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Current State of Hand Transplantation

GRADUATE THESIS

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Summary

The loss of one or both hands causes a major psychological and social impact. Throughout history there have been numerous attempts at trying to restore normal function to the amputated hand by using prosthesis. Hand transplantation was not attempted until 1964 and the first successful hand composite tissue allotransplantation (CTA) was performed in 1998 in Lyon France. Both hand transplantations and prosthetic devices have advantages and limitations. Lifelong immunosuppression is required for hand (CTA) and the prosthetic devices are heavy and require mandatory visual control when using the device. Hand transplantation leads to great functional outcomes with physical rehabilitation, in the long run. Prosthetic devices do not require immunosuppressive therapy or surgery. The ideal candidate for hand transplantation is a bilateral distal trans-radial amputee already on immunosuppressive therapy due to a life-saving procedure. The functional outcome of many of the patients are excellent and enables them to return to daily activities such as personal hygiene, grooming and driving a car. Many were able to return to work after one year. Psychologically it was toughest for a patient in a review, the 6^{th} week after surgery. This was due to initial emotions of helplessness and dependence following the operation. Moreover, it was felt that initial functional capabilities of the transplant were very limited. After this period, however, when more functionality was restored the patient felt much better psychologically. Cortical reintegration and nerve regeneration is imperative for achieving a functional result of the hand transplant. Rehabilitation after surgery is very tough lasting 4-6h on an almost daily basis, but is gradually decreased. There are acute and chronic complications of the hand transplant surgery. The acute complications are categorized into medical and surgical. Chronic complications are mostly due to the immunosuppressive therapy. The future of hand transplantation is closely related to the development of better prosthetic devices that can match the functionality of a hand transplant. There has been

research about induction of chimerism by infusing donor bone marrow in the recipient. This brings the possibility of being able to decrease the amount of immunosuppressive therapy given to the patient.

1. Introduction

The hand is a fundamental part of the human body with major social and functional capabilities. Loss of one or both hands will lead to major psychological stress due to huge functional impairments in daily activities. Most cases of upper extremity amputations occur in males due to either combat or occupational injuries. However, some other cases also worth mentioning includes patients with congenital amputation of upper extremity. (Olson JL, Zuo KJ 2014) Prosthetic devices have traditionally formed the mainstay of treatment for upper extremity amputations. Patients have, however, often rejected them because of their discomfort, weight or limited usefulness. Newer prosthetics, including myoelectric prosthetics feature improved voluntary control and complex motion but are very costly, less durable and still heavy.

The emerging field of composite tissue allotransplantation (CTA) has made it possible to transplant an entire hand with all tissues included. This relatively new type of surgery has been able to accomplish far superior reconstructive results than any present prosthetic device. With hand transplantation the patient receives one or two hands that are nearly identical in both function and appearance to the missing limb. Moreover, the transplant may improve the psychological state from having lost one or two extremities.

There is, however, a requirement for lifelong immunosuppression and rigorous physical rehabilitation with prolonged functional recovery of the transplant. (Elliott RM et al. 2013)

2. History

Throughout history it has been pursued to rehabilitate and find alternative ways to restore function to individuals with an upper extremity amputation. The first way of restoring some kind of function to the hand was by the use of prosthetic hands. In the encyclopedia Naturalis Historia, from 77 AD, it was described by Roman scholar Pliny the elders, a use of prosthetics. These prosthetics helped the roman general Marcus Sergius to return successfully to battle in the Second Punic War (218-201BC). Since then there has been numerous other constructions of prosthetics, each becoming more advanced and restoring more functionality to the user. In more recent times the two world wars resulted in many casualties among a great number of these being due to explosive injuries and amputations of extremities. This great volume of injured people led to the creation of several associations worldwide pertaining to Prosthetic and Orthotic devices. Since then major improvements in mechanical prosthetics have been made, including the introduction of myoelectric prosthetics.

One of the major developments in the hand "prosthesis", however, is the composite tissue allotransplantation (CTA) which involves transplantation of many different types of tissues, including skin, muscle, nerve, vessel and bone. Transplantation has been available for some time, however, including solid organ transplantation. (Olson JL, Zuo KJ 2014) The hand is a complex structure including many different types of tissues each having their own antigenicity, compared to the more homogenous types if tissue included in solid organ transplantation.

The first documented attempt at hand transplantation was performed by a team of surgeons in Ecuador in 1964. However, immunosuppressive therapy which is needed to prevent rejection, was at the time in its infancy. The therapy used was azathioprine and prednisone. Unfortunately, they were unsuccessful in preventing the acute rejection that occurred after

two weeks. This acute rejection eventually led to the amputation of the hand. After this event there was a standstill in CTA, however, solid organ transplantation saw major improvements in the next thirty years. These improvements include enhanced immunosuppressive drugs including calcineurin inhibitors and antimetabolites. This new arsenal of drugs sparked new interest in CTA among researchers. The animal models used were rat hind limb allografts. By 1980s a team of researchers managed to demonstrate a long term survival of limb transplantation using low dose cyclosporine.

The first human hand transplantation was performed in September 1998 by a team of French surgeons in Lyon. The team was led by surgeon Jean-Michel Dubernard. They transplanted the right forearm of a brain-dead donor to a male recipient (age 48) with a traumatic mid-forearm amputation. The surgery was a success. However, the patient had problems with adapting psychologically to having to implement "someone else's" hand as their own. This lead to him not being compliant anymore with the immunosuppressive therapy. Eventually there was an acute rejection due cessation of therapy and the graft had to be amputated in 2001.

Within one year of the first hand transplantation, a surgical team in Louisville in the USA managed to achieve long-term hand graft survival. In January 2000 the first bilateral hand transplantation was performed in Lyon in France. In May 2002, Dubernard created the International Registry on Hand and Composite Tissue Transplantation (IRHCTT). The purpose of this was to improve CTA by combining all clinical experience on a global scale and making the information easily available to all transplant specialists. (Errico M et al. 2012) There have been 107 upper extremity transplantations in 72 patients performed in 26 centres worldwide. (Aszmann OC et al. 2016)

3. Advantages and limitations of hand transplantation and prosthetic devices

Fitting of a prosthetic device can take place quickly after an injury requiring short hospitalization and rehabilitation. Both hand transplantation and prosthetic fitting have their advantages and limitations. Unlike solid organ transplantation, which will prolong life significantly, limb transplantation may risk a shortened life expectancy but may significantly improve its quality. The risk–benefit ratio becomes very delicate, subjective, and therefore slightly controversial.

A successful hand transplantation will replace a lost body part while at the same time being worn constantly, looking aesthetically pleasing, being warm to touch and hold, and also being able to self-generate due to its being a biologic tissue. Moreover, motor function and sensation abilities may be restored. Long term results in different groups of patients seem to be excellent.

When the operation is finished and the hand is attached, the hand is not instantly able to be used with full functionality. After the operation comes long lasting physical therapy and lifelong immunosuppression. It is this immunosuppression that is the biggest problem, as there are numerous know side effects of the drugs used. Every patient has been recorded to have at least one acute episode of rejection. This rejection has been proposed to have a negative impact on the motor and sensory recovery. Moreover, the lifelong immunosuppression requires the patient to abide to a strict time schedule taking numerous drugs at the same time. Even though the transplant care is very strict it is reported in a recent review of worldwide experience with hand transplantation a high risk of acute rejection. It was reported that 24 grafts were lost (22.4% loss rate for all limbs) because of death of the patient, acute or chronic loss of the limb. The first transplant in France 1998 resulted in failure due to loss of patient compliance in taking immunosuppressive therapy. It is imperative to select an ideal patient who is psychologically capable of undergoing the

procedure, as well as adequate post-operative treatment. If all goes according to plan the hand transplantation can lead to excellent hand function and a huge improvement in the patient's quality of life.

It has for long been considered that prosthetic replacement in upper limb amputation has been the standard of care. However, the prosthesis makes it very challenging in helping the patient with daily activities such as grooming and hygiene. There has been a significant economic problem for manufacturers of prosthetics and orthotics due to abandonment of its products by the amputee. In a literature review from 2007 it is shown that the average rejection rate of all prostheses is 1 out of 5 individuals with upper limb deficiency over the last 25 years. Myoelectric prostheses are more capable in helping the amputee in assisting in daily life activities. There are, however, still major limitations due to the lack of any sensory information. Thus, precise motor commands tend to be difficult because of the mandatory visual control. The missing sensory feedback is a major problem, especially in bilateral amputees using prosthetics.

On the other hand, prosthetic fitting can early be undertaken after then injury and learning how to control the prosthesis is intuitive, especially for below elbow amputees, during adequate rehabilitation. Moreover, there is no need for any additional surgery or lifelong immunosuppressive therapy and the patients can return to a near normal life reasonably quickly. (Aszmann OC et al. 2016)

4. Indications

A survey from 2009 revealed that the majority (78%) of hand surgeons in the American society supported bilateral below elbow amputation as an important indication for hand transplantation. On the other hand, only 32% supported unilateral amputation of the dominant hand. In the same survey it showed that a majority (69%) of the participants considered hand transplantation a high risk endeavor.

In a unilateral amputee the new hand, being either a prosthesis or a transplant, will mostly serve as a helping hand. It is very likely that a unilateral amputee losing the dominant hand will develop dominance in the remaining healthy hand. Moreover, the loss of a dominant hand is likely to cause a major psychological and social impact on the patient due to the inability to shake hands, assuming the majority of the population is right handed. It is also important to mention that there will be a noticeable difference in size, skin texture and hair growth between the normal and the transplanted hand. (Aszmann OC et al. 2016) "A survey of amputee patients, organ transplant recipients and healthy subjects showed that hand/arm amputees did not see a great benefit in a single hand transplant. The amputee patients were significantly less willing to accept the risks of a single hand transplant than the group of organ transplant recipients and also less willing to accept a single hand transplant compared to the healthy volunteers. The risk acceptance for a bilateral hand transplantation was nearly twice as high as for unilateral transplantation, and the organ-transplanted group were willing to accept nearly the same amount of risk for bilateral hand or kidney transplantation" (Aszmann OC et al. 2016) These results suggests that the amputees still having one normal hand and one prosthesis are able to cope successfully with this give combination. This leads to the fact that the risk acceptance to the immunosuppression, inherently involved in the procedure, is low. There are, however, claims that the psychological impairment in unilateral amputees is cause enough to include this group as one of the major indications.

IRHCTT showed in their report from 2011 that 44% of the upper extremity transplantations were performed on bilateral amputees. A review from 2015, however, that covers the worldwide experience of upper extremity transplantation shows a paradigm shift from an initial dominance of unilateral hand transplantation to bilateral hand transplantation in recent years.

Transplantations have been favored at the distal trans-radial level. “The ideal patient for hand transplantation would be a bilateral distal trans-radial amputee suffering a sharp traumatic injury who is already under immunosuppression because of a life-saving procedure.” (Aszmann OC et al. 2016)

5. Surgical procedure for hand transplantation

“Transplant surgical technique is adapted from the replantation technique introduced by Dr. Malt in his 1962 publication “Replantation of Severed Arms.” The operation is completed under tourniquet using general anesthesia with regional block for vasodilatation and pain control. Optimally, two teams are used for a single transplant and four teams are used for a double transplant. Ideally, the recipient and donor teams are in the same room for coordination.

Patient stump preparation can begin once the donor limb is procured and the logistics of travel are settled. Yet, if there is any concern about the quality of the allograft, recipient preparation should be delayed until the donor limb arrives. at the transplant site. The recipient undergoes preoperative vein mapping in the OR holding area. In the operating room, mid-lateral incisions are made and subcutaneous dissection is performed with care to preserve superficial veins. Each structure is tagged using a piece of Esmarch labelled with indelible ink using 2-0 silk. Dorsal/volar mid-axial incisions with long skin flaps are utilized to expose the graft. The volar incision is extended to allow for release of the carpal tunnel. Subcutaneous dissection from proximal to distal is completed on iced sponges to minimize warm ischemia time. All structures are left longer than the anticipated need. Each structure is individually tagged with a piece of Esmarch bandage labelled with indelible ink using 2-0 silk. The donor is provisionally plated. The typical surgical sequence for a mid-forearm transplantation will be described. This is modified with more proximal amputations, as muscle bulk does not tolerate prolonged ischemia well. Hand transplant sequence differs

from that of hand replantation to allow for restoration of bone length and relative tendon tension as well as completion of dorsal vein and nerve anastomosis with group fascicular repair in a bloodless field. For osteosynthesis, the goals are length, alignment, and rotation. Perpendicular osteotomies are used to allow for maximal compression. Tendon repairs can be completed by the surgeon's method of choice. A Pulvertaft weave is used by many because it provides a strong repair amenable to early motion.44 Wrist extensors are repaired first and then thumb and digit extensors. The digits should extend with 20° to 30° of wrist flexion (tenodesis effect). For both extensors and flexors, proximal muscle repairs are usually limited to epimysium and perimysium. Tendon transfers are completed as needed. Vein repair is end to end. Two to four dorsal veins should be anastomosed. During vessel repair, it is important to avoid iatrogenic damage. Single artery repair can be done first if it is difficult to identify veins. An implantable Doppler is used around one vein. Nerve repair includes median (with palmar cutaneous if possible), ulnar (with dorsal sensory if possible), and radial (or PIN and radial sensory) using microscope. Distal repairs allow for more precise, group fascicular repair. Proximal repairs can be completed with epineural sutures. Radial and ulnar arteries are anastomosed using end-to-end repair distal to mid-forearm and end-to-side repair proximal to mid forearm to prevent disrupting branches to muscle bellies. One artery is repaired to complete initial revascularization, and then the graft is warmed with sterile saline to decrease vasospasm. Radial artery injury is common, and angiogram, embolectomy, TPA, or bypass may be necessary. Initial revascularization is followed by anastomosis of a second artery and additional veins with repair of the flexor tendons to restore a normal resting finger cascade. Skin flaps are then trimmed, drains are placed, and flaps are inset. Full thickness skin grafts from the donor are used if necessary. The four flap interposing incision allows versatility and maximal exposure without a circumferential scar contracture. A non-constrictive dressing and splint are placed. The composite graft is monitored with an

implantable Doppler and pulse oximeters on a finger from each hand for comparison." (MacKay BJ et al. 2014)

6. Immunosuppression

The immunologic profile of a hand CTA is very different from solid organ transplants due to the presence of different types of tissues. Skin is a particularly antigenic tissue type.

There is currently no standard immunosuppression protocol for hand transplantation. (MacKay BJ et al. 2014) However, the therapy frequently used consists of a multidrug regimen of tacrolimus, mycophenolate mofetil and a steroid. Furthermore, it has been found that tacrolimus enhances nerve generation, which is beneficial to the recovery of the graft. Induction therapy is very important as its purpose is to deplete the recipient's immune response and prevent acute rejection. It is typically consisting of either a polyclonal or a monoclonal antibody. These therapies have been derived from protocols that are commonly used within solid organ transplantation.

Chronic immunosuppression increases the risk for opportunistic infection, malignancy, diabetes, hyperlipidemia, nephrotoxicity, neurotoxicity, problems in wound healing and others. It is not uncommon that acute rejection occurs regardless of a rigorous use of immunosuppression therapy. Compiled data from the IRHCTT indicates that 85% of hand transplant recipients will experience a minimum of 1 episode of acute rejection after the transplant. This acute rejection is clinically often seen as an erythematous maculopapular rash. (Elliott RM et al. 2013) During the acute rejection in the first bilateral hand transplantation performed, topical steroid cream and oral prednisone was used to reach complete clinical and histological resolution within 10 days. (Dawahra M et al. 2003) Observing the skin is therefore of great importance. Moreover, a skin biopsy during acute rejection will include lymphocytic infiltrates classically seen in solid organ transplants.

The lifelong immunosuppression restrains the growth of the CTA and has led to increased scientific interest towards reducing immunosuppression or modulation of the recipient's immune system. Prior work in this has been done in the field of solid organ transplants, where donor bone marrow cells was included in the induction therapy. The idea of this was to create a state of immunologic chimerism in the recipient. This signifies a very critical step in including tolerance of donor antigens in the recipient. Upper extremity transplants often include vascularized bone marrow which increases the potential to induce chimerism in the patient.

Human trials in cell-based therapy have been performed at the University of Pittsburgh. An attempt at inducing tolerance through chimerism was made by infusing donor bone marrow. All patients experienced acute rejection and were treated with altezumab and prednisone for induction therapy and tacrolimus as monotherapy. Even though this was a limited trial it showed that following donor bone marrow infusion the CTA could be maintained using monotherapy of tacrolimus. However, it is an important find as induction of chimerism actually decreased the need for postoperative immunosuppression. (Elliott RM et al. 2013)

7. Functional outcomes

The IRHCTT has collected information on every case of hand transplantation since 2002 and has its own functional scoring system (Hand Transplantation Score System, HTSS). "The HTSS is a 100-point scale that evaluates six functional areas: appearance (15 points), sensibility (20 points), movement (20 points), psychological and social acceptance (15 points), daily activities and work status (15 points), patient satisfaction and general well-being (15 points). A total score of 81 to 100 points is graded as an excellent outcome, 61 to 80 as good, 31 to 60 as fair, and 0 to 30 as poor." (MacKay BJ et al. 2014) It has been shown to have good test-retest reliability and responsiveness and correlation with Disability of the

Arm, Shoulder and Hand (DASH) score. There have been excellent outcomes around 6 years' post-transplant using both HTSS scoring system and DASH questionnaire. Protective sensibility was developed by all patients with a surviving unilateral or bilateral hand transplants (90% have tactile sensibility and 84% have discriminative sensation). Intrinsic and extrinsic function improves over variable time frames depending on level of amputation (usually 9 to 15 months postoperatively, confirmed by EMG if possible). Improvement of quality of life is reported by 75% of hand transplant recipients. Most patients can accomplish daily activities (eating, writing, dressing, and driving) 1-year post-transplant and many may return to work. (MacKay BJ et al. 2014) In an article from the division of plastic surgery in Brigham and Women's hospital, they followed their index patient, a 68-year old formerly left hand dominant man who lost all 4 limbs due to sepsis in 2002. He underwent bilateral hand transplantation in 2011. Since then he was followed closely for 3.5 years and several video clips have been taken to show new aspects of function as they occur in time. At 9 months post operatively he is seen in different video clips mowing the lawn using both hands, driving the car and swimming using both hands. In another clip taken 1 year postoperatively it shows the patient transferring water into a glass from a container. Lastly, the patient completes a 9-hole peg test, with his left dominant hand, in 21.96 seconds 2.5 years postoperatively. Moreover, there was a study of 703 healthy adults that reported the timing of a 9-hole peg test, for a 66-70-year-old man to be 21.23 seconds for the dominant hand. The patients result was very close to the "normal" result at 2.5 years. (Benjamin MJ et al. 2015)

8. Psychosocial outcomes

There are no standardized measurements for psychosocial outcomes as of yet. However, the need for it is definitely there with the increasing amount of hand transplantations performed globally. The first attempt at successful hand transplantation eventually led to amputation due cessation of patient adherence to immunosuppressive therapy. The reason for this was

psychological incompatibility of the recipient with the transplant. (Errico M et al. 2012) A standardized measurement for psychosocial outcomes can be very useful in adequate screening and follow up of patients having underwent hand transplantation.

A review of serial follow-up of a 68-year-old male patient with a bilateral hand transplantation follows this patient over 3.5 years using different metrics to study psycho social outcomes. Numerous psychosocial self-reported measures were used including, Medical Outcomes Survey Short Form 12 (SF-12), Centre for Epidemiological Studies Depression (CES-D), Dyadic Adjustment Scale (DAS), Rosenberg Self-Esteem Scale (Rosenberg SE) and EuroQOL 5-Dimension Questionnaires (EQ-5D). Marlowe-Crowne Social Desirability Scale (MC-SDS) was used for preoperative social desirability.

SF-12 assesses 8 domains including, general health, physical functioning, physical role, bodily pain, vitality, social functioning, emotional role, and mental health. This is further subdivided into physical component summary (PCS) which includes the first 4 domains and the latter 4 domains constituting mental component summary (MCS).

CES-D measures depressive symptoms among the general population by using a 20-item scale.

DAS includes 32 items measuring the relationship with a partner.

Rosenberg-SE is a 10 item scale that assesses global self-worth by measuring both positive and negative feeling about self.

EQ-5D assesses function in mobility, self-care, usual activities, pain-discomfort and anxiety-depression. It is also accompanied by a Visual Analogue Scale (VAS) which provides self-assessment of one's own health.

The results showed no evidence of preoperative depression (CES-D), a non-stressful relationship with his partner (DAS), normal self-esteem (Rosenberg SE). The depressive symptoms did fluctuate after the operation but remained well below the clinical cut-off for depression. The relationship adjustment scores (DAS) also fluctuated within the normal range. EQ-5D and EQ-VAS were generally stable. The SF-12 MCS was frequently slightly higher than US norms. SF-12 PCS worsened at 6 weeks post operation, which was consistent with the patient experiencing increased disability and dependency during surgical recovery. It continued to fluctuate around the baseline over the remaining time of follow up. (Carty MJ et al. 2015)

9. Cortical reintegration

To achieve functional results cortical reintegration and nerve regeneration are imperative. There is an early concept in 1950 by Penfield and Rasmussen that describe the homunculus. Basically, specific areas in the brain were identified as being responsible for functionally and anatomically different regions of the body.

There have been many studies that have shown that cortical reorganization occurs after amputation with decreased cortical representation of the missing limb and increased cortical representation in adjacent limb. Dubernard and colleagues, who performed the first successful hand transplantation, published the results of functional MRI studies done before and after a bilateral hand transplantation was performed. It was shown that the cortical activation that was associated with movement of the transplant migrated, during the post-operative course, migrated towards the region of the brain that was expected to be responsible for hand function. What is more, it was seen that the size of the cortical area activated by hand motion grew with time. (MacKay BJ et al. 2014)

10. Rehabilitation

Post-operative care of hand transplantation is very similar to that of hand replantation and thus, has adapted from replantation protocols for rehabilitation. Functional recovery following hand transplantation is a long process with improvements occurring even years after the surgery. The rehabilitation team must help the patient under this long post-operative period to continuously evolve treatment protocols.

Brigham and Women's Hospital (BWH) have developed a generalized rehabilitation protocol for recipients of hand CTA and it provides a solid foundation upon which individual modifications can be made for each patient. The protocol was specifically developed for recipients of mid-forearm transplants, but is flexible and can be used for other levels of transplantation. Among therapy modalities included there is splinting (protect repair of the tissues and coaptation of tendons by keeping transplanted hand in optimal position for healing), edema and scar management (prevent inhibition of motion and adhesions), range of motion exercises (avoid tendon and joint adhesions and maintain gliding mechanisms), Activities of daily life (ADL) (training the recipient to perform complex tasks required of the hands), electrical stimulation (pain control, reduction of edema, muscle strengthening and wound healing), cognitive training (help augment re-learning of the cortical map of the hands in the brain), strengthening.

Moreover, the therapy protocol is divided into four phases with each having its own goal. The phases include pre-operative phase which aims to inform and educate the patient, asses, make recommendations and provide preparatory treatment. After that there is the initial phase (post-operative days 0-14) with goals to protect the transplanted hand or hands, minimize swelling, provide education and plan discharge. Moreover, there is also the intermediate phase (3-8 weeks) with goals to prevent/decrease scar adhesion, increase tensile strength of

tissues, flexibility and function as well as prevent joint contractures. Lastly, there is the late phase (8 weeks onwards) with goals to maximize function, increase strength, monitor sensory recovery and transition to routine activities.

The rehabilitation requires a great amount of work on the patient's behalf, with almost daily rehabilitation for hours (4-6h) that begins with hospital stay and later on in out-patient rehabilitation. Finally, it ends up at home with the possibility of involvement of the family in the physical rehabilitation. The intensity of the rehabilitation is gradually tapered, but nevertheless requires a lot of effort and willpower from the patient to achieve maximum functional recovery.

Formal testing of the patient was performed at week 6, 12 and 24 post-transplant and every 6 months thereafter. (Carty MJ et al. 2015)

11. Complications

Complications of hand transplantation can be divided into early and late complications. The early complications can be categorized into surgical or medical. For surgical complications it is common to see vessel thrombosis, hematoma, skin necrosis, arteriovenous fistulae, acute limb loss and death. Medical complications include pneumonia, sepsis, other infections not caused by surgery, and adverse reactions to medications.

Late complications are most commonly related to immunosuppression. The use of tacrolimus and sirolimus may worsen cardiovascular disease by causing hypertension, diabetes and hyperlipidemia. Moreover, infectious complications such as CMV, herpes and cutaneous mycoses may be caused by immunosuppression. The transplant literature has shown that

there is a 3 to 5 times increased risk of malignancies compared to the general population. However, only one basal cell carcinoma has been reported in hand transplantation recipients. (MacKay BJ et al. 2014)

12. The future of hand transplantation

The future of hand transplantation is closely related to the future of prosthetic devices. This present day it is evident that the functional outcome of hand transplantation, in the long run due to prolonged recovery time, is superior to that of prosthetic devices. "Hand transplantation as well as prosthetic devices will most definitely further improve within the next years. The successful induction of donor-specific tolerance would have great impact on the range of indication, as the risk of chronic rejection could be reduced or even eliminated, resulting in a safe transfer and most probably improved motor and sensory outcomes." (Aszmann OC et al. 2016) "Ongoing research is focusing on providing the prosthesis user with tactile and proprioceptive feedback; however, to date, these systems are not available for clinical use. Thus, future developments of prosthetic devices will have great impact on the indications for composite tissue transplantation." (Aszmann OC et al. 2016)

13. Conclusion

Hand transplantation is a relatively new treatment option for upper extremity amputees. The long term functional outcome is excellent in the majority of patients. It currently provides better functional outcome than prosthetic devices. However, there are requirements of life long immunosuppressive therapy that can be potentially harmful to the patient. For the best results the patient needs to adhere to rigorous physical therapy. It is very important to properly screen the patients that will undergo transplantation to make sure that they are psychologically ready to comply with the prolonged therapy that waits after the transplantation is finished. The first case of a successful transplantation eventually led to amputation due to psychological incompatibility of the patient with the transplant, which led

to cessation of adherence to immunosuppression. This example shows the importance of proper psychological screening. Moreover, it would also be beneficial to implement some standardized methods where psychosocial outcome is measured. There is promising research ongoing regarding the induction of immunologic chimerism in the recipient. This would theoretically make it possible to lower the amount of immunosuppressive drugs used, which in turn would decrease the amount of adverse effects. At the moment it also seems like the major indication for hand transplantation is a patient with bilateral trans-radial amputation. The future of hand transplantation is closely related to that of prosthetic devices. If there would be a prosthetic device available that could give the amputee fine motor control and complete sensation it might be favored as a treatment method over hand transplantation due to the lack of immunosuppressive therapy and any major surgical procedure. It is important to make a risk-benefit ratio to really make sure that the patient benefits from then transplantation. This topic, however, is controversial.

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