

Original Article

The effect and prognosis of combinative implantation by autologous-fat granule and prosthesis for breast reconstruction after radical mastectomy

Shensong Liu^{1*}, Shaoshan Chen^{2*}, Yongcheng Yang¹, Weiwei Guan²

¹Department of Plastic Surgery, Hainan Ruihan Medical Cosmetology Hospital, Haikou 570204, Hainan, China;

²Department of Stomatology, Affiliated Kaikou Hospital of Xiangya Medical College, Central South University, Haikou 570204, Hainan, China. *Equal contributors.

Received January 1, 2021; Accepted February 2, 2021; Epub May 15, 2021; Published May 30, 2021

Abstract: Objectives: In this study, we analyzed the effect and prognosis of combinative implantation of autologous-fat granule and prosthesis for breast reconstruction after radical mastectomy. Methods: 73 cases of breast cancer patients hospitalized from March 2015 to March 2017 were chosen and separated into observation group (n=41) and control group (n=32) on the basis of the surgical methods. Both the two groups underwent modified radical mastectomy. In addition, the control group received prosthesis implantation for breast reconstruction, and the observation group was implanted with combination of prosthesis and autologous-fat granule transplantation. Thereafter, the surgical indexes, postoperative complications, aesthetic effects of breast reconstruction and prognosis of the two groups of patients were evaluated. Results: The surgical duration of the observation group was obviously longer than that of the control group ($P<0.05$), while the two groups had insignificant difference in postoperative drainage duration and postoperative hospital stay ($P>0.05$). FACT-B score of both groups of patients one year after surgery was dramatically higher than that before surgery ($P<0.05$), and patients in observation group had remarkably higher scores than those in control group ($P<0.05$). The incidence of postoperative complications in observation group was substantially lower than that in control group ($P<0.05$). In addition, the aesthetic evaluation of the observation-group patients postoperatively was notably higher than that in control group ($P<0.05$), and there was no statistically significant difference in progression-free survival between the two groups ($P>0.05$). Conclusion: The combinative implantation of both prosthesis and autologous-fat granule for breast reconstruction after radical mastectomy is simple in operation procedure, and has better aesthetic outcome and safety. It satisfies the aesthetic demand of patients while having lesions resection, and does not affect the surgical effect of modified radical mastectomy, which is worthy of clinical promotion.

Keywords: Autologous-fat granule, implantation of prosthesis, breast cancer, radical surgery, breast reconstruction

Introduction

Breast cancer is currently one of the malignant tumors in women with highest incidence. The epidemiological investigations and studies in recent years have shown an increasingly high incidence of breast cancer, among which menopausal female is the high-risk group [1]. The occurrence of breast cancer seriously affects physical and mental health in women, and even poses a huge threat to the life safety of patients, which has aroused great attention of the medical profession [2]. For the clinical treatment of

breast cancer at present, the radical surgery is the mostly adopted method. The breast, as a unique part of women, has both aesthetic and lactation effects. Complete excision of the breast may impose adverse effects on patient's physiology, psychology and family life [3, 4]. In the modified radical mastectomy of breast cancer, the basic shape of the breast can be preserved while removing the tumor tissues, and the trauma of radical surgery could be eased [5]. Meanwhile, the good aesthetic effects can be obtained for patients that receive immediate breast reconstruction, and their postoperative

psychological trauma can be reduced, which is conducive for them to regain confidence in integrating into the society [6]. In this study, we analyzed and discussed the effect and prognosis of combinative implantation of both prosthesis and autologous-fat granule transplantation in patients undergoing breast reconstruction after radical mastectomy.

Materials and methods

Research objects

73 breast cancer patients hospitalized from March 2015 to March 2017 were chosen and separated into observation group (n=41) and control group (n=32) on the basis of their surgical methods. The study was carried out under the approval of the hospital ethics committee.

Inclusive criteria

(1) Those who had been diagnosed with breast cancer by pathological examination during surgery; (2) Tumor diameter ≤ 3 cm; (3) The age of patients ranged from 25 to 70 years; (4) The distance between tumor edge and areola > 3 cm; (5) Patients had normal communication skills; (6) The patients were informed and voluntarily signed the consent form.

Exclusive criteria

(1) Patients with severe organic lesions; (2) Patients with autoimmune diseases; (3) Patients with distant metastasis; (4) Patients had a history of breast surgery; or (5) Patients who received immunotherapy, radiotherapy or chemotherapy before surgery.

Methods

The control-group patients underwent breast reconstruction with prosthesis implantation immediately after the modified radical mastectomy. We determined the location of the patients' lesion, and evaluated the volume of the breast and marked the incision. After the general anesthesia and routine disinfected drapes were prepared, the patient was placed in a supine position, with both upper limbs abducted vertically. We performed a small shuttle incision to dissociate the skin flap in the breast, removed the subcutaneous fat, exposed the mass and excised. The excised tissues were sent to laboratory for biopsy. After confirmation of malignant tumor, the patient's

skin flap was dissociated to the lower edge of the clavicle. The medial side of the flap was free to the sternal edge, the lower side to the sixth rib, and the lateral side to the front edge of the latissimus dorsi, reaching the lower fold of the breast. The areola and nipple of patient were removed sequentially and sent to sentinel lymph node biopsy. Patients with negative biopsy results were retained with armpits, and those with positive results underwent axillary lymph node dissection to make sure the lesion was completely removed. Subsequently, the pectoralis major muscle of patient was isolated, a hairy silicone prosthesis was implanted behind the pectoralis major muscle, and the breast morphology was reconstructed. After well recovery of morphology, the patient's surgical cavity was cleaned, a drainage tube was placed on the front edge of the latissimus dorsi muscle for negative pressure drainage, and the chest was pressurized and bandaged.

Patients in observation group underwent modified radical mastectomy, and immediately received breast reconstruction by implanting both prosthesis and autologous-fat granule transplantation. The modified radical mastectomy was the same as that conducted in control group. After the modified radical mastectomy was completed, the pectoralis major muscle was bluntly separated to the posterior space, and the dilator was placed into inferior wall of the submammary fold cavity after sufficient hemostasis. We isolated the lateral side of the patient's pectoralis major along the deep front of the serratus anterior muscle and ensured that the prosthesis could be completely covered by tissues. A round dilator with appropriate volume was selected according to the breast size of the contralateral side of patient, and a silicone prosthesis was implanted along the posterior pectoralis major space. Expanded the dilator, injected with 80-150 ml saline solution, and checked the tension of skin incision and the blood flow of the flap. The expander was placed in mid-axillary line, and autologous-fat granule transplantation was performed. The patient's inner and outer thighs, buttocks, rectus abdominis and other areas rich in fat particles were selected as autologous-fat granule for transplantation. 20 ml of 2% lidocaine, 1 ml of 0.1% epinephrine and 1000 ml of 0.9% normal saline were used for infiltration and swelling anesthesia. After the subcutaneous tissue was firm and swollen, a needle plug was drawn with a disposable

Table 1. Comparison of clinical data

Clinical data	Observation group (n=41)	Control group (n=32)	t/ χ^2	P
Age (years, $\bar{x} \pm s$)	42.85 \pm 7.29	42.17 \pm 7.06	0.401	0.690
Tumor diameter (cm, $\bar{x} \pm s$)	2.10 \pm 0.64	2.03 \pm 0.58	0.483	0.631
TNM staging				
TNM stage I	15	12	0.530	0.596
TNM stage IIa	17	16		
TNM stage IIb	9	4		
Pathological types				
Invasive ductal carcinoma	26	20	0.509	0.953
Invasive lobular carcinoma	12	11		
Others	3	1		

compared between the two groups.

(4) The postoperative aesthetic effect of the two groups of patients was evaluated according to Harris aesthetic evaluation criteria [8]. Excellent: Both breasts are symmetrical, basically in same size and normal appearance, and free of surgical scars; Good: There are surgical scars, partial pigmentation, telangiectasia on the affected side, and the areola

and nipple are basically alive; Acceptable: Nipple displacement and skin color change on the breast, but are still acceptable to the patient; Poor: There is telangiectasia, fibrosis and retraction of breast. The overall efficiency = (excellent + good + Acceptable)/total number of cases \times 100%.

(5) Patients in both groups were followed up postoperatively, and their progression-free survival (PFS) was recorded. PFS refers to the time from the day after the operation to the patient's first disease progression or death from any cause. The follow-up deadline was July 1, 2020.

Statistical analysis

Data analysis was performed with statistical software SPSS 25.0. The comparison of measurement data was done by *t*-test, the enumeration data were analyzed by χ^2 test, the survival stage by drawing of Kaplan Meier survival curve and the survival conditions were analyzed by Log-rank test. The difference was statistically significant if $P < 0.05$. The graphic software adopted was GraphPad Prism 8.0.

Results

Clinical materials

The difference of gender, tumor diameter, TNM stage and pathological type between the two groups of patients was not statistically significant ($P > 0.05$) (Table 1).

Comparison of surgical-related indexes

The surgical duration of the observation group was obviously longer than that of the control group (3.97 \pm 0.61 h vs. 3.18 \pm 0.36 h) ($P < 0.05$),

syringe to form a manual negative pressure, and repeatedly and slowly sucked in subcutaneous fat layer to obtain the fat suspension. Centrifuged the fat suspension for 3 min to remove the swelling fluid and blood, and placed the middle-level transferred fat particles into a 2 ml disposable syringe. Before the expander was removed, we adopted a fat transplantation needle with 17G blunt head to inject fat granule into the intermuscular space and subcutaneous of the pectoralis major. Slowly pulled out the pinhole and gently massaged the subcutaneous tissue to promote the uniform distribution of fat. The injection volume was 100-150c each time. The edges of pectoralis major and serratus anterior were sutured with negative pressure drainage, and subcutaneous tissue, incision and compression bandage were sutured in turn.

Observation of indexes

(1) The surgical indicators, including duration of surgical time, postoperative drainage time and postoperative hospital stay, were compared between the two groups.

(2) The Functional Assessment of Cancer Therapy-B (FACT-B) was adopted to evaluate the living quality of the two groups respectively before and 1 year after surgery [7]. The scale includes items of physical well-being, functional well-being, social/family well-being, and emotional well-being, with full score of 100 points. The higher score refers to the better living quality of patient.

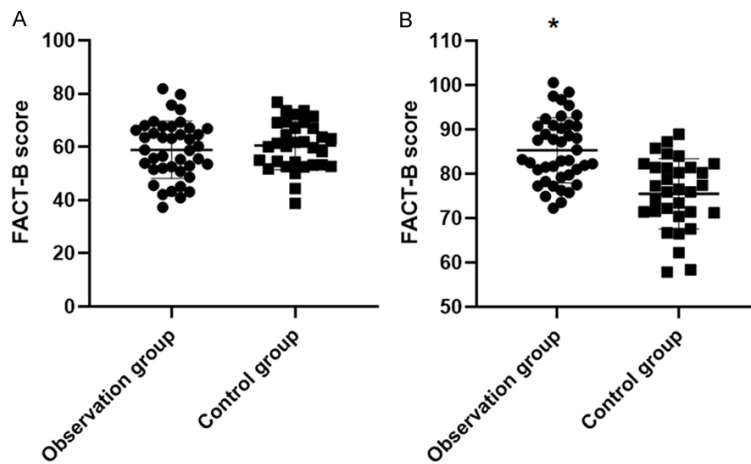
(3) The postoperative complications, including hemorrhage, lymphedema, necrosis of skin flap and subcutaneous fluid accumulation, were

Table 2. Comparison of surgical-related indexes between the two groups ($\bar{x} \pm s$)

Group	Number of cases	Operation time (h)	Postoperative drainage time (d)	Length of hospital stay (d)
Observation group	41	3.97±0.61	4.18±0.83	12.38±3.11
Control group	32	3.18±0.36	4.26±0.91	12.64±3.52
t	-	6.491	0.392	0.335
P	-	<0.001	0.696	0.739

Table 3. Comparison of FACT-B scores before and after surgery between the two groups (points, $\bar{x} \pm s$)

Group	Number of cases	Before surgery	1 year postoperatively	t	P
Observation group	41	59.84±9.39	86.50±7.38	14.293	<0.001
Control group	32	60.17±10.22	78.29±8.95	7.545	<0.001
t	-	0.143	4.295	-	-
P	-	0.886	<0.001	-	-

**Figure 1.** FACT-B score of two groups before and after surgery. Note: A: Before surgery; B: 1 year postoperatively. Compared with the control group, * $P < 0.05$.

60.17±10.22) ($P < 0.05$), and patients in observation group had remarkably higher scores than those in control group ($P < 0.05$) (86.50±7.38 vs. 78.29±8.95) (Table 3 and Figure 1).

Comparison of postoperative complications

The incidence of postoperative complications in observation group was 14.64%, and that of the control group was 40.63%. The incidence in observation group was substantially lower than that in control group ($P < 0.05$) (Table 4).

while the two groups had insignificant difference in postoperative drainage duration and postoperative hospital stay (4.18±0.83 d vs. 4.26±0.91 d; 12.38±3.11 d vs. 12.64±3.52 d) ($P > 0.05$) (Table 2).

Comparison of FACT-B scores between the two groups before and after surgery

The comparison of preoperative FACT-B scores between the two groups was not statistically significant (59.84±9.39 vs. 60.17±10.22) ($P > 0.05$). The FACT-B score of both groups of patients one year after surgery was dramatically higher than that in prior-surgery (86.50±7.38 vs. 59.84±9.39; 78.29±8.95 vs.

Evaluation of postoperative breast aesthetics

The overall effective rate of postoperative breast aesthetic evaluation in observation group was 92.88%, and that of the control group was 71.88%. The aesthetic evaluation of the observation-group patients postoperatively was notably higher than that in control group ($P < 0.05$) (Table 5).

Comparison of prognosis

The postoperative progression-free survival of the two groups of patients was compared, and the difference was statistically insignificant ($\chi^2 = 0.460$, $P = 0.498$) (Figure 2).

Breast reconstruction after radical mastectomy

Table 4. Comparison of postoperative complications between the two groups [n (%)]

Group	Number of cases	Hemorrhage	Lymphedema	Flap necrosis	Subcutaneous effusion	Total
Observation group	41	2 (4.88)	2 (4.88)	0 (0.00)	2 (4.88)	6 (14.64)
Control group	32	5 (15.63)	2 (6.25)	3 (9.38)	3 (9.38)	13 (40.63)
χ^2	-	-	-	-	-	6.306
P	-	-	-	-	-	0.012

Table 5. Evaluation of postoperative breast aesthetics in two groups of patients [n (%)]

Group	Number of cases	Excellent	Good	Acceptable	Poor	Overall effective rate (%)
Observation group	41	23 (56.10)	8 (19.51)	7 (17.07)	3 (7.32)	92.68
Control group	32	11 (34.38)	7 (21.88)	5 (15.63)	9 (28.13)	71.88
χ^2	-	-	-	-	-	5.665
P	-	-	-	-	-	0.017

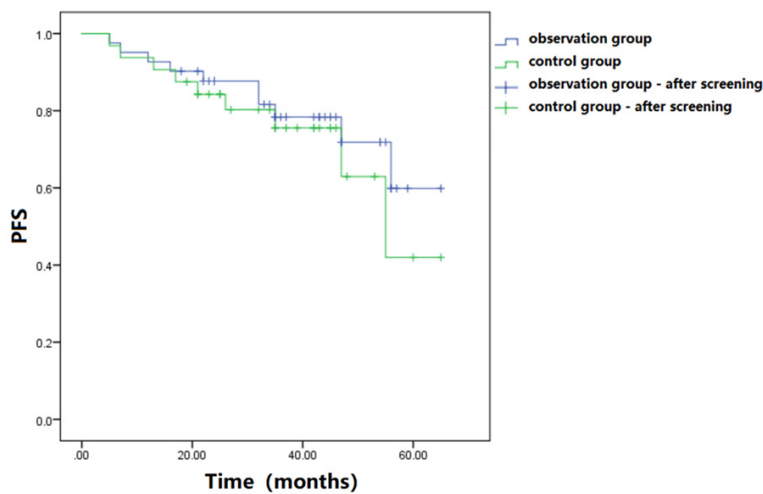


Figure 2. Analysis of progression-free survival between the two groups.

Discussion

The surgical operation of breast cancer, along with the progressive development and progress of modern surgery techniques, has been developing towards the goal of minimally invasive and aesthetic in recent years. For patients with early and mid-stage breast tumor, the traditional radical mastectomy has brought huge scars and loss of breast, which not only makes patients suffer from pain of comprehensive treatment such as surgery, but also need to bear additional psychological and social pressure [9].

The modified radical mastectomy of breast cancer is suitable for breast cancer patients with TNM stages I and II, with small lesions and non-metastasis. The improvement, which is based

on the traditional radical surgery, enables the pectoralis major, nipple and areola preserved to maintain the normal breast shape, thus reducing the surgical trauma to patients [12, 13]. However, patients may still have varying degrees of breast loss even with the modified radical mastectomy. Breast reconstruction is an important aesthetic plastic technique for postoperative treating of breast cancer. Through this method, the problems of postoperative breast tightening, depression, and breast asymmetry could be solved [14, 15]. However,

there is still a lack of unified standards in specific scheme of breast reconstruction surgery after radical mastectomy. In this study, we analyzed the effect and prognosis of combinative implantation of prosthesis and autologous-fat granule transplantation for breast reconstruction after radical mastectomy.

Augmentation mammoplasty with implanting prosthesis is the most commonly used procedure for breast atrophy. Followed by the specific needs of patients, the artificial prosthesis materials are placed in the breast to improve the symptoms of breast sagging and atrophy, and restore the position, volume, height and distance between the nipple and the sub-breast plica to a good state. Therefore, the aesthetics of the patient's breast, and the impact of breast atrophy on physical and mind of the

patient have been improved [16, 17]. However, the transition between the prosthesis and the chest wall is prone to be unnatural due to surgery or other reasons. In addition, due to the small amount of breast fat and thin skin tissue, the ideal status of the touch and shape of breast is difficult to be recovered. Autologous-fat transplantation is a common method of plastic surgery. Through this method, the fat granules of the patients themselves were transplanted to fill the breast and improve the breast aesthetic. The use of injection for fat granule transplantation can improve the minimally invasiveness of the operation without increasing the surgical wound, and also improve the surgery safety [19, 20]. At the same time, since the transplanted particles of autologous-fat are taken from the tissues of patients themselves, they have good biological characteristics and will not cause rejection, immune response or changes in endocrine environment, which are safe to use [21]. Through the combination of implantation, the prosthesis can be fully covered to make up for the defects of prosthesis transplantation. At the same time, the patient's breast shape is permanently corrected, which makes the breast feel more real and soft, and will not affect later breastfeeding and childbirth of patients [22]. The modified radical mastectomy enables the lower folds of the breast to be preserved, and the immediate breast reconstruction surgery can provide timely and correct breast repair. Therefore, patients do not need to bear breast loss, and the incidence of postoperative psychological disorders can be reduced. In addition, less surgical complications are conducive to the postoperative recovery of patients, so that the surgical treatment effect can be optimized and the disease-free survival rate of patients can be improved [23, 24].

The results of this study show that the FACT-B score of both groups of patients one year after surgery was dramatically higher than that before surgery, and patients in observation group had remarkably higher scores than those in control group; the aesthetic evaluation of the observation-group patients postoperatively was notably higher than that in control group. These results suggested that the combinative implantation of both prosthesis and

autologous-fat granule transplantation, compared with simple prosthesis implantation, can better improve postoperative aesthetic evaluation of patients, and contribute to the improvement of postoperative living quality of patients undergoing modified radical mastectomy, which are similar to the results reported by other scholars [25, 26]. The incidence of postoperative complications was remarkably lower in observation group than in control group, indicating that the combinative method can improve the aesthetic of breast, prevent the breast retraction, and has high surgical safety. In addition, the postoperative progression-free survival of the two groups of patients was compared with insignificant difference. It suggested the influence-free effect of the combined treatment on disease-free survival after surgery, and the therapeutic effect of modified radical mastectomy.

Due to the limited number of patients included in this study, there may be bias existed in the results obtained. In the follow-up research, the sample size should be expanded, and the follow-up time needs to be extended in order to obtain more valuable clinical research results.

In summary, the combinative implantation of both prosthesis and autologous-fat granule transplantation for breast reconstruction after radical mastectomy is simple in operation procedure, and has better aesthetic effect and safety. It satisfies the aesthetic demand of patients while having lesions resection, and does not affect the surgical effect of modified radical mastectomy, which is worthy of clinical promotion.

Disclosure of conflict of interest

None.

Address correspondence to: Shensong Liu, Department of Plastic Surgery, Hainan Ruihan Medical Cosmetology Hospital, No. 75 Binhai Avenue, Longhua District, Haikou 570204, Hainan, China. Tel: +86-18256966856; E-mail: liushensong@126.com

References

- [1] Kamali P, van Bommel A, Becherer B, Cooter R, Mureau MAM, Pusic A, Siesling S, van der

- Hulst RRJW, Lin SJ and Rakhorst H. Immediate breast reconstruction in the netherlands and the united states: a proof-of-concept to internationally compare quality of care using cancer registry data. *Plast Reconstr Surg* 2019; 144: 565e-574e.
- [2] Jonczyk MM, Jean J, Graham R and Chatterjee A. Surgical trends in breast cancer: a rise in novel operative treatment options over a 12 year analysis. *Breast Cancer Res Treat* 2019; 173: 267-274.
- [3] Qi X, Wang K, Sun D and Zhang L. Does choice of reconstruction type affect survival in patients with metastatic breast cancer? *J Surg Res* 2020; 247: 479-489.
- [4] Ho AY, Hu ZI, Mehrara BJ and Wilkins EG. Radiotherapy in the setting of breast reconstruction: types, techniques, and timing. *Lancet Oncol* 2017; 18: e742-e753.
- [5] Perea AH and Rosselli D. Immediate versus delayed breast reconstruction in breast cancer patients in colombia: a costutility analysis. *Bio-medica* 2018; 38: 363-378.
- [6] Chen W, Lv X, Xu X, Gao X and Wang B. Meta-analysis for psychological impact of breast reconstruction in patients with breast cancer. *Breast Cancer* 2018; 25: 464-469.
- [7] Maxwell J. Reconstruction in the setting of metastatic breast cancer: a challenging clinical question. *Ann Surg Oncol* 2018; 25: 3107-3108.
- [8] Homsy A, Rüegg E, Montandon D, Vlastos G, Modarressi A and Pittet B. Breast reconstruction: a century of controversies and progress. *Ann Plast Surg* 2018; 80: 457-463.
- [9] Steffen LE, Johnson A, Levine BJ, Mayer DK and Avis NE. Met and unmet expectations for breast reconstruction in early posttreatment breast cancer survivors. *Plast Surg Nurs* 2017; 37: 146-153.
- [10] Lagendijk M, van Egdom LSE, Richel C, van Leeuwen N, Verhoef C, Lingsma HF and Koppert LB. Patient reported outcome measures in breast cancer patients. *Eur J Surg Oncol* 2018; 44: 963-968.
- [11] Zahedi S, Colvill K, Lopez M and Phillips LG. Implications of demographics and socioeconomic factors in breast cancer reconstruction. *Ann Plast Surg* 2019; 83: 388-391.
- [12] Hauck T, Horch RE, Schmitz M and Arkudas A. Secondary breast reconstruction after mastectomy using the DIEP flap. *Surg Oncol* 2018; 27: 513.
- [13] Fanakidou I, Zyga S, Alikari V, Tsironi M, Stathoulis J and Theofilou P. Mental health, loneliness, and illness perception outcomes in quality of life among young breast cancer patients after mastectomy: the role of breast reconstruction. *Qual Life Res* 2018; 27: 539-543.
- [14] Bhat D, Heiman AJ, Talwar AA, Dunne M, Amanjee K and Ricci JA. Access to breast cancer treatment and reconstruction in rural populations: do women have a choice? *J Surg Res* 2020; 254: 223-231.
- [15] Lembrouck C, Nicolet G, Nguyen A and Tunon de Lara C. Current situation of breast reconstruction after breast cancer in Reunion Island. *Gynecol Obstet Fertil Senol* 2019; 47: 297-304.
- [16] Fu RH, Baser O, Li L, Kurlansky P, Means J and Rohde CH. The effect of the breast cancer provider discussion law on breast reconstruction rates in New York State. *Plast Reconstr Surg* 2019; 144: 560-568.
- [17] Lee GK and Sheckter CC. Breast reconstruction following breast cancer treatment-2018. *JAMA* 2018; 320: 1277-1278.
- [18] Dobke MK, Yee B, Mackert GA, Zhu WY and Blair SL. The influence of patient exposure to breast reconstruction approaches and education on patient choices in breast cancer treatment. *Ann Plast Surg* 2019; 83: 206-210.
- [19] Mazur S, Zołocińska A, Siennicka K, Janik-Kosacka K, Chrapusta A and Pojda Z. Safety of adipose-derived cell (stromal vascular fraction - SVF) augmentation for surgical breast reconstruction in cancer patients. *Adv Clin Exp Med* 2018; 27: 1085-1090.
- [20] Retrouvey H, Kerrebijn I, Metcalfe KA, O'Neill AC, McCreedy DR, Hofer SOP and Zhong T. Psychosocial functioning in women with early breast cancer treated with breast surgery with or without immediate breast reconstruction. *Ann Surg Oncol* 2019; 26: 2444-2451.
- [21] Santosa KB, Qi J, Kim HM, Hamill JB, Wilkins EG and Pusic AL. Long-term patient-reported outcomes in postmastectomy breast reconstruction. *JAMA* 2018; 153: 891-899.
- [22] Tsuji W, Valentin JE, Marra KG, Donnenberg AD, Donnenberg VS and Rubin JP. An animal model of local breast cancer recurrence in the setting of autologous fat grafting for breast reconstruction. *Stem Cells Transl Med* 2018; 7: 125-134.
- [23] Browne JP, Jeevan R, Gulliver-Clarke C, Pereira J, Caddy CM and Meulen JHP. The association between complications and quality of life after mastectomy and breast reconstruction for breast cancer. *Cancer* 2017; 123: 3460-3467.
- [24] Sinaei F, Zendehdel K, Adili M, Ardestani A, Montazeri A and Mohagheghi MA. Association

- between breast reconstruction surgery and quality of life in iranian breast cancer patients. *Acta Med Iran* 2017; 55: 35-41.
- [25] Spartalis E, Tsilimigras DI, Charalampoudis P, Karachaliou GS, Moris D, Athanasiou A, Spartalis M, Bolkas V, Dimitroulis D and Nikiteas N. The “Yin and Yang” of platelet-rich plasma in breast reconstruction after mastectomy or lumpectomy for breast cancer. *Anticancer Res* 2017; 37: 6557-6562.
- [26] Hehr T, Baumann R, Budach W, Duma MN, Dunst J, Feyer P, Fietkau R, Haase W, Harms W, Krug D, Piroth MD, Sedlmayer F, Souchon R, Wenz F and Sauer R; Breast Cancer Expert Panel of the German Society of Radiation Oncology (DEGRO). Radiotherapy after skin-sparing mastectomy with immediate breast reconstruction in intermediate-risk breast cancer: Indication and technical considerations. *Strahlenther Onkol* 2019; 195: 949-963.