

Early or late recurrences of breast carcinoma are to be researched in relation to fat grafting

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Local relapse after mastectomy is sporadic for early breast cancer (stage 1 or 2) adequately treated, excepting some subtypes. The highest rates of local relapse occur in the first years. Loco-regional recurrences occurred within 2 years from primary surgery in 50-60% of patients and in 80-90% within 5 years.¹⁻³ When lipofilling is immediately performed after cancer surgery, the development of early recurrences is already expected according to cancer profile and the relationship with the fat injections will be complex to be demonstrated through retrospective studies and with short periods of follow-up. On the contrary the unusual growth, if present, of the number of loco-regional recurrences at long-term or recurrences following delayed fat injections should be better considered as an alert.⁴ Two case reports published in 2014 are paradigmatic of this dual behavior of the biology of recurring breast cancer.^{5,6} I found very interesting the presentation of local recurrences after bilateral mastectomy for invasive ductal carcinoma and lipofilling.⁵ We would lay stress on the time intervals between mastectomy (2006), two sets of lipofilling (2011-2012) and the skin recurrence after 10 months (2013). The histological analysis of the mastectomy scar is also paradigmatic showing extensive and multifocal tumor recurrence associated with subcutaneous remnants of fat necrosis, in particular oil cysts. The primary tumour is described as ductal invasive carcinoma, grade 2, in a breast related cancer antigen type 2 patient. No information was displayed on staging, nodal status, estrogen/herceptin receptor status that is known to affect the risk of cancer recurrence. Chaput *et al.*^{6,7} described a different pathological pattern of local recurrence following lipofilling after mastectomy: tumour cells in bundles along the tunnels created by autologous fat grafting. Extension to the sternum was also reported and supposed to be related either with dissemination through the cannula or with metastatic progression of the tumour. This aggressive, invasive carcinoma recurrence occurred 4 months after fat injections and two years after mastecto-

my and axillary dissection. Unfortunately, the biological characteristics of the invasive carcinoma were not reported and the report of a single case remains anecdotal. Nevertheless, the case history suggests a discussion on the timing between transfer of fat and adult stem cells and growth of a recurrent or new tumour. Based on cancer biology, we should assume that the local relapse was already present in a subclinical onset, before fat grafting, or not investigated by imaging in the previous months. The smallest detectable size of breast cancers (in optimal conditions) is 2 mm by mammography.⁸ Most of them have minimal doubling time of 50-200 days. Therefore, a cluster of tumour cells may take years to become large enough to be detected.^{9,10} The fat tunnels could have facilitated more dissemination than multiplication of pre-existing tumour cells. On the other hand, the hypothesis of a direct carcinogenesis in such a short period of 4 months is less plausible even if angiogenic cytokines and stem cells can supply cancer proliferation *in vitro* and *in vivo*.¹¹⁻¹⁵ Nevertheless, the cases of Smit *et al.*⁵ and Chaput *et al.*⁷ show common aspects, such as invasive carcinoma, recurrence after modified radical mastectomy and radiotherapy, mastectomy scar at site of either extensive fat grafting or recurrence origin, long free-disease times from primary surgery to lipofilling (5 and 2 years respectively). Based on the local relapse histology (*i.e.*, signs of fat grafting in the tumour specimen) and timing (*i.e.*, 7 years after primary surgery and two from the first lipofilling), the case of Smit *et al.*⁵ seems to be more suggestive for the hypothesis of a new fat-linked tumour cell growth.

According to our institutional experience,¹⁶ a retrospective series of 60 breast cancer patients (55 with invasive carcinoma), with 12 years of oncological follow-up, showed features analogous to the cited case reports. Although there are some limitations mentioned in the inherent discussions, our study did not report higher risks than those usually expected after total mastectomy. The intervals from fat injection to recurrence (found in two patients) were nearly 2 and 6 years; they are much longer than the 10 and 4 months respectively reported by Smit and Chaput.^{5,7} The cumulative risk of local recurrence after lipofilling were respectively 7.25% (95% confidence interval [CI], 0-15.4%) for loco-regional recurrences and 7.6% (95% CI, 0.2-15%) for distant metastases.^{4,16} Fat grafting was meanly performed 56.5 months after mastectomy. Overall 12-year incidence of local relapse was almost 5%: 1.6% before and 3.3% after lipofilling. It occurred only in patients with stage 2 and

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none with stage I. It stated a rate of local recurrence per year per 100 patients that might be oncologically safe: 0.43 compared to 0.36 of the observation period from mastectomy to lipofilling; the same rate was 1.04 when only Stage 2 cases were considered. After reading both these reports in literature, we have revised the histology of our post-mastectomy local recurrence after lipofilling in order to find any peculiar pattern. Histology only describes dermo-hypodermal localization of tumour cells without signs related to prior fat grafting.

This discussion may be useful to the future researchers. We should start to debate about early and late local recurrences in the presence of adipose-derived stem cells or adipose-cell and stromal microenvironments,¹⁷⁻¹⁹ and also to study the behavior of different molecular patterns associated with fat injections. Ribelles *et al.*²⁰ analyzed stage 1-3 breast cancer recurrences and found: i) slow risk increase in Luminal A, with peak after 3 years and then steady; ii) risk increase in the first 5 years in Luminal B; iii) a peak nearly 20 months after surgery in Her 2, with a greater risk in Ki-67=14% (a second peak can occur at 72 months); iv) low proliferation rate in triple negative tumours, except of those with Ki-67=14% that shows the peak at nearly 18 months. Nevertheless, the same authors assume that proliferation pathway can play a key role in the growth of early recurrence after surgery regardless of the intrinsic subtype involved. We should start to distinguish a fast progression of subclinical tumors in presence of vascular growth factors and stem cells from the hormonal activity of grafted fat that can conceivably induce a late carcinogenesis. Furthermore, mature adipocytes can alter the epithelial cell phenotype and produce a more motile cell type increasing

the risk of breast cancer.²¹⁻²⁴ The current literature may not solve the uncertainty still present about the risks of loco-regional relapse following lipofilling. Most of these studies enrolled and gathered groups of mastectomy and quadrantectomy patients after conserving surgery with different radiation protocols (standard, ELIOT, none), and patients at low risk with high-risk for local relapse. Most recent studies have focused on delayed lipofilling and monitored recurrences after five years from the event, but they predominantly concern the effect after conserving surgery. We have preferred not to debate it in this short paper.^{25,26} Local recurrence after mastectomy should be studied aside from quadrantectomy or lumpectomy, in particular if the primary aim is to evaluate risk of fat injections in the residual breast. Furthermore, as reported by Arriagada *et al.*²¹ the risk of local recurrences before and after 5 years is significantly different in mastectomy compared to conserving surgery ($P=0.0001$). In our study that included 55 early breast cancers, and the local relapse occurring in high-grade invasive carcinoma, the loco-regional risk still remains within the safe limits recognized by the oncological standards. Our favorable outcome concerns delayed fat grafting in women with early breast cancer, invasive carcinoma, and mastectomy, followed for 7 years after lipofilling. In 2019 Krastev *et al.* have published a comparative study reporting no significant differences in the locoregional recurrence rates between autologous fat grafting and control groups observed retrospectively for 5 years of follow-up after fat grafting; incidence rates of 0.53% and 0.83% per year respectively.²⁷ Krastev *et al.* also analyze the local recurrence after fat grafting in conservative treatment, 139 of 287 breast cancer patients and the findings are favorable at long term. Nevertheless, the question about the sufficient length of observational time is not yet solved. The recurrence dynamics changes with the molecular patterns and with patient adiposity. We should expect early recurrences if related to adipose-derived stem cells or late recurrences if related to adipose-cell and stromal microenvironments respectively.²⁸ All these findings suggest that lipofilling is not associated with increased risk for cancer relapse within 5 five years from the fat grafting but the current literature has not yet solved the uncertainty that concerns the possible dynamics of local recurrences that could start following fat grafting in the breast. Clinical evidence concerning latent late recurrences related to fat is still lacking. Sporadic reports of local recurrence do not add new insights to the issue but testify to the diffi-

cult management of women affected by breast cancer using plastic procedures.

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