

Safety of Lipofilling in BRCA Mutated Breast Cancer Patients

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Abstract

Introduction: In the last years the use of autologous fat grafting (lipofilling) has become a widely used procedure in breast reconstruction after surgery for breast cancer but experimental and clinical studies reported conflicting results about the risk of local recurrence. In fact adipocyte, preadipocyte and progenitor cell can stimulate angiogenesis and cell growth. Among breast cancer population the BRCA carriers are about 5-10% but have higher risk of relapse. We investigated the safety of lipofilling in this subgroup.

Materials and methods: We performed a monocentric retrospective review of clinical data of all women BRCA1-2 mutated underwent surgery for primary breast cancer from March 2011 to June 2017. We then selected those patients (pts) who underwent reconstruction with lipofilling. Following we analyzed pts and tumour characteristics, treatment administered, number of lipofilling, BRCA mutation type and tumour relapse.

Discussion: Our research identified 12 cases. The median age was 48 (range 34-61). Every cancer was invasive, 50% were triple negative, 25% overexpressed human epidermal growth factor receptor-2 (Her2). The pathological stages were I (42%) and II (58%). Every patient received chemotherapy, 66% radiotherapy, 50% (pts who had estrogen receptor positive cancer) the hormonal one and the 25% (those overexpressed Her2) trastuzumab. The median follow up from primary surgery was quite long: 60 months (range 20-93) whereas from lipofilling was 27 (range 10-64). The median number of lipofilling was 3 (range 1-6). 50% had a BRCA1 mutation, 42% a BRCA2 and 8% a variant of uncertain significance in BRCA2. We reported 3 cancer related events: two local relapse (one contralateral) and one systemic.

Conclusion: To our knowledge this is the first study to investigate the safety of lipofilling in BRCA carriers. Given the small sample size and the data prematurity we can only suppose that this technique can be possible in this subtype of patients too.

Keywords: Breast cancer; Lipofilling; BRCA

Introduction

Autologous fat transfer or lipofilling is a technique known since the first years of twenty century and widely used to improve the aesthetic results after breast surgery both for benign and malignant lesions [1,2]. The possible indications are various and include the correction of segmental surgery, mastectomy, radiotherapy deformity, nipple reconstruction, micromastia, Poland syndrome [3]. This procedure consists

of fat harvesting through lipoaspiration of abdomen, thigh, flanks or knee, purification, centrifugation and the transfer around required area [4]. Nowadays there is not an international agreement about the use of lipofilling following surgery for breast cancer, because of the lack of solid data regarding its safety [2,5,6]. In fact the majority of conducted trials had investigated lipofilling complication and esthetic results [2,4]. Furthermore some *in vitro* and animals studies have hypothesized a possible cancer promoting role of adipose

tissue-derived progenitor and differentiated cells released by autologous fat transferred [7,8]. Generally patients affected by breast cancer have a risk of recurrence, even though the exposition to any effective treatments known: surgery, radiotherapy, chemoimmunotherapy and or monotherapy [9]. The risk is different according to the tumor biology and cancer features [10]. Pts harboring germline mutation in BRCA 1 and 2 had an increased lifetime risk of developing early-onset and bilateral breast cancer [11,12]. Given this, the application of autologous fat transfer in BRCA mutation carriers required particular attention. For this reason, we had investigated the safety of lipofilling in this pts treated in our institution.

Materials and Methods

We performed a retrospective study collecting data of all women harbouring BRCA1-2 mutations who underwent surgery and lipofilling for invasive breast cancer in our institution from March 2011 to June 2017. Pts who developed breast cancer harbouring BRCA mutation of uncertain significance (vus) were included too. Combined data for mastectomy and segmental surgery were reported. We included in the study only invasive breast cancer and referred the presence or not of *in situ* carcinoma as appeared in the histological report. We analyzed patients and tumour characteristics, type of surgery, treatment administered, timing from oncologic surgery to lipofilling, number of lipofilling, BRCA mutation type, tumour relapse and radiological follow up characteristics. The exclusion criteria were hereditary cancer syndrome associated with other genes, other concomitant cancers, prophylactic bilateral mastectomy without previous breast cancer diagnosis and lack of follow up. We did not study the absorption rate. Given the high recurrence risk of these patients, to detect early breast relapse we set up an intensive follow up program, consisting on an annual thoracic radiography and abdomen ultrasonography, breast ultrasound alternated to mammography and breast magnetic resonance imaging.

Results

Our research identified 12 cases. The median age was 47 years (range 32-65). Clinical and pathological characteristics are reported in table 1. Half of patients had triple negative cancer and the other half had an estrogen receptor positive tumor, among these 3 patients (25%) overexpressed receptor tyrosine-protein kinase *erbB-2* (Her2). All patients had early stage breast cancers, including stage I (5 pts) and stage II (7). Carcinoma *in situ* was reported in all histological exam. 5 pts (42%) received a conservative surgery immediately, the other 7 (58%) a mastectomy. Half pts had a BRCA1 mutation, 5 (42%) a BRCA2 and 1 (8%) a vus in BRCA2. All patients underwent primary surgery and received diagnosis of BRCA mutation after those, 2 pts (16%) underwent prophylactic contralateral mastectomy and 6 (50%) a prophylactic oophorectomy (4 BRCA1 mutation carriers and 2 BRCA2).

All pts received adjuvant chemotherapy, and those with estrogen receptor positive breast cancer received the hormonal treatment with tamoxifen and LHRH analogue where as Her2 positive the entire treatment with trastuzumab. 8 pts (66%), those who underwent conservative surgery and those with node positive at histological exam, received radiation therapy. The median follow up from primary surgery was quite long: 60 months (range 20-93) whereas from the first lipofilling was 27 months (range 10-64). Median time between surgery and lipofilling was 16 months (range 9-78) and the median number of lipofilling was 3 (range 1-6).

Three pts experienced disease recurrence after lipofilling: in one case was a contralateral ductal *in situ* breast cancer, in another an invasive carcinoma and the latter was systemic recurrence. All these patients have been previously treated with hormonal, chemo and radiotherapy.

As complications, we collected one liponecrosis and five cysts, no local infection or seroma.

Table 1: Patient characteristics. L: lipofilling, S: conservative surgery, M: mastectomy, D: lymphadenectomy

Pz	Stage	N	Re	PgR	Ki67	Multicentric Yes/no	Mutation type	Type of surgery	Date of surgery	n°L	Relapse After L	Date of first L
1	II	+	+	+	20	no	BRCA1	M+D	2011	3	no	2012
2	I, II	-	+	+	20	yes	BRCA2	Mb+D	2014	4	no	2015
3	I	-	-	-	80	no	BRCA1	S, D	2010	2	no	2015
4	II	+	-	-	95	no	BRCA1	S,D	2009	3	no	2016
5	I	-	-	-	90	no	BRCA1	S	2010	2	no	2015
6	I	-	-	-	80	no	BRCA1	S,S,M	2000, 2005, 2013	4	no	2015
7	II	+	+	+	20 30	yes	BRCA2	M,D	2011	1	yes	2014
8	II	+	+	+	33	no	BRCA2	M,D	2013	6	no	2014
9	I	-	-	-	70	no	BRCA1	S,S,M	2002, 2015	3	yes	2016
10	II	-	+	+	80	yes	BRCA2	S,D	2012	1	no	2013
11	I	-	-	-	30	no	BRCA2	M	2009	6	no	2011
12	II	+	+	+	40	no	BRCA2	S,D	2015	1	no	2016

Discussion

Breast cancer is the most common tumor in female with about 250,000 new cases of invasive cancer diagnosed annually in United States of America [13]. Theoretically patients underwent radical surgery are free of disease and the risk of recurrence derives from the biology of cancer removed. Unfortunately some *in vitro* and animals studies suggested an increased locoregional recurrence risk associated with lipofilling [10]. In fact although fat is the ideal filler, autologous and biocompatible, it is also a dynamic tissue composed by many components (fibroblasts, endothelial cells, stem cells, adipocytes and pre-adipocytes) with secretive and regenerative property due to the presence of adipose-derived stem cells [14,15]. In ischemic situation this tissue can secrete vascular endothelial growth factor, hepatocyte growth factor and transforming growth factor β , stimulating angiogenesis and tissue regeneration [16,17]. Due to this property, Rigotti G et al. [18] suggested a possible use of autologous fat transfer in the treatment of degenerative chronic lesions induced by radiotherapy. However for the same reason a possible link between fat transfer and cancer developing has been hypothesized and investigated. In *in vitro* studies adipocytes stimulated through endocrine, paracrine and autocrine mechanisms results in breast cancer [10] but this data has not been confirmed with *in vivo* trials. In the literature only one case of late osteosarcoma was reported [19]. In 2011 Petit JY et al. [5] described the results of a retrospective multicenter study enrolling 646 pts underwent surgery and lipofilling for breast cancer. In this study a higher risk of local relapse in patients with *in situ* carcinoma than those with invasive one was found, raising an important alert in using this technique in these pts. However the majority of them had received only intraoperative radiotherapy after conservative surgery. In contrast other studies supported the safety of lipofilling [7,10,20-22], although a possible role of hormonal therapy in fostering a microenvironment favorable for cancer was suggested [23,24]. On the contrary, Narod SA et al. [25] reported a reduction in contralateral breast cancers with the use of tamoxifen. In our study the hormonal therapy was represented only by tamoxifen and LHRH analogue and concerns the 50% of our pts. Also the oophorectomy seems to be related to a reduction of risk of secondary breast cancer in BRCA1 mutants [26] and a 50% of our pts underwent prophylactic oophorectomy. Therefore, on one hand, we could suppose to have a low recurrence rate but every our pts had *in situ* component in their histological reports, consequently, as Petit suggested, we could expect a higher recurrence rate, but it is not occurred. We in fact reported three disease relapse. One case concerns a ductal *in situ* breast cancer that difficulty can be correlated to lipofilling performed on the contralateral breast; in another case we described the development of bone metastasis after one lipofilling, too early to consider a possible link to these events. In the last case was reported an invasive carcinoma presented after three

autologous fat transferring but the cancer characteristics are the same of primary tumor diagnosed so we could not exclude particular aggressive cancer biology. Therefore although three recurrences have been reported, only in one a possible link with reconstructive procedure could be hypothesized. Theoretically, the number of lipofilling administered should have a role in the relapse; in our report the median lipofilling administered was 3 that is a limited number. We also recognize that the timing is crucial, because the microenvironment changes during the time. In fact if lipofilling is performed at the time of surgery the fat transferred can reactive the acute inflammatory cytokines influencing the adipocytes' secretion, but if it is performed later the original tumor bed might be fibrotic and the hypoxia can modify the adipokine secreted [27]. We performed lipofilling after median 16 months from primary surgery (range 9-78), quite early in comparison with other institutional experiences, but we did not find a higher recurrence rate.

Our study has some limitations. The most important is the small sample size, such that we cannot provide a definitive proof regarding the safety of lipofilling in this population but we can make only some hypotheses. In fact although the huge number of diagnosis of invasive breast cancer the number of BRCA mutation carriers results in 5-10% of the population. So it is very difficult to find a huge number of pts which required characteristics. Furthermore in our institution the use of autologous fat transfer has been introduced only in the last seven years. Therefore our data collection is limited. Our data are also premature if we consider that in BRCA mutated population the risk of recurrence remains high also after 6-8 years from initial diagnosis. In our study the follow up was quite short with a median of 60 months. We are also aware that it is a retrospective, not randomized study. However to know whether autologous fat transfer can be associated with high risk of recurrence is very important item, above all in pts harboring BRCA mutations because the risk of ipsilateral and second or bilateral cancer are higher than in sporadic groups and this risk remains high also after many years from the diagnosis [13,15]. The lifetime breast cancer risk is, in fact, 57% for BRCA1 and 49% for BRCA2 mutant [13-15]. Indeed we think that particular attention is required with this category of pts that often are young and very interested in the aesthetic results. In our knowledge this is the first trial investigated this important item, some other available data derived from subgroup analysis of other retrospective controlled study conducted to study the safety of lipofilling in breast cancer patients.

Conclusions

BRCA mutation carriers had an aggressive disease with a higher risk to develop second tumor. Given the greater worldwide used of lipofilling, its application in this population is an interesting item and required a particular attention and further investigations. Our results are interesting but premature given the small sample size and the short follow up. We will continue to collect the data.

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