Additive manufacturing and tissue engineering to improve outcomes in breast reconstructive surgery

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***Abstract*— Many women with early breast cancer undergo mastectomy as a consequence of an unfavorable tumor/breast ratio or because they prefer this option to breast conservation. As reported, breast reconstruction offers significant psychological advantages. Several techniques are currently available for the breast oncoplastic surgeon and offer interesting results in terms of aesthetic and patient-reported outcomes, using both breast implants and autologous tissues. On the other hand, advanced methodologies and technologies, such as reverse engineering and additive manufacturing, allow the development of customized porous scaffolds with tailored architectures, biological, mechanical and mass transport properties. Accordingly, the current research dealt with challenges, design methods and principles to develop 3D additively manufactured structures in breast reconstructive surgery.**

***Keywords*— additive manufacturing, breast reconstructive surgery, design, fat grafting, reverse engineering, scaffold design.**

I. INTRODUCTION

Breast reconstruction offers significant psychological advantages for women who undergo mastectomy for the treatment of breast cancer [1].

Immediate reconstruction does not affect oncological outcomes without significantly delaying adjuvant therapies and impairing the effectiveness of oncological surveillance [2,3].

New mastectomy techniques, the so-called conservative mastectomies, allow the surgeon to completely preserve the breast envelope in patients without involvement of the nipple areola complex [4-6].

Many techniques for breast reconstruction are actually available for the breast oncoplastic surgeon to offer the woman the best results in terms of aesthetic and patient-reported outcomes, both using alloplastic materials (i.e. breast implants) and autologous tissues [7].

Nowadays breast reconstructive surgery should derive from a shared decision with the patient with the duty for the surgeon of tailoring the surgical treatment on each single woman, never forgetting patients' wishes [8,9].

Implant-based techniques remain the most widely used form of breast reconstruction, even though they are not exempted from complications and the aesthetic results could not always be long lasting [7,10].

The silicone implant will be considered as a foreign object and a tissue reaction will be mounted, resulting in a scar-like tissue around it, known as a capsule. The capsule could thicken and contract, leading to the so-called capsular contracture.

Other complications have been described in association with the use of breast implants, as late seromas and the development of an extremely rare form of lymphoma, the Anaplastic Large Cell Lymphoma [11].

Recently, several doubts about the safety of silicone breast implants have been highlighted considering the extremely rare development of Breast Implant-Associated Anaplastic Large Cell Lymphoma (BIA-ALCL).

Many surgeons are looking for alternatives to implants for breast reconstruction, myocutaneous pedicled and muscle-sparing free flaps being the first considered alternatives to silicone implants.

However, according to several studies, breast reconstruction with autologous tissue flaps is not free from

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complications and high rates of re-interventions and the flap surgical procedures are time consuming and expensive (when compared to implant-based reconstruction).

The Mastectomy Reconstruction Outcomes Consortium Study, a prospective multi-center trial, recruited patients undergoing breast reconstruction (implant based and autologous-tissue based) following mastectomy from 11 centers across North America from February 2012 to July 2015.

The results of this trial in terms of patient-reported outcomes and post-post-operative complications have been presented in several reports [12,13].

Reported 2-year complications rate following autologous tissue based reconstruction is 47% versus 26.6% with implant-based techniques, reported re-operations rates are 27.4% with autologous tissues versus 15.5% with implants.

These data must be taken into account when considering autologous flaps as alternatives to silicone implants for breast reconstruction.

With the aim of reducing surgical aggressiveness, improving cosmetic outcomes and achieving long-lasting results, we developed a new reconstructive technique, involving tissue regeneration supported by 3D morphologically controlled scaffolds obtained through additive manufacturing methods.

This method could represent a further evolution of the so-called “hybrid reconstructive” option, we already presented with the combined rationalized use of silicone implants and autologous fat tissue transplantation [14,15].

3D-printed bioresorbable scaffolds will be positioned subcutaneously following a conservative mastectomy and filled with autologous fat tissue in 2-3 sessions achieving a natural-shaped breast mound with soft consistency and long-lasting aesthetic results.

This reconstructive option could also be offered to women undergoing post-mastectomy radiotherapy (PMRT), as the material will not be influenced by irradiation, representing a significant advantage when compared to silicone implants in the radiotherapy setting [16].

Future clinical application of the 3D-engineered breast reconstruction will validate this innovative technique, that will probably become a standard for the next generation breast surgeon.

II. DESIGN METHODS AND PRINCIPLES TO DEVELOP 3D ADDITIVELY MANUFACTURED STRUCTURES IN BREAST RECONSTRUCTIVE SURGERY

The employed gel-filled breast implants were generally based on a gel-like core consisting of a polydimethylsiloxane (PDMS) with a lower cross-linking degree and a shell made of an elastomeric material (i.e ., PDMS).

The nonlinear and large-deformation behavior together with the complex viscoelastic properties can be reproduced to develop innovative breast devices, taking into account the knowledge of the structure-property relationship of the materials and advanced technologies.

Different strategies can be considered for breast tissue repair/reconstruction and regeneration, combining additive manufacturing techniques with an appropriate selection of materials currently employed in tissue engineering and prosthetic fields [17-19].

In particular, over the past years great efforts have been devoted to the design of devices in the form of gels/hydrogels and 3D additively manufactured scaffolds [17-19].

The use of non-degradable polymers and the design of advanced customized prostheses should represent a first approach.

A suitable material-geometry design must be used to properly reproduce the mechanical properties of the native tissue and the exact shape and size of the defect.

Shell-core or multilayer devices may be developed, using rubber-like and gel-like materials as well as the combination of additive manufacturing with conventional techniques.

A second route would involve the use of synthetic or natural biodegradable polymers to design customized porous scaffolds with tailored architectures, biological, mechanical and mass transport properties.

With regard to tissue engineering applications, aliphatic polyesters such as poly(ε-caprolactone) (PCL) have been widely investigated.

In this context, the design of an innovative breast device would also involve reverse engineering and additively manufactured scaffolds combined with autologous fat grafting.

3D additively manufactured scaffolds with autologous adipose derived stem cells have been taken into account for breast tissue engineering.

The devices should be properly placed and filled with autologous fat tissue in some sessions.

The custom-made scaffold filled with autologous fat tissue should allow to maintain the breast shape and natural consistency.

Adequate technical improvements (i.e., Stromal Vascular Fraction derived growth factors) will be also considered.

For this reason, to design an advanced 3D scaffold with tailored architectural features and properties for breast tissue regeneration, a combination of the basic principles of regenerative medicine with reverse engineering and additive manufacturing is needed.

3D virtual models of breast can be generated through image capture and analysis techniques, using medical scans (i.e., magnetic resonance imaging – MRI, computed tomography - CT).

The physical structures can be then fabricated by additive manufacturing techniques based on injection/extrusion methods (i.e., fused deposition modelling – FDM/3D fiber deposition).

Specifically, 3D porous structures can be manufactured layer-by-layer according to specific lay-down patterns.

In the field of additive manufacturing, 3D fiber deposition (Figures 1 and 2), which represents a modified technique of 3D plotting for the extrusion of highly viscous polymers, is a fused deposition technique where the materials are injected/extruded through a nozzle and then properly deposited [17-19].

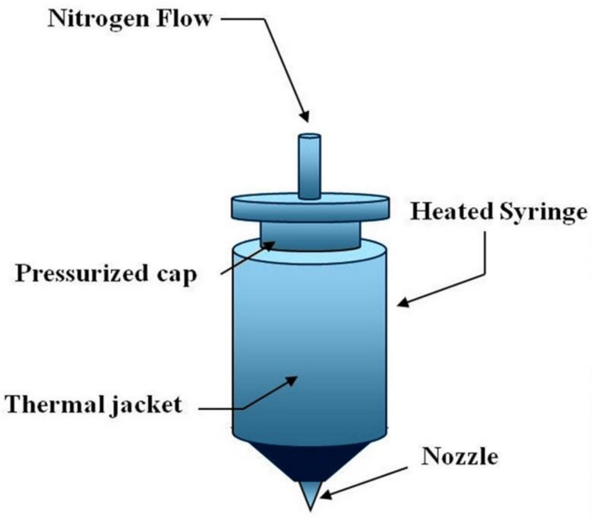

Fig. 1. Additive manufacturing technique: 3D fiber deposition and key elements.

Fig. 2. 3D fiber deposition technique: an image of cartridge unit and needle/nozzle (Bioplotter - EnvisionTEC GmbH, Germany).

Unlike the conventional fabrication methods, the higher control of the architectural features allows for the improvement of the mass transport properties [17-19].

Using fabrication methods based on CAD/CAM systems, 3D customized porous scaffolds with a defined structure and architecture were manufactured.

Such scaffolds may be considered as the basis for a novel breast reconstruction approach.

The mechanical and mass transport properties, as well as all the functional features of the 3D scaffolds, were properly tailored by varying the sequence of stacking (i.e., lay down patter) and porosity (Figures 3 and 4).

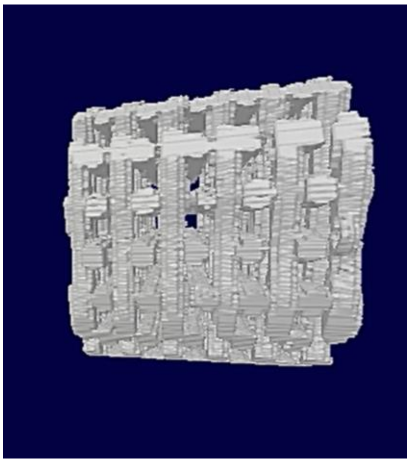

Fig. 3. Typical results from micro-CT analysis performed on 3D scaffolds with specific lay-down pattern and geometric features.

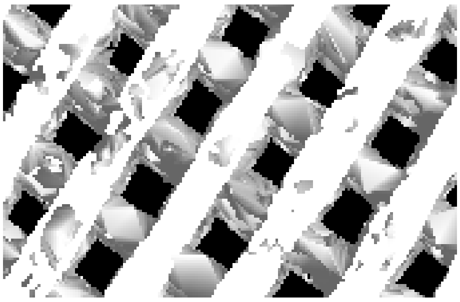

Fig. 4. Results from micro-CT analysis performed on 3D scaffolds. 3D reconstruction showing the architectural features and the interconnected pore network.

In general, results from compression tests on 3D additively manufactured scaffolds provided stress-strain curves where an initial linear region was evident. Beyond this region, the slope of the curve first decreased and then increased.

With regard to the effect of the architecture on the properties of the developed structures, as an example, Table 1 reports the compressive modulus (E), which was evaluated from the slope of the initial linear region of the stress–strain curve, for poly(ε-caprolactone) (PCL) scaffolds with fixed fiber diameter, fiber distance and layer thickness.

TABLE I. TYPICAL RESULTS FROM COMPRESSION TESTS. EFFECT OF THE SEQUENCE OF STACKING ON COMPRESSIVE MODULUS OF 3D ADDITIVELY MANUFACTURED PCL SCAFFOLDS WITH FIXED FIBER DIAMETER, FIBER DISTANCE AND LAYER THICKNESS. RESULTS ARE REPORTED AS MEAN VALUE ± STANDARD DEVIATION.

Sequence of stacking	E (MPa)
0/90°	62.3 ± 6.5
0/60/120°	42.3 ± 4.2
0/45/90/135°	31.1 ± 3.2

Thus, the sequence of stacking influences the mechanical performances of the designed scaffolds.

At fixed fiber diameter, fiber distance and layer thickness, structures with a 0/90° pattern showed a compressive modulus which was higher than those found for 0/60/120° and 0/45/90/135° lay-down patterns.

In many cases, according to the material compositions and the morphological and architectural features, the designed 3D structures were able to reproduce the tissue properties and the complex anatomical shape, also benefiting from the advances in the design of high performance materials and innovative methodologies, which have led to the development of multifunctional devices for different applications [20-30].

The 3D additively manufactured scaffolds were also loaded with gel-like materials to develop a complex hybrid structure which would be able to guide the regeneration process.

Considering hybrid devices, the properties of the gel-like materials were clearly assessed through appropriate rheological analyses (i.e., steady shear measurements, dynamic-mechanical tests) and confined compression stress-relaxation tests.

As for the uniaxial confined compression tests, the experimental stress relaxation data, the constitutive law for the extra-stress, the governing equations for finite deformation, together with initial and boundary conditions, were considered to evaluate important properties for biphasic materials, such as aggregate modulus and permeability.

III. CONCLUSIONS

Design methods and principles in the development of 3D additively manufactured structures in breast reconstructive surgery were proposed, starting from a critical analysis on the breast reconstruction techniques and the current scenario.

The possibility to manufacture 3D morphologically controlled scaffolds with a fully interconnected pore network, tailored functional and structural features, by varying material, porosity and sequence of stacking, was stressed

The reported experimental findings together with the reverse engineering approach suggested the feasibility to develop new strategies and customized structures in breast reconstructive surgery.

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