Introduction and General Background

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Abstract

The last years have registered an important activity in the specialty of plastic and reconstructive surgery. In particular, a real revolution in reconstruction has occurred. The not-so-old dream of restorative surgery, namely, the replacement of damaged parts of the body by new unharmed preformed tissues, has become a reality. The development of techniques aimed at transplantation of vascularised composite tissues (VCA, vascularised composite allografts) has provided clinicians with a new robust tool for the reconstruction of deformities that were, not so long ago, impossible to achieve. History, development and classical attempts for VCA are not a new one. More than four decades ago, doctors in Ecuador attempted the transplantation of a hand limb. The transplant failed, but the dream survived. Pioneering laboratory work in experimental animals showed the path to clinicians for the achievement of human VCA. The works of Dr. Siemionow and Dr. Butler are milestones of the development of this discipline. They showed how tissues could survive after transplantation and implemented the basis for the surgical technique in the clinical scenario. More than ever, this is a perfect example of translational research and implementation of bench work to the bedside.

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Dr. Siemionow and Dr. Butler are milestones of the development of this discipline. They showed how tissues could survive after transplantation and implemented the basis for the surgical technique in the clinical scenario. More than ever, this is a perfect example of translational research and implementation of bench work to the bedside. Not so long ago, Dr. Pribaz et al. at Harvard and Brigham and Women's Hospital illuminated the plastic surgery community with the revolutionary concepts of flap prelamination and prefabrication. These elaborated techniques, well documented in literature, pursue the goal of fabricating new flaps and parts in the human body ready for autotransplantation. There is no surprise that few years later the same institution is at the forefront of face VCA in the USA. On the other hand, VCA has opened a new era not only in reconstructive surgery but also in transplant surgery. To date, there have been reports of successful transplantations of the knee joint, hand (unilateral and bilateral), arms (unilateral and bilateral), face (partial and total), abdominal wall, larynx, penis, digits and lower limbs. All recipients presented with deformities and/or amputations that were not amenable to be reconstructed by means of classical or traditional techniques. Such deformities affected nonvital parts and/or organs, and all of them had in common the impossibility to restore form, function and cosmesis by means of conventional techniques and reconstructive surgery. The results of face transplantation in humans demonstrate that face transplantation is no longer an abstraction but a clinical reality. It has been implemented in the latest years with increasing interest and great success. The limits of indications are still, though, desperate catastrophic face disfigurement. Today, we are in a position to say that it has been possible to perform face transplantation both in animals and humans in a short period of time.

Similarly to that learnt in many other transplant and plastic surgery disciplines, the development of face transplantation programs calls for a strong team approach, building a multidisciplinary team that involves all necessary and diverse specialists to make a robust protocol and an experienced team that warrants excellency in outcomes. This multidisciplinary team is formed by all transplant disciplines usually involved in transplant medicine (surgeons, immunologists, infectious disease specialists, renal disease specialists) but should include also experienced health professionals more involved in the plastic and reconstructive scenario, namely, rehabilitation specialists, physiotherapists, occupational therapists, psychologists, psychiatrists and social workers. VCA procedures must be organised in tertiary centres with a strong commitment to transplant surgery and medicine. Such institutions have in common the required laboratory, clinical services and research units that are necessary to perform this new clinical discipline.

The general objective of our intense efforts in basic, clinical research and implementation in the human clinic is the standardisation and introduction of a new treatment for patients suffering from severe face deformities and destructions caused by burns, trauma, congenital defects and the extirpation of malignant tumours. It introduces technical aspects, immunological, psychological, ethical and legal methodologies and the necessary surgical proficiency for the performance of face transplantation.

1.1 General Aspects

The face has important functional and aesthetic roles. Phylogenetically related, the face has delicate structures to host the senses and to allow for correct nutrition and communication with the environment. However, as human beings, the face plays a central role in personal identity and in social interaction. It is well represented in different languages with different words to refer to the face as an organ ("cara", "faç", "faccia") or as an identity ("rostro; faz" or "visage", "viso"). We are what we see in others, and we recognise people by the face construction, the expression of emotions and the psychosocial input that the face imprints into each other. The face incorporates other exigent functions that merge together anatomy and emotions, such as the discourse, the communication competence and the emotional

expression. The latter is very significant from the social and psychological standpoint, since the communication with other human beings involves face expression in non-verbal communication. Its consequences are the following: the importance of the reconstruction of both anatomy and function is fundamental and accepts no controversy, and this requires the application of meticulous and innovative techniques, although total recovery of functions, social and emotional recovery and global aesthetical reconstruction remain extremely difficult. The main reason for such difficulty to obtain an optimal reconstruction of function, emotion and aesthetics of the "face–visage" is the highly specialised organisation of the face as an organ, which has to be approached with exigent technique to form function and aesthetics.

Burns, ballistic trauma (gunshots), benign tumours and malformations (neurofibromatosis and vascular malformations) and cancer ablation may produce important face deformities. The whole scope of plastic surgery does apply for the reconstruction of these defects. However, when important functional anatomical structures such as muscle sphincters (orbital, oral) are involved, final outcome is normally less than optimal. In order to obtain good cosmetic and functional results that match those of absent or deformed tissues, texture, colour and elasticity of tissues should be as similar as possible to the original tissues. Traditional reconstructive face surgery includes the utilisation of skin grafts (partial or full thickness), local flaps, tissue expansion, free flaps and face prelamination. Other nonsurgical options may include custom-made prosthetic reconstruction. When final, long-term results are analysed at follow-up, the overall results are usually that of a mask-type appearance. Even in experienced hands, when sophisticated techniques have been used, the lack of an effective function, especially of active competent muscle movement, prevents patients from regaining a normal appearance and correct face functions. Patients are confronted on a long, never-ending number of surgical procedures that in many situations render limited outcomes. Reasons for such important concerns and limitations include technical, anatomical and physiological issues.

The human face is a unique structure in nature, both by its anatomical basis and its function. Specific features such as the nose, mouth and eyelids cannot be reconstructed or transplanted from another part of the human body. Reaching a final, long-lasting solution for these deformities, making the deformed face a human spirit anew, experimental and translational researches for the last 20 years have been dedicated to study the technical, biological, immunological and ethical possibilities of vascularised composite tissue allotransplantation in humans.

This is not a new idea in reconstructive surgery. The most common method for the reconstruction of face defects is the transplantation (auto) of tissues from adjacent or distant parts of the same patient (Figs. 1.1 and 1.2). Local/regional flaps or grafts are commonly used. Microsurgery is necessary if distant tissues are autotransplanted from the same patient (Figs. 1.3 and 1.4). In some instances, though, prosthesis, osteointegration and biomaterials are utilised (Fig. 1.5). There is no doubt regarding the best outcome possible: it is obtained when tissues from neighbouring areas of the face are the donor areas for the defect. However, when we face severe deformities, these tissues may be absent or destroyed. This situation forces surgeons to search for other techniques that can render the desired outcome, which is no other than "restitutio ad integrum" of the face aspect, the face function and the quality of life. Classical, traditional (including sophisticated microvascular tissue transfers) reconstructions fill defects and repair deformities. However, in the majority of cases, they do not provide patients with a satisfactory aspect, since they do not repair the feeling of avoidance and isolation. It is not uncommon for patients to follow a long series of surgical interventions (some require more than 100 operations in a time span of 10–20 years), not obtaining, though, the desired outcome: social and functional reintegration.

In general terms, conventional techniques are the common option when skin coverage is the main goal of the surgical treatment. However, in

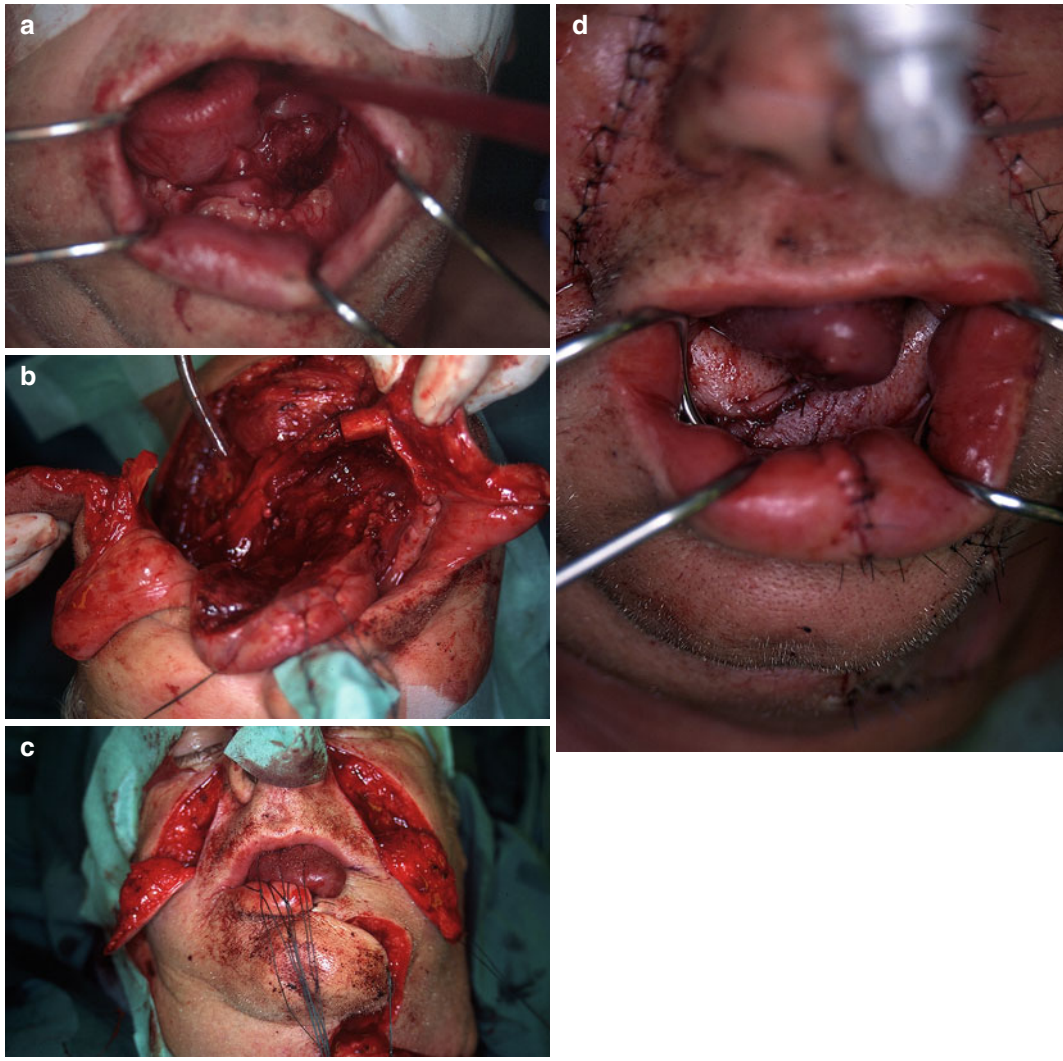

Fig. 1.1 Flap advancement and rotation are workhorses in plastic surgery reconstruction. (**a**) Cancer of the floor of the mouth. (**b**) Defect after resection and mandibular split. (**c**) Nasolabial flaps are elevated to reconstruct the defect. (**d**) Reconstruction with flaps in place

some cases, when extensive damage and severe scars are present and multiple operations with limited outcomes are expected (i.e. burns; Fig. 1.6), face transplantation may be indicated and taken into consideration. It may not improve much the functional outcome of that individual, although it will reintegrate him/her into society and it will avoid multiple conventional operations. Face deformity is a devastating disability that induces depression, social isolation and risk of suicide. Anger, shyness and avoidance are some of the feelings that face deformity patients feel and receive from society, worsening their recovery after trauma and burns or hindering the adaptation in congenital deformities. Our face is fundamental for physical attraction and is a primary characteristic of our identity. Consequently, a severe deformity, traumatic, innate or acquired,

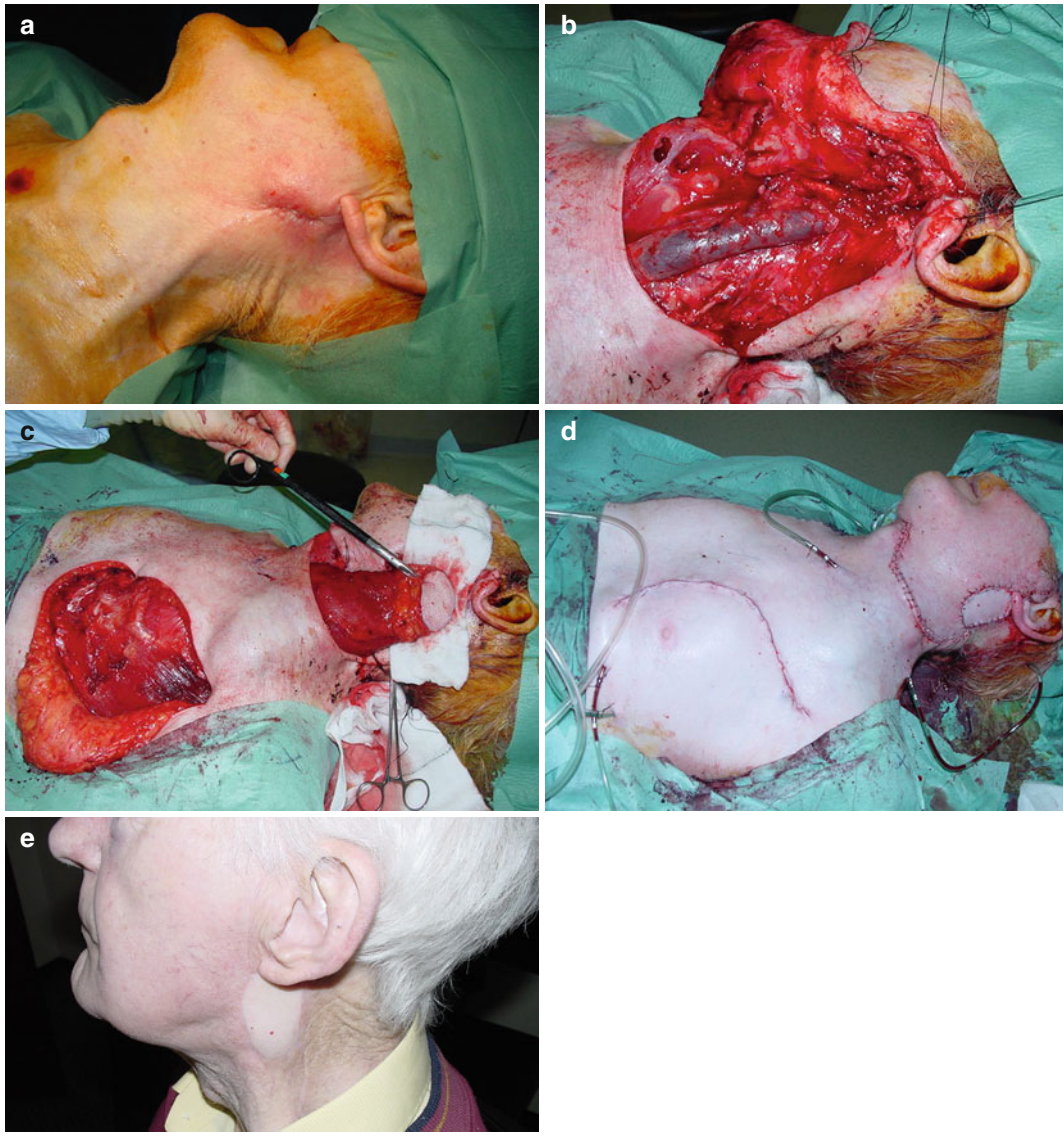

Fig. 1.2 Regional flaps are required when a more complex lesion shall be reconstructed. (**a**) Recurrent parotid tumour involving the cervical skin. (**b**) Defect after resection and modified radical neck dissection. (**c**) Elevation of a pectoralis major myocutaneous flap. (**d**) Result after reconstruction. (**e**) Long-term result

signals that person as "different or diverse". The consequences are social and emotional introversion.

It is estimated that in the USA alone, there are thousands of people that are severely disfigured and live in social isolation and they do not show in public. In general terms, few of them are real candidates for face transplantation. Only those patients that cannot be reconstructed with conventional techniques are candidates for face VCA. On the other hand, it should be stated also that those patients that cannot achieve the same excellent functional outcome offered by face transplantation shall not be offered conven-

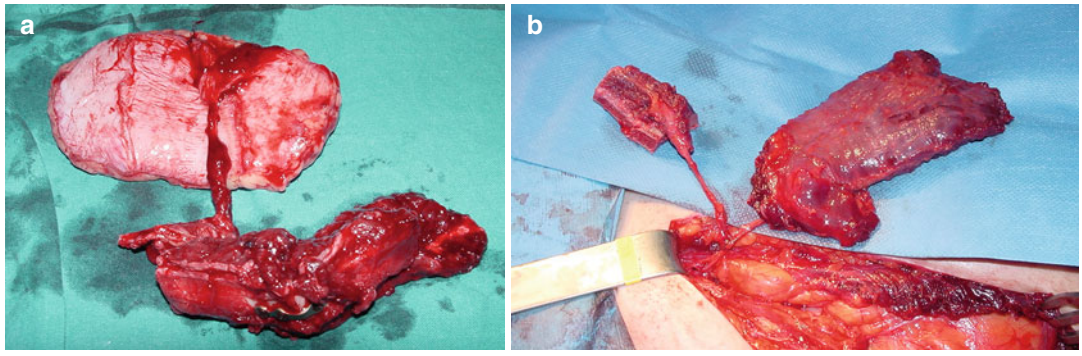

Fig. 1.3 Autotransplantation of flaps/composite tissues is based on reconstructive microsurgery. It joins all important issues in composite tissue allotransplantation with the exception of immunosuppression. (**a**) Free fibula osteocutaneous flap prepared for reconstruction of the mandible and floor of the mouth. Note the preformed fibula with miniplates in place. (**b**) Free deep circumflex iliac artery osteomuscular flap prepared for reconstruction of high-energy traumatism to the forefoot

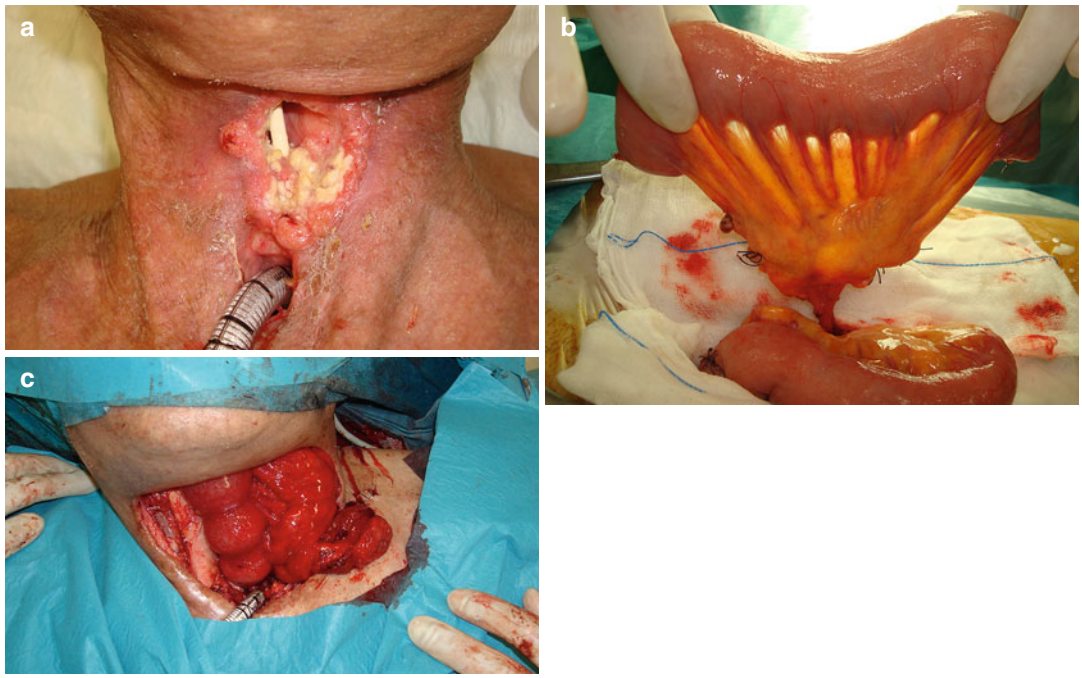

Fig. 1.4 Autotransplantation of a jejunal free flap for the reconstruction of the hypopharynx. (**a**) Recurrent laryngeal tumour after laryngectomy and radiotherapy. (**b**) Preparation of a free jejunal flap. (**c**) Reconstruction of the hypopharynx and oesophagus

tional reconstruction and be evaluated by face transplantation teams. After extirpating all scarred tissues and deformed face units, it is expected that patients recover good functional and aesthetic outcomes in 1–2 years (the time for motor and sensitive nerve recovery). Smiling, laughing, smelling, drinking, eating and speaking shall become again a normal daily living activity, making face transplantation the "gold standard" for these patients.

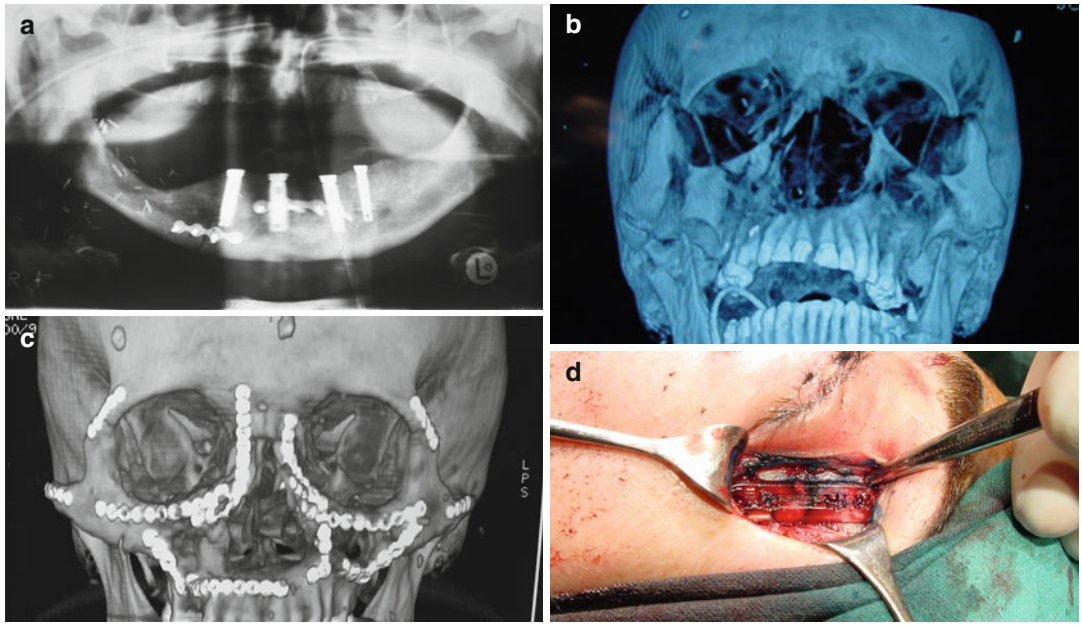

Fig. 1.5 The use of different biomaterials and titanium-based implants aids in craniofacial reconstruction. (**a**) Reconstruccion of a cancer defect of the floor of the mouth a radial forearm free flap and osteointegrated implants. (**b**, **c**) Titanium miniplates are the current foundation for reconstruction of face fractures. (**d**) Resorbable plates are new biomaterials that disappear between 6 months and 1 year

Fig. 1.6 Severe destruction of superficial face structures may indicate face VCA

1.2 Background

The idea of replacing the loss of human anatomical parts (especially limbs) has been depicted by many artists, and it is as old as human history and the history of trauma care. It has been recognised for decades that this objective was far from the human clinic due to immunological and technical barriers. The science behind the immunology of transplantation was initiated with the clinical objective of skin resurfacing and the reconstruction of severely deformed tissues in British pilots and burned navy soldiers injured by U-boat attacks during the Second World War. Physicians such as Tom Gibson and Peter Medawar and other collaborators developed the first experimental studies after tissue immunogenicity, especially skin transplantation and the paradox of

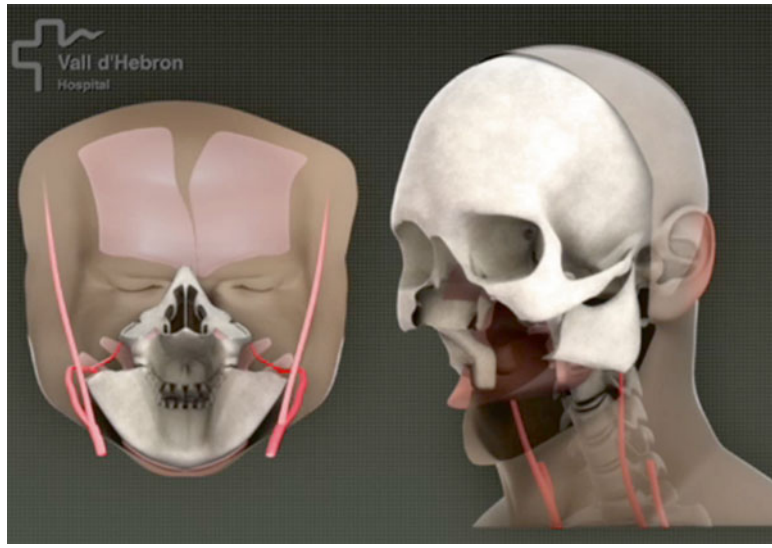

Fig. 1.7 The first full-face transplant performed in March 2010 in Barcelona, Spain

foetal and gestation tolerance. Their work founded the grounds for transplantation and brought a Nobel Prize in 1960. Soon afterwards many other pioneers in transplantation immunology joined these efforts. The lack for a good proper progression in skin transplantation and the initial encouraging data on experimental renal transplantation shifted the scientific attention from skin and soft tissue transplantation to human renal transplantation, which showed a more promising outcome. In 1954, Joseph Murray performed the first successful renal transplantation in humans between identical twins. Renal transplantation across the MHC followed, with the introduction of azathioprine as immunosuppressive agent. For this achievement, Murray received the Nobel Prize in medicine and physiology, and he remains the only plastic surgeon that has received such honour to date. These pioneering works and efforts were the opening of a new era in transplantation medicine. The evolution of renal transplantation encouraged other solid organ transplantation (SOT) programmes in the last decades of the twentieth century, such as heart, liver, lung, pancreas and small bowel transplants. During the same period, though, there was little progress on the exploration of clinical skin and soft tissue transplantation, most probably by the conception that skin was one of the most immunogenicity tissues in the human body. The former being reinforced by the pioneering experience of Gilbert in Ecuador, were doctors performed the first-hand transplantation ever in 1964, which was rejected despite the implementation of prednisone and azathioprine immunosuppression. More than 30 years elapsed between this first exploration of VCA and the first successful hand transplantation in 1998. The improvement in immunosuppression regimes and the introduction of new drugs (calcineurin inhibitors, cyclosporine A and tacrolimus, and mycophenolate mofetil) were grounds for improvement in survival (liver, heart, pancreas, lungs) and for the introduction of new SOT programmes such as small bowel transplantation. Their introduction in experimental models showed promising results in VCA in experimental animals. These impressive results prompted authors to organise a research team on human VCA at the University of Louisville, Kentucky, which showed good results in big experimental animals with long-term survival, proving the role of this preclinical study protocol. At the same time, other clinical scientists at the Cleveland Clinic (Strome and coworkers) developed experimental studies on laryngeal transplantation, and Hoffman and

co-workers, experimental studies on knee joint transplantation. Few years of research brought these types of transplantations to the clinic. Other teams were formed in Louisville and Lyon, aiming to perform human hand and upper extremity allotransplantation. The first human hand allotransplantation was performed in France (Lyon) in September 1998, followed by the Louisville team in January 1999. All initial efforts helped to the development of the initial VCA teams to date that have made a reality in the human clinic vascularised composite tissue allotransplantation of the hand, larynx, knee, femur, abdominal wall, upper and lower extremities and face (Fig. 1.7).

The initial development of hand allotransplantation programmes helped in the understanding of the performance of immunosuppression protocols, rejection episodes and their treatment and functional and midterm outcomes of VCA. Similarly, the initial outcomes of different VCA programmes have shown that a robust team and VCA protocol and good patient selection allow for excellent clinical results and good survival.