed only one case of recurrence. A clinical analysis on the efficacy of early breast cancer patients recovering from BCT by Zai et al. found that the local recurrence rate was 8.2% (3 out of the 37 patients) during the 1-year follow-up. Cowher et al. reported 7 cases with local recurrence in a 5-year follow-up of 587 patients who underwent BCT. About 5%–10% of patients who underwent BCT had tumor recurrences within 2–4 years of post-surgery.

Prognosis of autologous fat transplantation in breast repair after surgery

Post-BCT, a considerable number of patients needed breast reconstruction in order to improve their quality of life. In the present study, autologous fat is one of the most common reconstructive methods, and its safety and low-rate complications after breast surgery have been widely recognized. Rietjens et al. indicated that among 158 patients who received fat grafting technique by Coleman after BCT, only four patients showed slight postoperative changes in breast structure during mammography. Lohsiriwat et al. also published their findings on postoperative follow-up of fat grafting in 2011. In the 18 months of follow-up on 158 fat grafting patients, only one case had cancer recurrence. A 45-month follow-up was conducted on 151 patients after fat grafting and it was found that there was no metastasis or recurrence of cancer. Autologous fat graft is a promising tool to correct defects after BCT. The procedure is simple and associated with low rates of postoperative complications. Local recurrence (LR) rate was not higher than expected for this low-risk group of patients. Petit et al. collected data on 321 consecutive primary breast cancer surgery patients who subsequently underwent lipofilling for reconstructive purposes between 1997 and 2008. Lipofilling may be used safely to treat tumor node metastasis stage 1 subjects after mastectomy. The local risk is low. For stage 2 patients, local failure was not significantly higher. Breast conserving treatment needs further investigation due to the high risk of local relapse.

It can be concluded from the above cases that during the 18–45 months of follow-up after breast reconstruction by fat grafting, recurrences were relatively low. However, despite the LR, complications like necrosis, liquidation and infection have been a problem for its prognosis.

Cell-assisted lipotransfer

Cell-assisted lipotransfer (CAL) divides fat obtained through liposuction into two parts; stromal vascular fraction (SVF) and extracellular matrix (ECM). The two parts are injected into affected areas after mincing. Part of the fat tissues obtained through liposuction is maintained around the aorta while the other is released into the components of liposuction fat liquid resulting in only half-complete adipose tissue in adipose-derived stem cells (ADSC), and the fat cell’s viability is quite low upon fat grafting. It was also discovered that ADSC divided easier in mature adipocytes. Upon mixing with insulin and platelet-derived growth factor, it can quickly change into adipocytes. By accelerating microvascularity and collagen synthesis, SVF can increase the survival rates of autologous fat grafts. Therefore, adipose stem cells (ASC)/SVF assisting autologous fat grafting can effectively prevent complications of fat grafting, such as fat necrosis, cyst formation and fat calcification.

Clinical application of CAL in breast reconstruction after surgery

At present, CAL has been used in clinical trials and has produced good results. A prospective multi-center clinical trial, RESTORE-2, selected 71 patients of BCT receiving local breast tissue defect reconstruction after ADSC-assisted lipotransfer. 67 patients had follow-ups for 12 months and 50 patients were satisfied with their results. Through MRI evaluation, 54 patients had improved chest deformity among which 10 cases showed partial cyst formation with no tumor recurrences.

Brenelli et al. analyzed 59 cases of BCT patients receiving ADSC-assisted lipotransfer. In the 34-month of postoperative follow-up, there were three patients with local tumor recurrences. Techanukul et al. reported that there was no clear evidence that the rate of tumor

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recurrence in patients receiving fat grafting would increase, and tumor recurrence rate after fat grafting did not change even after the addition of SVF in ASC\(^2\)\(^3\)\(^4\)\(^5\).  

**Laboratory studies of ADSC and breast cancer**

ASC secretes large amounts of growth factors, such as vascular endothelial growth factors and hepatocyte growth factors. Due to its own characteristics, ASC may be involved in the formation of tumor-associated matrix that has been shown to promote tumor cell metabolism and infiltration, and SVF promotes microvascular and collagen synthesis\(^2\)\(^5\)\(^6\)\(^7\). Thus, it is believed that ASC/SVF may promote tumor formation.

In a co-culture of breast cancer T47D cells and adipose stem cells, Kuhbier et al. noted that T47D cells changed in morphology and phenotype after 14 days\(^2\)\(^7\). Moreover, it was found that cellular activity of T47D was also significantly increased. These evidences showed communication between T47D and stem cells. Eterno et al. indicated that the expression of HGF/c-Met signal may indicate breast cancer recurrence\(^2\)\(^8\). The study found that fat stem cells did not directly induce normal breast cells to become cancer cells but instead provided appropriate inflammatory microenvironment for the growth and vascularization of cancer cells by increasing the occurrence of tumorigenic behavior of breast cells. As a communication marker for fat stem cells and tumor cells, HGF/c-Met enhanced the metastasis of tumor cells and played a role in maintaining self-renewal of tumor cells.

Breast cancer cells can release a soluble factor that can break fat stem cell’s differentiation to adipocytes\(^2\)\(^9\). Simultaneously, it will also increase proliferation, vascularization and fibrosis in ASC. These mutated ASCs can give rise to deposition and reduction of many ECM which harden normal breast tissue and ultimately produce cancerization. This mutation mechanism is similar to current chemical signals found in tumor cells.

**Challenges and prospects**

Autologous fat transplantation is a new option for breast reconstruction after surgery. However, like other new technologies, there are still many problems that need to be resolved. Based on the above research data, cancer recurrence rates with or without cell-assisted lipotransfer are very low and there is no significant difference between them. The reason may be due to the patients’ assessment of their own health conditions before making the choice to perform fat grafting repairs. Therefore, some systematic errors are possible in selecting observational targets in such clinical observational studies. Subsequent to fat grafting, fat-induced tumor recurrence also exists. Meanwhile, the above mentioned studies are also preliminary evidences of mutual influence between breast cancer cells and adipose stem cells. Based on the current status of the 5-year follow-up on patients undergoing ADSC-assisted lipotransfer after BCT, it was found that the safety rate is relatively high.

There has not been any opinion or views on the influence of ADSC-assisted lipotransfer on breast cancer recurrence rate and no clear clinical evidence indicated that CAL will increase breast cancer recurrence. Thus, it is relatively safe and can be used in clinical practice but the patients’ breasts should be evaluated to ensure safety and feasibility of surgery. In addition, more clinical observations and laboratory studies prior to further explorations are required.

**References**

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