

Recent Studies & Advances in Breast Cancer

Chapter 1

Breast reconstruction – current practice and future directions

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Abstract

Rates of mastectomy are increasing internationally due to phenomena such as contralateral and bilateral prophylactic mastectomies and women eligible for breast conserving surgery opting for mastectomy. Breast reconstruction has been demonstrated to improve psychosocial and quality of life outcomes in this patient cohort, and has become the standard of care in the treatment of breast cancer. With an ever increasing emphasis being placed on this aspect of care, there have been significant advances within the field over recent decades. The development of skin and nipple sparing mastectomy has done much to enhance cosmetic outcomes. Refinement of breast implants to reduce complications and development of free autologous flaps have revolutionised patient outcomes. Results are still heavily influenced by adjuvant breast cancer therapies such as radiation and chemotherapy, and much has been accomplished in making breast reconstruction more compatible with these treatment modalities. However, breast reconstruction is still evolving and novel technologies such as tissue engineering hold promise for the development of superior techniques of breast reconstruction post-mastectomy.

1. Introduction

Breast cancer is the most commonly diagnosed cancer in females, with approximately 1.7 million women diagnosed and treated worldwide annually [1]. While significant progress has been made in the multimodality management of breast cancer, complete surgical resection with disease free margins remains the cornerstone of effective therapy. In order to achieve adequate locoregional control approximately 40% of patients will undergo a total mastectomy [2,3]. In recent years there has been an increase in the number of patients undergoing mastec

tomy; this is explained by an increase in prophylactic risk-reducing surgery in patients with cancer predisposing genetic mutations and increasing numbers of patients with breast cancer opting for contralateral prophylactic mastectomy (CPM) [4-10]. Furthermore, a trend has also been reported of women who are eligible for breast conserving surgery opting to undergo mastectomy [3,9,11,12]. For patients who undergo mastectomy, breast reconstruction is known to improve psychosocial and aesthetic outcomes [13]. Recent guidelines recommend that breast reconstruction should be discussed and offered as an option for the majority of women undergoing mastectomy [14,15]. Post-mastectomy breast reconstruction (PMBR) has thus been incorporated into the contemporary surgical treatment of breast cancer patients, resulting in increasing reconstruction rates as reported in audits of both the US and UK populations. Rates of breast reconstruction post-mastectomy are increasing by 5% per annum [16]. As a consequence of both the increasing number of mastectomies being performed and improved survival of breast cancer patients, surgical techniques have evolved in an effort to maximise aesthetic and quality-of-life outcomes. Refinement of the mastectomy technique itself has included the development of skin-sparing and nipple-sparing mastectomies which preserve the skin envelope +/- the nipple-areolar-complex (NAC). These procedures are increasingly performed for patients with breast cancer and those with genetic predisposition. Correspondingly, the range of reconstructive techniques on offer for patients undergoing PMBR is expanding due to the innovation of breast and plastic surgeons. Recent advances have seen the addition of novel autologous reconstructive approaches in addition to the expansion of indications for prosthetic reconstruction facilitated by the use of Acellular Dermal Matrices (ADM). Advances in the fields of tissue engineering and regenerative medicine hold enormous potential for novel reconstructive approaches and recent efforts have focused on stem cell-based regeneration of adipose tissue.

This chapter provides an overview of the current/contemporary approaches for post-mastectomy breast reconstruction and the challenges that must be overcome in the development of future novel reconstructive techniques.

2. Historical perspective / evolution of breast reconstructive techniques

The primary goal of surgery for breast cancer is to achieve local disease control. Historically this was achieved with extensive surgery in the form of the Halstead radical mastectomy, which achieved a 6% rate of local recurrence, albeit at the expense of significant associated physical and psychosocial morbidity [17]. The development of adjuvant therapies which effectively reduce both distant and loco-regional recurrence [18-20], and the recognition that tumour biology also impacts local control [21] have contributed to a paradigm shift towards increasingly conservative therapeutic surgical approaches [22]. Despite this, approximately 40% of women still require mastectomy to achieve locoregional control. Mastectomy is proven to have adverse psychosocial effects on breast cancer patients including anxiety, depression and

negative body image, all of which impact negatively on quality of life in a cohort of patients who are already dealing with cancer diagnosis, treatment and the fear of disease recurrence [23]. The practice of breast reconstruction has evolved to afford clearly defined psychosocial and aesthetic benefits for women undergoing mastectomy [23-25] and it is for this reason that PMBR has become an important component of multidisciplinary breast cancer care. The evolution in breast reconstructive approaches over time is outlined in figure 1.

The first post-mastectomy breast reconstruction was successfully carried out in 1895 by Vincent Czerny by transplanting a lipoma from the patient's flank to the chest wall, "the left breast was well formed, perhaps somewhat smaller than and firmer than the right but the disparity in any case was far less than with the usual mastectomy" [26]. The pectoral muscle was first used as a mound to reconstruct the breast in 1905 by Ombredanne [27]. In 1906, Tanzini was cited as the first to utilise a musculocutaneous flap for the purposes of breast reconstruction when he developed a pedicled flap of latissimus dorsi muscle and overlying skin paddle. However, as a result of Halsted's beliefs that breast reconstruction was a risk factor for disease recurrence, Tanzini's LD flap breast reconstruction technique was not utilised and forgotten [28]. Different forms of pedicled flaps were subsequently developed over the 20th century with limited success, mainly due to the requirement for multiple operations to complete the reconstructive process. These included use of the opposite breast as a donor site and a thoracoepigastric flap with prosthesis pioneered by German surgeons Hohler and Bohmert [29] (figure 1).

Autologous flap reconstructions were popularised with the reintroduction of the Latissimus Dorsi flap for breast reconstruction in 1977 by Schneider, Hill and Brown [30], and Muhlbauer and Olbrisch [31]. These were also used in conjunction with an implant as they often did not produce adequate breast volume alone. An extended LD flap (harvesting of the LD muscle and accompanying lumbar fat without the use of an implant [32] was developed with positive aesthetic outcomes; however, donor site morbidity was a significant problem with this procedure. The Transverse Rectus Abdominis (TRAM) flap was first described in 1982 which allowed for a more aesthetic donor site than that of the LD, leading it to become widely used as a method of breast reconstruction post-mastectomy.

Free microvascular tissue transfer was first described in 1973 for the primary closure of a compound leg injury, a development which broadened the horizons of breast reconstruction [33, 34]. Microvascular free flaps have increased in popularity in recent years, particularly in the case of immediate breast reconstruction and have been associated with lower rates of flap necrosis. Free TRAM and Deep Inferior Epigastric Artery Perforator (DIEP) flaps are the most commonly utilised free flaps for breast reconstruction, though other donor sites are also utilised including deep circumflex iliac artery flaps, lateral thigh (tensor fascia latae) flaps, superior and inferior gluteal musculocutaneous flaps, gracilis flaps and triceps flaps [29].

Perforator flaps were developed from the principles of free microvascular tissue transfer which have further minimised donor site morbidity associated with harvesting the musculocutaneous flap. Deep inferior epigastric perforator (DIEP), latissimus dorsi perforator and gluteal artery perforator (GAP) flaps have had successful outcomes [29]. The DIEP flap is the most commonly performed for breast reconstruction and relies on microdissection of the branches of the deep inferior epigastric vessels that perforate the rectus abdominis and its fascia. The internal mammary vessels are currently the most commonly used recipient vessels on the chest wall for microvascular anastomosis after transfer of the flap to the chest wall [35].

Prosthetic breast reconstruction began with the introduction of the silicone breast implant in 1963, which was originally performed as a delayed reconstruction but then became more commonly used in immediate reconstruction [28]. This trend changed in the 1980's when Radovan published on the use of immediate-delayed reconstruction using tissue expander implants in 1982 [36]. This was a popular breast reconstructive option as it was deemed to have superior outcomes in the case of postmastectomy radio therapy. Over time, modifications have been made to the shape, texture, site of ports and integrated valves of expander implants, lowering complication rates and increasing their effectiveness. Permanent implants and their design have also evolved over time with modifications being made to their shape, silicone shell thickness, gel viscosity and texture. When the safety of silicone implants was questioned, and they were eventually withdrawn from the market in 1992, there was an increased use of saline-filled implants which were shown to be superior with regard to implant rupture, capsular contracture, ease of revision surgery and cost [37]. However, they can be associated with a “rippling” effect which significantly reduces patient satisfaction and cosmetic outcome [38]. Textured implants, which have a rough external surface giving traction once implanted, are currently widely utilised as they have been shown to have lower rates of capsular contracture than smooth implants. Polyurethane-coated implants have also been used to prevent capsular contracture, which is effective until the breakdown of the polyurethane coating after years in situ [39]. The introduction of Acellular Dermal Matrices (ADMs) in 1994 has helped to overcome limitations of prosthetic breast reconstruction such as inadequate infra-mammary fold support, reduced expansion of the inferior pole and inadequate soft-tissue coverage of the implant [40]. It also allows for direct-to-implant reconstructions without the need for insertion of a tissue expander, speeding up the reconstructive process [41]. ADMs are soft tissue matrix grafts produced by a process of tissue decellularisation while leaving the extracellular matrix (ECM) intact. They were first used in breast implant reconstruction in 2005 [42] and later used in conjunction with tissue expander breast implants in 2007 [43].

The evolution in mastectomy technique has also influenced PMBR. The advent of the “skin sparing mastectomy”, first reported in 1991, has had a significant impact on the improvements seen in contemporary breast reconstruction techniques [44,45]. The skin envelope is

preserved with this technique as it involves the removal of only the nipple-areola complex and skin involved with or in close proximity to the tumour. Preserving the skin results in superior symmetry due to matching skin colour and texture. It also aids the surgeon in shaping the breast mound in reconstruction. Skin sparing mastectomy is suitable in most breast cancer patients, though it is contraindicated in inflammatory carcinoma, locally advanced breast cancers, and is relatively contraindicated in smokers. Necrosis of the mastectomy flaps must be avoided and in patients who are also undergoing placement of expanders, it is crucial to ensure complete coverage of the implant, either with a complete muscular pocket or an ADM. Despite the lack of a randomised controlled trial, SSM is as safe oncologically as simple mastectomy, with similar rates of local recurrence, as shown in a meta-analysis, in 2010, of 3739 patients (1104 SSM and 2635 non-skin sparing mastectomy) [46].

Nipple reconstruction has become an accepted part of the breast reconstruction process, with tattooing the reconstructed nipple areola being commonly carried out. Nipple sparing mastectomy, first described in 1962 [47], is also becoming popularised, obviating the need for this reconstructive step and improving aesthetic outcomes [28]. Preservation of the nipple-areolar complex (NAC) has been shown to be oncologically safe with no increased risk of breast cancer recurrence in women with sporadic breast cancer. There have been some concerns raised regarding its safety in BRCA gene mutation positive patients as this procedure requires a small amount of tissue to be left behind the NAC to maintain an adequate blood supply [48]. However, the procedure has been deemed oncologically safe by a meta-analysis of 5594 patients with a follow up of greater than 5 years [49]. Nipple sparing mastectomy is becoming more widely performed and has a central role in improving patient satisfaction outcomes [50].

3. Contemporary reconstructive approaches

There are two primary decisions involved when planning breast reconstruction in post-mastectomy patients; (a) Timing i.e. immediate vs. delayed reconstruction and (b) Type i.e. implant vs. autologous [51].

4. Timing of breast reconstruction

The rate of immediate breast reconstruction (IBR) has risen dramatically in the last two decades, with one study reporting a 78% increase from 1998 to 2008, an average of 5% per year [16]. IBR results in better aesthetic outcomes in those patients who do not require post-mastectomy radiation therapy (PMRT), superior psychosocial and patient satisfaction outcomes than delayed breast reconstruction (DBR). Breast reconstruction can also be achieved in fewer surgical procedures with IBR. IBR is oncologically safe, with no increased risk of locoregional disease recurrence or in the ability to detect recurrence [51]. The National Institute for Clinical Excellence (NICE) guidelines state that IBR should be offered to all suit-

able patients undergoing mastectomy, however there is a decreased likelihood of this in older patients, those of African-American race, patients who are married or from rural locations and those with increased comorbidities [52]. Despite the aesthetic advantages of IBR, its cosmetic outcomes are said to deteriorate over time independent of radiotherapy, type and volume of implant, patient age or mastectomy incision [53]. There are no clear indications with regard to timing or technique of PMRT administration in IBR, thus, capsular contracture is the most common limitation, with a rate of 40.4% in IBR compared to 17% in DBR. PMRT negatively influences outcomes of both implant and autologous reconstructions. The challenge lies in being able to predict the need for PMRT when deciding about reconstruction timing. Therefore, in cases where the need for PMRT is ambiguous, the patient should be offered an immediate-delayed or delayed procedure in order to ensure optimal aesthetic results [51].

4.1 Type of breast reconstruction

4.1.1 Prosthetic reconstruction

There has been a change in the trends of breast reconstruction most commonly carried out in recent years. Autologous methods of breast reconstruction were most popular early in the breast reconstruction era. However, this has been surpassed by the use of implant based reconstructions. This trend is also evident in those patients undergoing PMRT [54]. Breast reconstruction utilising implants can be carried out either as (a) single stage, direct to permanent implant (DTI) procedures or (b) two-stage procedure with the insertion of a tissue expander, which is inflated with saline over time and then replaced by a permanent implant. Several advantages such as shorter operation times, lack of a donor site and the associated morbidity, and quicker return to normal activities make this an attractive reconstructive option to both patients and surgeons. The FDA and WHO have recently confirmed an association between breast implants, particularly those with textured surfaces, and anaplastic large cell lymphoma (ALCL). This is a rare T-cell lymphoma requiring surgical management. It usually presents as a peri-prosthetic fluid collection 8-10 years after breast implant insertion. It is imperative that patients are counselled about the risk of breast implant associated anaplastic large cell lymphoma (BIA-ALCL) prior to breast reconstruction [55].

Direct to implant (DTI) reconstructions, carried out in one procedure were commonly associated with problems such as pectoralis muscle retraction, implant malposition and capsular contracture. More modern DTI procedures make use of Acellular Dermal Matrices (ADMs) which overcome these issues by fixing the pectoralis muscle and forming a complete pocket around the inferior pole of the implant in the required position. This also decreases the stress on the inferior skin envelope, resulting in lower rates of contracture [56]. Traditionally, DTI with total muscle coverage of the implant was only possible in small-breasted women as it was limited by the degree of expansion of the overlying pectoral muscles. This limitation

has also been overcome by ADMs as they obviate the need for total muscle coverage [57]. DTI reconstruction is suitable for women with small to moderate sized breasts who wish to remain a similar breast size (figure 2). Those patients who wish to be a significantly larger size should undergo a two-stage procedure with a tissue expander [56]. During their early use, there was concern that ADMs were associated with a higher risk of infections and complications such as seroma [58-61]. “Red breast syndrome” (RBS) was a phenomenon synonymous with ADM use, first described in 2010 [62,63]. It was described as a non-infectious erythema, appearing days to weeks after ADM implantation, localised to the areas of ADM placement, typically along the inferior pole of the breast [64]. However, more recent research has shown that there is no increase in complication rates [65-67]. It is postulated that the reason for this incongruity in data is due to the learning curve associated with the introduction of a new product or technique [56,68]. The cost of ADMs are offset by completing the reconstructive process in a single procedure [56].

For those patients for whom there is a possible need for post-mastectomy radiation therapy (PMRT), which has deleterious effects on implant reconstructions, an immediate-delayed reconstruction is an option where a tissue expander is inserted at time of mastectomy and inflated over time. This can then be replaced by a permanent implant after completion of PMRT. This approach allows for the preservation of the skin envelope and matching of skin colour and texture. Preservation of the breast skin envelope allows for immediate placement of a permanent implant post-PMRT, reduces the need for the use of autologous flaps and lessens the size of the skin paddle required from an autologous flap [53].

4.1.2 Complications of prosthetic reconstruction

Capsular contracture, haematoma and infection are the most commonly cited complications of prosthetic breast reconstruction, and rates of these complications have been shown to be higher than in those patients who undergo autologous reconstruction, especially post-radiation therapy [69]. Reconstructive failure is associated with patient factors factors such as smoking, obesity type 2 diabetes, tumours of a higher grade, nodal disease involvement and tamoxifen use, and technical factors including incomplete muscle coverage of the implant, large implant volume (>400ml), thin mastectomy flaps [53].

Capsular contracture is a significant complication of prosthetic reconstruction, with risk factors such as bacterial colonisation, type of implant used (smooth), implant placement, smoking, haematoma, and most significantly, delivery of PMRT [70]. *Staphylococcus epidermidis* is the bacteria most commonly implicated in capsular contracture, and forms a biofilm around the silicone implant [71]. Higher rates of capsular contracture exist in IBR (20% - 40.4%) than in DBR (17% - 26.4%). Radiotherapy is the greatest predictor of capsular contracture with rates of 87% being reported compared to 13% in patients who did not undergo radiotherapy.

The risk of capsular contracture is seen to decrease when an autologous flap is used in conjunction with the implant [53].

A controversial relationship exists between implant breast reconstruction and PMRT. The delivery of ionising radiation has direct toxic effects on both malignant cells and healthy tissue. It's mechanism for tissue damage includes direct tissue cellular damage with chromosomal alteration, ischaemia as a result of microvascular occlusion and prevention of fibroblast activity [72]. The deleterious effects of radiotherapy on breast reconstruction are unpredictable and tend to be biphasic in nature, with acute changes occurring in the days to weeks post-PMRT (e.g. desquamation or necrosis of tissue), and changes also occurring at a later stage, months to years' post-PMRT (atrophy, fibrosis, obstructed wound healing) [73]. A systematic review by Berber et al investigating complications after radiotherapy and reconstruction in general reported a rate of 37% which varied widely from 8.7% to 70% [74]. As previously discussed, radiotherapy is the greatest predictor of capsular contracture, a complication often requiring another operation to excise the capsule and replace the implant. However, some radiation oncologists are of the opinion that breast reconstruction interferes with the delivery of effective PMRT through alteration of the chest wall anatomy and therefore the radiation field, resulting in under/over-dosing the targeted tissues unpredictably [75,76]. Surveyed radiation oncologists report differing preferences in the degree of inflation of tissue expanders at time of radiotherapy delivery: 60% moderately inflated (150-250 CC); 13% completely deflated and 28% completely inflated [77]. Higher grades of capsular contracture (Baker III or IV) are more common with radiotherapy delivery [78,79]. Capsular contracture secondary to PMRT is also a risk factor for persistent pain post-operatively up to 2 years after reconstruction [80]. Radiotherapy is associated with a higher rate of complications overall in patients receiving both IBR (0-64%) and DBR (22-55%) compared to those patients not in receipt of PMRT, both IBR (0-12%) and DBR (13-34%) [81]. Overall, patients who undergo radiotherapy with implant reconstruction have worse psychosocial outcomes and lower satisfaction in comparison to non-irradiated reconstructed patients [82-84].

4.2 Autologous reconstruction

Autologous breast reconstruction remains an important option in post-mastectomy breast reconstruction, particularly in patients who have poor skin quality of the mastectomy flaps or for whom delayed reconstruction is preferred [85]. Some authors predict an increase in the need for autologous reconstructions secondary to the increasing number of indications for radiotherapy, and thus an unacceptably high rate of capsular contracture and radio-dermatitis in implant-based reconstructive procedures [86]. Autologous reconstructions are more cosmetically natural in shape and texture than implants. They provide skin coverage in cases of poor quality of the mastectomy flaps or delayed reconstruction. It is believed that DIEP reconstruction is more suitable in patients who will require PMRT. Conversely, the effect of

radiotherapy on an LD reconstruction can be catastrophic secondary to muscular atrophy [87]. Although initial complication rates may be higher, autologous reconstructions provide a more consistent and durable reconstruction over time [88]. This approach however is not without its unique set of complications; autologous reconstruction is associated with morbidity at the donor and reconstruction site. Tissue flap necrosis and loss may occur secondary to ischaemia of transferred tissue. Complications may arise from the donor site in the form of, for example, an incisional hernia in the case of a TRAM flap. These operations have a longer operative time, require longer admissions and recovery times [52]. Complex patient selection and requirement for pre-operative CT angiography to detect the perforator vessel supplying the skin flap (in DIEP flaps) make autologous reconstruction a less attractive reconstructive technique [51]. Autologous flap procedures are longer and more technically challenging, particularly in the case of free DIEP and TRAM flaps which require the formation of a microvascular anastomosis [89]. As surgical techniques have evolved, there has been a progression from pedicled and free musculocutaneous flaps to muscle-sparing perforator flaps [29]. Currently, the abdominal wall is the most commonly used donor site.

4.2.1 Transverse rectus abdominis (TRAM) flap

The TRAM flap was pioneered in 1982 by Hartrampf, Schefflan and Black [90]. The technique has since been refined, with improvements in blood supply. It has evolved from a pedicled flap with a necrosis rate of approx. 10% to a free flap with a possible success rate of 98%, producing a breast reconstruction potentially superior to any other technique. TRAM flaps make up approx. 20% of breast reconstructive procedures carried out in the US. Originally, the pedicled TRAM flap took its blood supply from the superior epigastric vessels via a series of vessels within the rectus abdominis. The more modern use of the inferior epigastric vessels in the free TRAM flap allows larger amounts of abdominal tissue to be removed completely from the body and transplanted to the chest wall with minimal risk of fat necrosis. In addition, limiting the muscle harvest to the portion of muscle containing the medial and lateral rows of perforating vessels reduces the risk of donor site morbidity by minimising violation of the abdominal wall [91]. The anterior rectus sheath is usually sutured closed, however, in cases of difficult closure, particularly if both rectus muscles are used, a synthetic mesh may be required to achieve closure [92].

4.2.2 Deep inferior epigastric perforator/superficial inferior epigastric perforator (DIEP/SIEP) flap

It is possible to preserve all of the rectus abdominis muscle when raising a TRAM flap. In this case, only the perforating vessels are taken with the flap and the inferior or superior epigastric vessels are left intact. A deep inferior epigastric perforator (DIEP) flap results if the primary vessels are the deep inferior gastric artery and vein, which was described for use in

breast reconstruction in 1994 [93]. If the primary vessels are the superior epigastric gastric vessels, the procedure is known as a superficial inferior epigastric perforator (SIEP) flap [94]. They are anastomosed to the internal mammary vessels preferably, though they may also be anastomosed to the circumflex scapular vessels [95]. Donor site morbidity is minimised even further with this technique, however, increased dissection and longer operative times are required for this method of reconstruction. Due to the minimal breach of the rectus sheath, DIEP or SIEP flaps are associated with minimal loss of function, reduced risk of hernia, less post-op pain and shorter length of stay. Reduced abdominal wall disruption makes a tension free closure possible without requirement of a synthetic mesh [91]. DIEP flaps are indicated in young healthy women, those undergoing prophylactic mastectomy and patients who do not require PMRT; and contraindicated in patients of ASA Grade 3, collagen vascular disease, previous abdominoplasty or radiation to the abdomen that may have damaged perforating vessels, patients with severe haematological disorders or contraindications to anticoagulation. Relative contraindications include obesity, older age (<70 years) or smoking [96,97].

4.2.3 Latissimus dorsi (LD) flap

Alternative donor sites to the abdominal wall are required occasionally, specifically in patients who have had previous abdominal surgery. Although its use has been surpassed by that of the TRAM and DIEP flap in recent years, the LD flap is still a widely used method of breast reconstruction. This flap produces a ptotic breast with projection and texture similar to that of native breast tissue. It may be used alone or in conjunction with an implant in order to recreate the breast mound depending on the volume required to achieve symmetry. LD flaps are useful in the case of failed expander/implant reconstructions. LD flaps have evolved over time, particularly in the late 1970's when a greater understanding of the vascular connections to the skin allowed for a skin paddle to be transferred along with the muscle, improving the skin coverage and replacement of the breast mound contour [98]. As a result, superior breast symmetry and cosmetic outcomes were achieved. Although the transfer of abdominal tissue is preferable in the setting of breast reconstruction, it is not suited to all patients. Indications suggested for LD reconstruction include: previous abdominal operations; a preferred dorsal donor site; failed implant or TRAM flap; patients who wish to become pregnant at a later stage. LD is suitable for use in the immediate and delayed setting. The latissimus dorsi, a large triangular muscle on the upper back, is dissected along with a "paddle" of muscle, vascularised by the thoracodorsal artery and vein, and the overlying skin and fat (musculocutaneous flap). Once raised, the muscle is tunnelled below the axilla and implanted subcutaneously under the axilla, into the breast pocket and then sutured in place. The LD is often augmented by implants or fat grafting to provide symmetry and cosmesis [99]. An "extended LD flap" allows for greater volume generation without the use of an implant by harvesting lumbar adipose tissue along with the muscle flap in order to reconstruct the breast mound.

4.2.4 Transverse upper gracilis (TUG) Flap

The TUG flap is a less commonly performed method of breast reconstruction suitable for those in whom the abdomen is unsuitable as a donor site. The TUG flap is harvested from the medial aspect of the thigh and is associated with advantages such as a relatively consistent anatomy, a reasonably inconspicuous donor site scar and relatively little functional morbidity. However, potential limitations include medial thigh paraesthesia, chronic lower limb lymphoedema and contour deformities of the medial thigh. The flap is supplied by the medial circumflex artery. For patients with large breast volumes, the volume requirement of the flap can result in severe donor site morbidity with large contour deformities, widened and lowered donor scars, impaired wound healing and higher rates of lower leg lymphoedema. This has led to the use of a bilateral TUG flap for unilateral breast reconstruction in selected cases. Harvest of tissue anterior or beyond the femoral axis should be avoided to prevent flap necrosis. In addition, the preservation of the saphenous vein preserves lymphatics that lie below [100].

4.2.5 Thoracodorsal artery perforator (TDAP) flap

The TDAP flap is a de-epithelialised flap taken from the lateral thoracic wall and the back that can be transplanted to the anterior thorax for breast mound reconstruction. It was first described for breast reconstruction in 2004 [101]. This method of breast reconstruction has sufficient volume to recreate a B cup-sized breast using a totally or partially de-epithelialised flap. The TDAP flap allows for harvesting of the same skin and subcutaneous tissue as that in an LD flap, without the muscle, thus avoiding the possible associated complications. TDAP flaps have a very low incidence of seroma, no impairment of shoulder motion and have a satisfactory aesthetic outcome. Distal tissue necrosis is the most commonly occurring complication [102].

4.2.6 Superior gluteal artery flap

The SGAP flap was first described in 1973 as part of a multistage procedure. It was refined to a one stage procedure in 1975 [29]. This is considered to be superior to the inferior gluteal artery flap as the IGAP flap requires exposure of the sciatic nerve. This flap utilises only fat and skin from the gluteal region, which creates good projection and volume of the reconstructed breast. The pedicle is anastomosed to the internal mammary vessels. The long pedicle of the GAP flap minimises the need for venous grafts at the site of anastomosis and it has been shown that an S-GAP flap can survive successfully on a single perforator [103].

5. Autologous fat grafting

Autologous fat grafting involves liposuction of adipose tissue from the abdomen, thighs or buttocks and subsequent reinjection of the lipoaspirate into an area in which there is a defect

for the purposes of reconstruction. Autologous fat grafting has been successful in small volume breast augmentation, filling small volume defects post-breast conserving surgery [104-108] and adds value in implant based reconstructions [109,110]. Although positive outcomes have been demonstrated in this setting, the larger volume of adipose tissue required to carry out breast reconstruction post-mastectomy has proven beyond its capabilities thus far [111]. Autologous fat transfer is limited by resorption, with rates ranging from 25-80% and complications such as fat necrosis, oil cyst formation and microcalcifications in patients receiving autologous fat transfer in addition to primary reconstructive procedure e.g. LD flap [112] or as a filler for small volume defects post breast-conserving surgery (BCS) [106,113].

Cell-assisted lipotransfer, first described by Matsumoto et al in 2006, involves enrichment of autologous lipoaspirates with ADSCs harvested from half of the lipoaspirate prior to reinjection [114]. Enrichment of autologous fat lipoaspirates with ADSCs, which have been expanded ex-vivo has had more successful outcomes in terms of volume retention, likely as a result of superior graft maintenance due to increased vascularisation and collagen synthesis within the graft [115]. Kollé et al demonstrated fat residual volume of >80% in 10 patients over 121 days utilising abdominal lipoaspirate enriched with ADSCs that had been expanded ex-vivo for 14 days prior to reimplantation into the upper posterior arm. Compared to controls, without ADSCs, there were higher amounts of adipose tissue, less necrotic tissue and newly formed connective tissue [116]. Yoshimura et al conducted a study in 40 healthy patients undergoing cosmetic breast augmentation, where a mean volume of 270ml ADSC-enriched fat was injected into the breast. There was minimal post-op atrophy of the injected fat which did not change significantly over 2 months. Small cystic formations and microcalcifications were observed in some cases; however the microcalcifications were readily distinguished from those associated with breast cancer. Post-op CT and MRI images showed that transplanted fat tissue survived and formed a substantial thickness of the fatty layer subcutaneously on and around the mammary glands and also between the mammary glands and the pectoralis muscle. Breast volume stabilised 2-3 months post-op. This data indicates that cell-assisted lipotransfer is suitable for repair of smaller breast defects [117].

There have been concerns regarding the oncological safety of autologous fat grafting. This issue has been addressed by several clinical studies. A small, retrospective series showed an increased risk of breast cancer recurrence in patients with intraepithelial neoplasia undergoing autologous fat grafting. Only patients with intraepithelial neoplasia (n=37) who underwent autologous fat grafting in this series demonstrated an increase rate of local recurrence (10.8%) [118]. A follow-up matched cohort study investigating fat grafting in 59 patients with intraepithelial neoplasia concluded that there is a higher risk of local recurrence in this patient cohort compared to age and stage matched controls (n=118) [119]. While these results are concerning, it must be noted that they are from a single centre retrospective study with small

numbers. More encouraging results are observed in larger studies with no increase in locoregional or systemic recurrence [120-122]. Delay et al retrospectively analysed outcomes in 880 patients who underwent fat grafting. They demonstrated , no increased risk of cancer recurrence or new cancer development after 10 years of follow up [113]. They also reported that the radiological appearance of the breasts post-lipofilling did not negatively influence the ability to identify a neoplastic process. To date, the largest retrospective carried out was by Kronowitz et al. where 719 patients underwent autologous fat grafting post-tumour resection. There was no increase in locoregional or systemic recurrence or of a second breast cancer [120]. The RESTORE-2 trial assessed the oncological safety of ADSC-enriched fat grafting in patients undergoing BCS with defects up to 150ml. 67 patients reported high levels of satisfaction with the cosmetic outcomes. No incidences of local recurrence were reported within 12 months of the procedure. While these results are encouraging, longer follow up is required to accurately investigate the oncological safety of this procedure [123]. Systematic reviews conclude that autologous fat grafting appears to be oncologically safe with low rates of complications and good patient and surgeon satisfaction [124-126]. However, all authors suggest that there is an urgent need for randomised controlled trials with adequate follow up to confirm this opinion, and to exercise caution in carrying out these procedures at high risk patients.

6. Breast reconstruction and neoadjuvant/adjuvant therapy

6.1 Chemotherapy and breast reconstruction

There is some concern over the relationship between breast reconstruction and the delivery of chemotherapy in the treatment of breast cancer. No clear evidence exists for the optimal time for initiation of adjuvant chemotherapy, however most guidelines state that chemotherapy can be safely initiated within 4 weeks of mastectomy. It has been previously suggested that breast reconstruction is responsible for delays in the delivery of adjuvant chemotherapy, therefore compromising oncological treatment and outcomes [127]. This has been disproven by several studies and it is now widely accepted that breast reconstruction does not pose a risk for delayed delivery of adjuvant therapies [128,129]. There have been reports of increased surgical complications post-breast reconstruction (e.g. wound healing, tissue necrosis and infection) in patients also in receipt of chemotherapy, secondary to its myelosuppressive and cytotoxic effects [72]. A limited number of studies have examined this; however, the largest of these studies did not find significantly higher complication rates in this patient cohort undergoing reconstruction and chemotherapy. There is a paucity of data relating to neoadjuvant chemotherapy and breast reconstruction, though it is accepted that neoadjuvant chemotherapy results in similar outcomes to adjuvant chemotherapy post-breast reconstruction [72].

6.2 Radiotherapy and breast reconstruction

A controversial relationship exists between post-mastectomy radiation therapy (PMRT)

and breast reconstruction, particularly in the case of implant only reconstructions. PMRT has deleterious effects on aesthetic outcomes and complication rates in implant-based reconstructions as it can affect the symmetry, volume and projection achieved at the time of initial reconstruction [130]. Implant-based reconstructions have a significantly higher rate of complications than autologous reconstructions in the setting of PMRT: infection (13.5% vs. 5.8%), mastectomy flap necrosis (10.5% vs. 5%), and reoperation secondary to complication (37.0% v 16.6%)(131). There is a reconstructive failure rate of 16.8% in implant reconstructions in the presence of PMRT [131]. The timing of PMRT is an important consideration in the avoidance of complications. For those patients who have already received PMRT, insertion of implants and tissue expansion techniques can be troublesome, with increased rates of infection, implant extrusion and capsular contracture. Autologous reconstruction gives a more predictable aesthetic outcome in those patients previously treated with PMRT. The reconstructive procedure itself is less complicated in those patients who have not received PMRT but exposure of the reconstruction to ionising radiation creates its own issues, both for implant and autologous reconstructions. In patients in whom PMRT is expected to be required, oncoplastic surgeons will insert a tissue expander implant which will be inflated over time and replaced by a permanent implant prior to delivery of PMRT [92]. In the case of autologous reconstructions, there is no difference in complication rates, flap failure or rates of revision surgery depending on the timing of PMRT. A systematic review of breast reconstruction before and after PMRT by Berbers et al recommend that definitive implant reconstruction be carried out before PMRT and autologous reconstruction be carried out post-PMRT to avoid radiation-induced fibrosis and compared cosmesis [74].

6.3 Hormonal therapy

A paucity of evidence exists in the literature regarding the effects of hormonal therapy on breast reconstruction. The principle consideration in this regard appears to be the increased risk of thromboembolic events associated with tamoxifen therapy in those patients who have undergone a breast reconstruction procedure involving a microvascular anastomosis (e.g. DIEP) according to a systematic review by Parikh et al [132].

7. Future Directions

Despite the clear aesthetic and psychosocial benefits of breast reconstruction [133], currently available techniques, including synthetic implants and autologous tissue grafts are limited by morbidity risks at both the reconstruction and donor sites. Increasing patient expectations for cosmetic/aesthetic outcomes means that surgeons are persistently attempting to optimise reconstruction methods through innovative development of a functional tissue substitute for postmastectomy reconstruction. The rapidly advancing fields of tissue engineering and regenerative medicine hold enormous potential in this regard and recent years have seen

key innovations in vascular, osseous, cutaneous and soft tissue regeneration [134]. For breast cancer patients, the ability to generate living functional tissue to fill disfiguring defects following tumour resection will have enormous implications for future quality of life. Recent efforts have focused on cell-based regeneration of adipose tissue to fill the defect following BCS or mastectomy [135]. Adipose-derived stem cells (ADSCs) offer the advantage of an abundant autologous source, a minimally invasive method of harvesting, significant proliferative capacity, and secretion of growth and angiogenic factors to stimulate tissue regeneration [136]. For these reasons,

ADSCs) have become the gold standard as a cell source for tissue engineering [137]. ADSCs can be easily isolated from lipoaspirates obtained at liposuction procedures, of which, approximately 400,000 are carried out in the US annually. Each procedure yields 100ml-3L of lipoaspirate, in which 90% of ADSCs are viable, which is usually discarded post-operatively [138]. ADSCs can be used as autologous and allogenic grafts. It has been determined that passaged ADSCs, as opposed to freshly isolated SVF cells, reduce histocompatibility surface antigen expression and no longer induce a lymphocytic reaction when cocultured with allogenic peripheral blood monocytes. Immunoreactions are suppressed by ADSCs, indicating that ADSCs may not elicit a cytotoxic T cell response in vivo though this hypothesis has yet to be tested comprehensively [137,139].

As discussed above, the use of autologous adipose tissue via fat-grafting is in widespread clinical use for breast augmentation and correction of small volume defects following breast conserving surgery [140]. The use of fat grafts supplemented with ASCs in “cell-assisted lipotransfer” has been reported to result in more durable outcomes than conventional fat grafting [141,142].

However, in order to regenerate sufficient tissue volume to fill a larger mastectomy defect it is likely that a de-novo adipose tissue engineering approach will be required; combining living cells (ADSCs), a biocompatible scaffold, and a microenvironment that will provide the appropriate cues to support cell growth, differentiation and long-term volume retention to promote tissue regeneration.

A scaffold acts as a template for new tissue formation. Correct scaffold material and design selection will be paramount in overcoming the obstacles of volume retention and vascularisation. A variety of synthetic and natural scaffold materials have been studied for this purpose [135,143-149].

Patrick et al was one of the first groups to investigate scaffolds in adipose tissue regeneration. Preadipocytes were isolated and cultured on a polymeric scaffold which was then implanted into a murine model. Good adipose tissue formation was evident at 2 months; however a decrease was noted at 3 months, with complete disappearance of all engineered adipose

tissue and the PLGA scaffold at 12 months [150-152].

Von Heimburg et al. investigated freeze-dried collagen sponges seeded with preadipocytes. These were implanted into immunodeficient mice and preadipocytes differentiated to mature adipocytes *in vivo*. The constructs were explanted at 3 and 8 weeks and histology revealed adipose tissue with rich vascularisation attached to the scaffold beneath a thin capsule layer of fibrovascular tissue [153]. A study on HYAFF11 sponges, a derivative of hyaluronic acid, concluded that these were superior to collagen sponges with regard to cellularity achieved in adipose tissue engineering [154]. This has been found to be a suitable scaffold material for the culture and *in vivo* differentiation of ADSCs [155,156].

Pati et al successfully bioprinted a 3D cell laden construct with decellularised extracellular matrix (dECM) that showed high cell viability and functionality [157]. A similar biomaterial adipose tissue construct was implanted into a mouse model, which demonstrated positive tissue infiltration, constructive tissue remodelling and adipose tissue formation.

One study 3D-printed patient-specific breast scaffolds with a poly-lactide polymer cultured for 6 weeks. The constructs were seeded with human umbilical vein endothelial cells and subcutaneously implanted in athymic nude mice for 24 weeks. Explanted samples were well-vascularised constructs of adipose tissue without necrosis, inflammation or cysts. There was an increase in adipose tissue produced from 37.17% to 81.2% 15 weeks [158].

One study seeded ADSCs onto decellularised adipose tissue (DAT) bioscaffolds and implanted them into female Wistar rats. At explantation at 12 weeks, 56.1 +/- 9.2% of the ADSC-seeded DAT had been remodelled into mature adipose tissue with a higher density of blood vessels within the areas of the implant that had been remodelled into mature adipose tissue [159].

The largest volumes of sustained regeneration of adipose tissue have been achieved by “additive biomanufacturing” utilised delayed fat injection into a custom-made scaffold implanted in minipigs for 24 weeks after a period of prevascularisation. The prevascularisation + lipoaspirate group had the highest relative area of adipose tissue upon explantation (47.32 +/- 4.12%) which was similar to native breast tissue (44.97 +/- 14.12%)[160]. Morrison et al are the first group to engineer clinically relevant volumes of adipose tissue in humans through the use of a porous chamber and an arterio-venous loop, producing 80ml of adipose tissue [161].

Although these results are promising from a technical and tissue regeneration perspective, a critical question is that of oncological safety; there is a recurrence rate of 20% at 10 years for breast cancer patients, indicating the persistence of dormant cancer cells even in the setting of contemporary multimodality therapy [162]. A major concern is the risk of stimulating tumour recurrence by the use of stem cells for breast tissue regeneration. There is conflicting

data regarding the possible interplay between breast tumour cells and transplanted ASCs; the ASC secretome has been shown variably to promote [163-165] and suppress tumour growth *in-vitro* [166,167]. Our knowledge of ASC behaviour *in-vivo* is limited [168] and the concept of a detrimental interaction between transplanted ASCs and residual/dormant cancer cells requires further clarification through *in-vivo* and clinical studies which should aim to clarify how ASCs can be exploited for their regenerative function in this setting without influencing tumorigenesis. If this can be achieved, translation to the clinical setting will offer the exciting potential to engineer a reconstruction, generated from autologous cells which may be surgically implanted without requiring tissue transfer, thereby eliminating or reducing donor site morbidity, and answering a clinical need for breast cancer patients.

8. Conclusion

Post-mastectomy breast reconstruction is an integral component of optimal multimodality breast cancer care. It is an ever-evolving field, partly due to increasing patient expectations with regard to aesthetic outcomes and due to the need to adapt to new oncological and radiation-based treatments. While historically, breast reconstruction has been composed of implant-based and autologous tissue techniques, research into the field of tissue engineering has yielded promising results, suggesting that this may be the future solution to the many limitations of current approaches and will maximise aesthetic and quality of life outcomes for breast cancer patients.

9. Figures

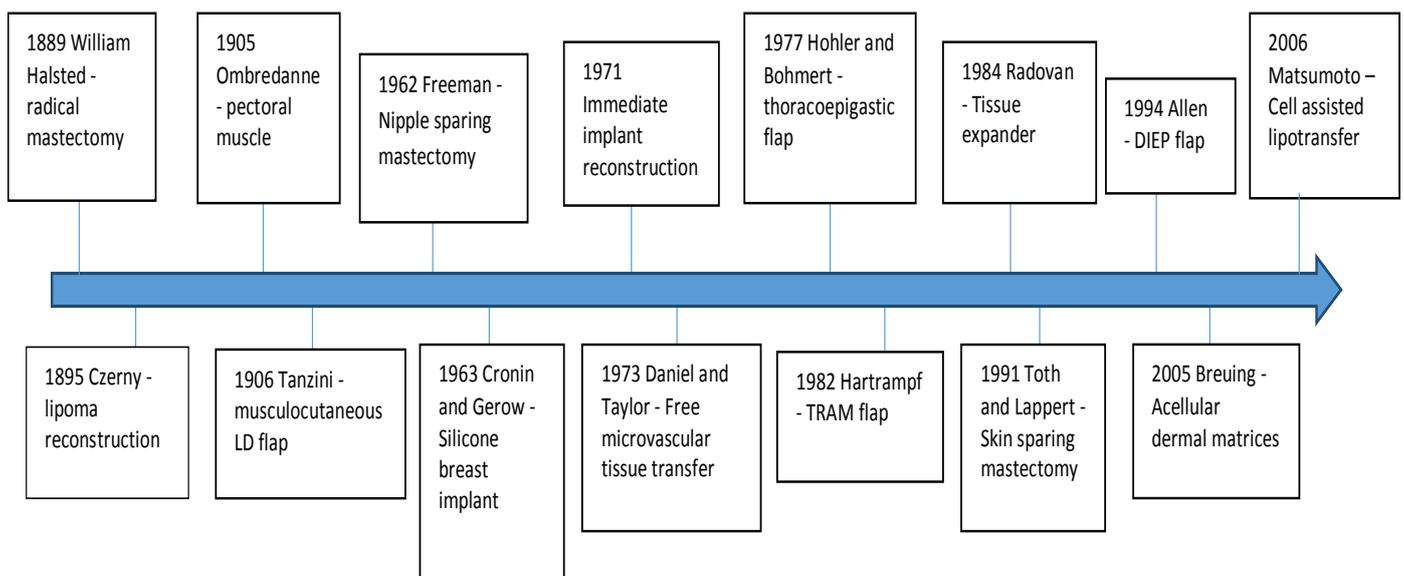


Figure 1: Evolution of Post-Mastectomy Breast Reconstruction



Figure 2: Bilateral implant reconstruction



Figure 3: LD flap reconstruction



Figure 4: TRAM flap reconstruction

10. Tables

Table 1: Commercially available Acellular Dermal Matrices (ADMs) used in direct-to-implant reconstructions or in conjunction with a tissue expander. ADMs are created by a decellularisation process that leaves the extracellular matrix of the original tissue intact.

Acellular Dermal Matrix (Trade Names)	Company	Tissue Source	Sterile	Advantages
Flex HD	Ethicon	Human allograft skin	No	<ul style="list-style-type: none"> • Little elasticity • Prehydrated
AlloDerm	Life Cell	Human cadaveric skin	No	<ul style="list-style-type: none"> • Can be irradiated • Widely used, extensive studies carried out • Rapid revascularisation • Allows lymphocyte migration
DermaMatrix	Synthes	Human skin	Yes	<ul style="list-style-type: none"> • Bacterially inactivated • Rapid rehydration • No refrigeration required
Permacol	Covidien	Porcine dermis	Yes	<ul style="list-style-type: none"> • Cross-linked for greater durability • No refrigeration or rehydration required • Available in larger sizes
Strattice	LifeCell	Porcine dermis	Yes	<ul style="list-style-type: none"> • Good biomechanical strength • Prevents adhesions • Allows revascularisation • Allows lymphocyte migration and cell ingrowth
SurgiMend	Polytech	Foetal bovine dermis	Yes	<ul style="list-style-type: none"> • Rapid rehydration • Easy to suture • Fenestration to allow fluid drainage
AlloMax	Bard Davol	Human dermis	Yes	<ul style="list-style-type: none"> • Virally inactivated • Hydrates rapidly • Little elasticity • Early cellular infiltration and neovascularisation 7 days post-implant

Table 2: Biomaterials used as scaffolds in adipose tissue engineering. A scaffold acts as a template for new tissue formation. They can be naturally occurring materials or synthetic, each with their own properties, advantages and limitations.

Natural Scaffolds	Advantages	Limitations
Collagen	Can be modified e.g. addition of growth factors Supports adipogenesis, vascularisation and ECM deposition Licensed for clinical use	Limited mechanical strength Short degradation time

HYAFF11	Longer degradation time than collagen Licensed for clinical use Good mechanical stability Supports vascularisation and ECM deposition	Decreased differentiation of ADSCs
Silk	Low immunogenicity Slow, controlled degradation Licensed for clinical use Supports adipogenesis in vitro and in vivo	No data on stability of degradation products Limited surface modification
Synthetic Scaffolds	Advantages	Limitations
PLGA	Biodegradable Easily mass produced Adipogenic differentiation of ADSC in vivo Surface modification improves tissue growth	Foreign body capsule formation Short degradation time Requires surface modification
PEG	Licensed for medical use Low toxicity Water soluble Biodegradable	Hydrogel Poor mechanical strength Rapid degradation
PLA	Easy surface modification Good mechanical strength Allows vascularisation Adipogenic differentiation of BMSCs	Rapid degradation

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