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Australia and New Zealand Horizon Scanning Network

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TERRITORY GOVERNMENTS OF AUSTRALIA
AND THE GOVERNMENT OF NEW ZEALAND

Horizon Scanning Technology Prioritising Summary

Autologous Fat Injection for Breast Reconstruction

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**Australian
Safety
and Efficacy
Register
of New
Interventional
Procedures -
Surgical**



**Royal Australasian
College of Surgeons**

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PRIORITISING SUMMARY

REGISTER ID S000085

NAME OF TECHNOLOGY AUTOLOGOUS FAT INJECTION FOR BREAST RECONSTRUCTION

PURPOSE AND TARGET GROUP PATIENTS REQUIRING BREAST RECONSTRUCTION FOLLOWING BREAST CANCER TREATMENT

STAGE OF DEVELOPMENT (IN AUSTRALIA)

- | | |
|---|---|
| <input checked="" type="checkbox"/> Yet to emerge | <input type="checkbox"/> Established |
| <input type="checkbox"/> Experimental | <input type="checkbox"/> Established <i>but</i> changed indication or modification of technique |
| <input type="checkbox"/> Investigational | <input type="checkbox"/> Should be taken out of use |
| <input type="checkbox"/> Nearly established | |

AUSTRALIAN THERAPEUTIC GOODS ADMINISTRATION APPROVAL

- Yes
 No
 Not applicable

INTERNATIONAL UTILISATION

COUNTRY	LEVEL OF USE		
	Trials Underway or Completed	Limited Use	Widely Diffused
France	✓		
Italy	✓		
United States	✓		

IMPACT SUMMARY

Autologous fat injection may be used to assist with breast reconstruction following a mastectomy or to correct deficits from more conservative breast surgery. The technology utilises a purified form of the patient's own fat harvested from another region of the body.

BACKGROUND

Breast cancer treatment is a common reason for requiring breast reconstruction. Breast cancer surgery may take the form of a mastectomy (partial or complete removal of the breast) for women with in situ ductal carcinoma, or early or locally advanced invasive breast cancer (infiltrating ductal carcinoma). Occasionally mastectomy may also be used as a prophylactic treatment in high-risk women, such as those with breast cancer (BRCA) gene mutations or in situ lobular carcinoma (Djohan et al 2008). Breast conservation therapy, where a portion of the breast is preserved, is a possible alternative to mastectomy in some patients. Both surgical techniques may be used in conjunction with radiotherapy, the side effects of which can include radiation damage to the surrounding healthy tissue (Rigotti et al 2007). Breast reconstruction can be performed following a mastectomy to correct the resulting physical disfigurement and assist in restoring the patient's emotional well-being (Djohan et al 2008). Reconstruction may also be used following breast conservation therapy if asymmetry or contour deformities are present, especially following adjuvant radiation therapy (Churgin et al 2008).

Traditional techniques for breast reconstruction include the implantation of silicone gel or saline filled prostheses or the use of the patient's own tissue (autologous reconstruction). Autologous breast reconstruction in the form of a tissue graft involves the transfer of abdominal, back or gluteal tissue (fat, skin and sometimes muscle) to the breast while ensuring adequate blood supply (Djohan et al 2008). Initially, a temporary tissue expander may be used to keep skin stretched before these more permanent techniques are undertaken. Complications from implants can include infection, rupture, extrusion through the skin and contraction of the fibrous capsule that forms around the implant (Djohan et al 2008). Autologous tissue transfer eliminates the use of foreign material; however drawbacks can include the additional scarring at the harvest site and complications such as abdominal herniation, if muscle is removed, or loss of blood supply to the harvested tissue (BASO 2007).

Another possible technique for breast reconstruction is the transfer of autologous fat via injection rather than as a tissue graft. The first breast augmentations using autologous fat injection were reported in 1987 (Bircoll and Novack 1987). Since then, the technique has only been used sporadically for breast augmentation, with controversy surrounding the procedure due to the potential risk that the injected fat could form lumps that may mimic breast cancer (ASPRS 1987). Recently, several studies have applied the technique to breast reconstruction rather than cosmetic breast augmentation. In such studies, autologous fat aspirated from the abdomen, hips, thighs, buttocks or back is used to correct contour deformities in breasts reconstructed by prosthetic or autologous methods, or operated on with a breast conserving technique (Spear et al 2005; Missana et al 2007). The procedure may be repeated if necessary. An extension of the autologous fat injection method is to use the adipose-derived adult stem cells present in the purified lipoaspirate to treat breast and chest wall tissue displaying severe radiotherapy side effects (Rigotti et al 2007).

CLINICAL NEED AND BURDEN OF DISEASE

The incidence of breast cancer in Australia has increased over the last two decades from 5,355 in 1982 to 12,235 in 2004, with the age-standardised incidence rate in women in 2004 being 112.8 per 100,000. Breast cancer accounted for 12.4% of all cancers diagnosed in 2004 and 27.9% of all cancers diagnosed in women. In 2005 the disease was responsible for 2736 deaths, and for 16.0% of all female deaths from cancer (AIHW 2007). From 2000 to 2001 the total healthcare expenditure on breast cancer was A\$241 million, with A\$72 million of this being spent on hospital-admitted patients (AIHW 2006). In the 2003–2004 period, there were 1762 breast reconstruction procedures. The most common reconstruction method involved the use of skin flaps (50% of procedures) (AIHW 2008).

DIFFUSION

The procedure of autologous fat or adipose-derived stem cell injection to assist in breast reconstruction is at an early stage of development, with trials having been conducted in France, Italy and the United States (Spear et al 2005; Missana et al 2007; Rigotti et al 2007). Fat injection for cosmetic breast augmentation has also been trialled in these countries, as well as Japan, Singapore, Spain, Switzerland and China.

The Food and Drug Administration (FDA) in the United States has approved the use of devices to harvest, filter and transfer autologous cells, including fat cells and adipose-derived stem cells. One such device is the autotransfusion apparatus Cytori Celution™ Cell Concentration Device (Cytori Therapeutics, Inc., San Diego, CA, USA), which received 510(k) regulatory clearance from the FDA in 2006 (FDA 2006). In Australia, the Therapeutic Goods Administration (TGA) Australian Register of Therapeutic Goods (ARTG) has also approved the use of several autotransfusion apparatus; however, these systems tend to be used for blood transfusion rather than fat injection procedures (TGA 2008).

COMPARATORS

It is difficult to define a direct comparator for autologous fat injection following a mastectomy because it tends to be used in conjunction with other reconstruction methods, rather than as the sole procedure. Following mastectomy, autologous fat injection may be used to correct contour deformities in breasts reconstructed by silicone or saline implants or by autologous methods. Autologous flap procedures include those sourced from the abdomen (for example, the transverse rectus abdominis muscle flap (TRAM) or the deep inferior epigastric perforator free flap (DIEP)), the buttocks (for example, the superior or inferior gluteal artery perforator flap (SGAP or IGAP)) or the back (for example, the latissimus dorsi flap) (Djohan et al 2008).

When breast conservation therapy has been performed, autologous fat injection can potentially be used as the sole treatment to correct contour deformities. Other reconstruction options when breast conservation therapy has been performed include

local tissue rearrangement, reduction mammoplasty (with contralateral breast reduction) and flap reconstruction (Churgin et al 2008).

SAFETY AND EFFECTIVENESS ISSUES

Fat injection

Study description

Two case series studies have been published which applied the technique of autologous fat injection to reconstructive breast surgery to address contour deformities. A retrospective study by Spear et al (2005) identified 37 patients (43 breasts, 47 discrete treatments) who underwent autologous fat injection between 1993 and 2003. The breasts had already been reconstructed with implants (25/43 breasts), TRAM flaps (17/43 breasts) or both (1/43 breasts). Fat was harvested using a lipoaspiration system, washed with saline until the blood products were removed and injected into depressions primarily around the periphery of the reconstructed breasts. The injections were performed with multiple passes through separate tunnels. The average fat injected per procedure was 116 cc (range 30 to 260). The mean length of follow-up was 15 months (range 3 weeks to 7 years) (Spear et al 2005).

A later study by Missana et al (2007) also used autologous fat injection in conjunction with other reconstructive techniques. From 2001 to 2005, 69 patients (74 breasts) (mean patient age 51 years, range 21 to 73) underwent fat injection for the following reasons: to correct defects from conservative treatment (9/74); to resurface following reconstruction with an implant (25/74); to fill defects remaining after reconstruction with a latissimus dorsi flap and implant (29/74); or to resurface following a latissimus dorsi flap reconstruction (5/74) or a TRAM flap reconstruction (6/74). Thirty patients had undergone radiotherapy prior to reconstruction. In this study, fat was harvested from abdominal subcutaneous tissues or an alternative site. The sampling syringes were sealed and centrifuged to remove oil and blood. The fat injections into the reconstructed breast were crossed over one another in layers (three-dimensional lattices), the skin was sutured and the site was massaged to achieve even distribution of the fat. The mean duration of the procedure was 115 minutes (range 60 to 165) and the mean volume of fat injected was 107.0 ml for the prosthesis patients, 147.2 ml for the latissimus dorsi and prosthesis patients, 142.5 ml for the latissimus dorsi only patients, 142.1 ml for the TRAM patients, and 75.0 ml for the conservatively treated patients. Mean follow up was 11.7 months (range 1 month to 3.2 years) (Missana et al 2007).

Safety

The study by Spear et al (2005) reported four complications in 47 treatments (8.5%) during the mean follow-up period of 15 months. One patient (with bilateral treatment) experienced cellulitis of the left breast after two weeks, which was resolved with antibiotics without implant removal. A further three patients had small superficial lumps in the area of fat injection (7.0% of treated breasts). Removal of these in two patients

revealed them to be liponecrotic cysts. No implant ruptures occurred as a result of fat injection (Spear et al 2005).

Missana et al (2007) reported no immediate complications, such as hematoma, infection, cellulitis or thromboembolism. Complications during the mean follow-up period of 11.7 months occurred in 6.8% (5/74) of treated breasts. Liponecrotic lesions occurred in one patient who underwent lipoinjection following an implant, and in four patients who underwent lipoinjection following latissimus dorsi flap reconstruction with an implant. No cases of microcalcifications suggestive of malignancy were observed on radiology (Missana et al 2007).

Efficacy:

In the study by Spear et al (2005), 8.1% (3/37) of patients required repeat fat injection procedures, while in the study by Missana et al (2007) 14.9% of breasts (11/74) required re-injection to obtain a satisfactory result (nine received one re-injection and two received two re-injections). Both studies measured postoperative improvement using an independent, blinded panel of physicians. Spears et al (2005) found that of 47 treatments (in 43 breasts), 10 (21%) showed substantial contour improvements, 30 (64%) showed minimal to moderate improvement and seven (15%) showed no improvement. Missana et al (2007) found that improvement was good to very good in 64 out of 74 breasts (86.5%) and moderate in the remaining 10 (13.5%). The moderate improvement in the 10 breasts was attributed to the insufficient quantity of adipose material that could be removed from these patients (Missana et al 2007).

Adipose-derived stem cell injection

Study description

Rigotti et al (2007) modified the autologous fat injection technique to assess both the presence of adipose-derived adult stem cells left in their natural scaffold in purified lipoaspirate and also the clinical effectiveness of transplanting the stem cell containing lipoaspirate to treat radiation side effects. The study commenced in 2002 and included patients suffering from progressive tissue lesions after radiation therapy for breast cancer. The results of the first 20 consecutive patients with severe symptoms (nine patients with Late Effects Normal Tissue Task Force – Subjective, Objective, Management, Analytic Scale (LENT-SOMA scale) grade 3) or irreversible functional damage (11 patients with LENT-SOMA scale grade 4) were reported. The mean patient age was 50.9 years (range 37 to 71). Among the 20 patients, the area damaged by radiation was the chest wall (post-mastectomy) without a prosthetic implant in eight, the chest wall (post-mastectomy) with a prosthetic implant in eight, the breast (post-quadrantectomy) in three and the supraclavicular region in one. Adipose tissue was extracted from the medial area of the knee, the abdominal region or the hip region. The lipoaspirate was purified and the stem cells were maintained in their natural three-dimensional scaffold. Following in vitro characterisation of the adipose-derived adult stem cells, the lipoaspirate was implanted in the affected area in single tunnels, planned using a computerised model. At each procedure, 60 cc to 80 cc of purified lipoaspirate was injected. The mean follow-up time was 30 months (range 18 to 33).

Safety

The safety of the injection procedure was not specifically reported by Rigotti et al (2007).

Efficacy

The number of injection procedures per patient ranged from one to six. Rigotti et al (2007) reported that generalised dramatic improvement of symptoms was observed in all but one of the 20 patients following lipoaspirate treatment (95% of cases), and LENT-SOMA scores improved significantly ($P < 0.00001$). Of the 11 patients with irreversible functional damage (LENT-SOMA grade 4), four patients progressed to grade 0 (no symptoms), five progressed to grade 1, one progressed to grade 2 and one had no improvement. In the nine patients with severe symptoms (LENT-SOMA grade 3), the fibrosis, atrophy and retraction improved, with five patients progressing to grade 0 and four progressing to grade 1. Overall, the procedure appeared to confer improvement in 10 of 11 (91%) patients with preoperative grade 4 LENT-SOMA and all nine (100%) patients who had preoperative grade 3 LENT-SOMA. Analysis of the structure of the treated areas showed progressive tissue regeneration over one year, including formation of new microcirculation, increased hydration and maturation of adipose tissue (Rigotti et al 2007).

COST IMPACT

There are no cost-effectiveness studies on the use of autologous fat injection for breast reconstruction.

ETHICAL, CULTURAL OR RELIGIOUS CONSIDERATIONS

Controversy remains as to whether autologous fat injection should be used for breast reconstruction or augmentation as it has the potential to affect subsequent mammography results and impede cancer diagnosis. No other issues were identified from the retrieved material.

OTHER ISSUES

Further breast reconstruction studies, which are yet to be published, combine the use of autologous fat cells to correct contour defects with the therapeutic use of autologous adipose-derived stem and regenerative cells for damaged tissue. One such study was conducted in Japan, with study data being presented at the 30th San Antonio Breast Cancer Symposium in December 2007 (Cytori Therapeutics 2007). In 21 women with tissue loss resulting from partial mastectomy, breasts were reconstructed with autologous liposuctioned fat that was combined and enhanced with autologous adipose-derived stem and regenerative cells. The procedure had a patient satisfaction level of 79% and there was a statistically significant improvement in average breast tissue thickness at one month following treatment and at final assessment (mean follow-up 7.7 months) compared to baseline. Cytori Therapeutics, Inc. is also initiating further studies to evaluate the effects of autologous fat cells and adipose-derived stem cells in treating both severe radiation damage and contour defects (Cytori Therapeutics 2007).

SUMMARY OF FINDINGS

There is a lack of high quality evidence on the technique of autologous fat injection for breast reconstruction. The technique has the potential to improve some contour defects; however, the results appear to be highly variable, with two case series finding that following autologous fat injection between 21% and 86.5% of patients showed substantial improvement at postoperative assessment. Patient satisfaction with the procedure was not reported. Longer-term follow-up is required to determine how much of the injected fat survives and how much is eventually reabsorbed by the body. There are also important safety issues with the procedure, particularly in association with the liponecrotic lumps which can form in the breast from the injected fat. Both case series reported this to occur in approximately 7% of cases, and there is concern that such lumps will impede future cancer detection. The therapeutic use of the adipose-derived stem cells present in the injected lipoaspirate is a novel, minimally-invasive approach to resolving severe radiotherapy side effects in breast and chest wall tissue. In the single included case series, the therapy improved or eliminated otherwise untreatable defects in 95% of cases. However, the long-term safety and efficacy of this procedure are yet to be established. Future studies are planned which will investigate the effect of combining the reconstructive aspect of fat injection to correct contour defects in the breast with the therapeutic effect of adipose-derived stem cell injection for treating radiation side effects.

HEALTHPACT ACTION

Based on the lack of evidence on the safety and efficacy of the technique of autologous fat injection in breast reconstruction, and the probability that high quality new research evidence will not be available in the near future, this procedure will be archived.

NUMBER OF STUDIES INCLUDED

Total number of studies 3
Level IV intervention evidence

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SOURCES OF FURTHER INFORMATION

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SEARCH CRITERIA TO BE USED

(fat OR lipoaspirate OR adipose)

AND

(injection OR transplant OR transplantation OR transfer)

AND

Breast