2.7 Follow-up

Introduction
Follow-up registry of corneal grafts is a requirement to control quality. Analysis of the numerous factors influencing the results will make it possible to continuously improve the quality of care in the chain of corneal transplantation by corrective and preventive measures.

At the outset of grafting only the surgeon and the patient were interested in follow-up results. Later on, eye banks became involved. With the increasing international exchange of tissue, health authorities consider it their duty to control safety by setting rules, making legislation and collecting follow-up data concerning serious adverse reactions and events. Defining outcome became important. The number of graft failures, clear grafts, central endothelial cell densities, graft survival, the extent of visual ability and patients’ satisfaction, adverse events and adverse reactions are measurable results.

The main interest of the patient is that he or she is satisfied with the procedure, the postoperative visual ability and the graft survival time. Today the degree of satisfaction is objectively assessed with Quality Of Life (QOL) score. The patient should be informed about the benefits as well as the risks of a corneal transplantation. This allows him to accept or reject the surgery. Providing the patient with the proper information and thus enabling him to make the choice to undergo surgery is legally required in the Netherlands “Wet op de Geneeskundige Behandelings Overeenkomst” (WGBO). In most cases the patient is not worried about the serious adverse events and reactions as the occurrence is very low (see chapter 2.3.1 and 2.3.2).

The surgeon is interested in all results: first of all to inform the patient correctly and second, to improve his surgical techniques and postoperative procedures by comparing own results to national and international data and third to analyze trends and developments.

The eye bank staff is interested whether their selection criteria resulted in clear grafts postoperatively.

Depending on the registration level of follow-up data and subsequent analysis (surgeon related, centre related, nationally or internationally related) more comparisons can be made. It is a pity that usually the clinical follow-up registration is not integrated with the eye bank registration, with the exception of the registration in the Netherlands in the period 1995-2006. Coupling data from eye banks with clinical follow-up is the most ideal situation as it offers the possibility to analyse the effect of donor and tissue processing related factors on clinical outcome. In this respect, fitting in the scope of this thesis the following outcomes are of importance.
Outcomes

Graft failure
Graft failure is defined as a non-functional graft due to an abnormal contour requiring re-grafting or due to loss of transparency as observed by the surgeon. The causes of graft failure may be diverse: primary failure, slow endothelial decompensation, high irregular astigmatism, infection, immunological failure, traumatic wound dehiscence, disease recurrence in the graft and epithelial problems are all possible reasons for graft failure. A high intraocular pressure may attribute to graft failure. Primary failure, slow endothelial decompensation and infections are failures, which may be ascribed to an impaired quality or safety of the donor tissue (see chapter 2.3.2 and 2.4). A slow endothelial decompensation or late endothelial failure (LEF) is described as a gradual decompensation and failure of corneal grafts without an apparent cause, unresponsive to corticosteroids and without a rejection episode, correlated to the time of graft failure. Once the follow-up period exceeds the 5 years’ limit, the majority of graft failures is due to LEF. Graft failure is often presented as percentage of the total number of grafts performed. This is only informative when all recipients have the same follow-up time. The Kaplan Meier survival curves are a more informative method for the analysis of graft survival.

Clear Graft
A clear graft is defined as a graft that has not lost transparency as observed by the surgeon. Unfortunately, no objective method is yet available. For the description of corneal transparency in the patient’s records descriptive qualifications are used varying from cloudy to crystal clear.

Graft transparency may be affected by epithelial, stromal or endothelial disorders and the causes may be both donor related and recipient related (see chapter 2.1). The donor related epithelial defects have been discussed together with the other serious adverse reactions. The donor related loss of stromal transparency is generally caused by the impaired function of the endothelium (see chapter 2.1 and chapter 2.4). In the first weeks after transplantation however a corneal swelling might occur due to osmotic processes and disturbance of corneal hydration, this as a consequence of the presence of remaining dehydrating agents such as dextran in the donor stroma (for example after OC). Different groups of factors affect the functioning of the endothelium. Procedures related are the surgical handling, surgical trauma and the number of early postoperative technical complications.

Recipient related factors are the indication and initial diagnosis for PK and the age of the recipient. These factors determine the peripheral endothelial cell density of the recipient part of the cornea.
Together with the donor ECD this contributes to the observed central cell density in the graft after continued re-distribution after grafting. Presenting percentages of endothelial cell loss is not very informative if data on the post transplant time are lacking.

Postoperative central endothelial cell density
Endothelial cell loss in corneal grafts takes place at an accelerated rate, even if an overt allograft rejection is absent or additional surgical interventions are required. Whereas initial endothelial cell loss has been found to be substantial and rapid, later cell loss appears to be slow (see chapter 2.1).\textsuperscript{349} As long as the ECD remains above a critical level (300-500 cells/mm\textsuperscript{2}), the grafts usually stay clear and functional (see chapter 2.1 and 2.4). Endothelial cell loss 15-20 years after perforating keratoplasty is 72-77\%.\textsuperscript{211,350} The hypothesis is that late endothelial cell loss may be caused by inflammation, a chronic break-down of the blood aqueous barrier or a chronic slow immunological rejection but not by an acute allograft rejection.\textsuperscript{35}

Every eye bank is interested in the post operative endothelial cell loss. Six weeks to three months after grafting, central endothelial cell loss will reflect the original donor cell density and the viability of the donor cells. Apoptotic and necrotic processes with an onset before and during surgery will proceed after grafting. Later on, the effect of surgical trauma (trephination and suturing) will be reflected, as the donor cells will rearrange to compensate the loss of cells at the wound margin. At even later stages, the remaining cells in the periphery of the recipient cornea may interfere with the observed central cell loss after wound closure.

Corneal thickness
Changes in corneal thickness reflect an impaired function of the endothelium. An increase in thickness results in loss of transparency. When corneal thickness is used as outcome measurement, it concerns the central corneal thickness (CCT).

This may be measured by optical pachymetry, interferometry, ultrasonic pachymetry, and the now most frequently used optical coherence tomography and topographic systems, based on the scanning slit principle.\textsuperscript{351,352} With the newer methods smaller inter-observer variations are achieved compared to the older techniques.\textsuperscript{352} With this the CCT as a parameter becomes more reliable.

The biological variability in corneal thickness between healthy individuals is believed to be caused by variation in the amount of corneal stroma tissue. It is therefore a measurement of tissue mass and corresponding biomechanical parameters such as bending rigidity. A central thickness of 0.523 mm and a peripheral thickness of 0.660 mm in healthy individuals is shown, with small differences between men and women. Differences in thickness in different age groups are described with significant thinning in the corneal periphery in the higher age groups.\textsuperscript{353} Corneal thickness measurements can vary during the day.\textsuperscript{219}
Until now corneal pachymetry played a minor role in the post-operative control of the graft. Authors described that the thickness in the first postoperative days is followed by a decrease in thickness in the following months and a stabilizing thickness after 3-6 months.\textsuperscript{351,354} Corneal grafts with a CCT of 0.59 mm or thicker at 3 months post transplantation have been described to be at greater risk of failure than those with thicknesses of less than 0.59 mm.\textsuperscript{350} Long after keratoplasty (> 10 years) some find the corneal thickness similar to the measurement 2 years after the procedure\textsuperscript{354,355} while others find a slight increase in corneal thickness.\textsuperscript{350} It is expected that with the currently more reliable methods to assess the CCT, it may be considered as a standard outcome measurement.

\textit{Graft survival}

The parameters for graft survival are the survival time and the percentage of clear grafts at a certain point in time. Graft survival time is defined as the time between surgery and the moment where failure or loss of transparency is assessed by the surgeon. To compensate for the variation in follow-up time Kaplan and Meier have developed a method where the results are grouped into time intervals. This method is often described as actuarial. The results are presented as a curve, where percentage cumulated survival is plotted against survival time or as mean survival time for different follow-up periods by life table estimates.\textsuperscript{347,348,136} The graft survival curve visualizes the overall story of grafting. In keratoconus patients corneal grafting is very successful,\textsuperscript{338,356} while in patients with highly vascularised corneas the outcome is less favourable and compared to organ transplants even poor.\textsuperscript{123,136,225,357} Although many clinical factors affecting graft survival are well known less is known about the relation between eye banking procedures and graft survival (see chapter 5).\textsuperscript{225,228} Long-term graft outcome is relevant for at least two reasons. Many recipients are young and like to know the long term expectations for their graft, as it is well known that re-grafting has a less favourable prognosis. The second reason is that the final impact of various surgical techniques is only visible after decades of observation.

\textit{Serious adverse events}

A serious adverse event (SAE) is defined in the EU directive as “any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalisation or morbidity”.\textsuperscript{144,145,146}
SAEs may occur at any stage from procurement to distribution of the cornea. Their registration is important for the professionals in the eye bank, for the corneal surgeons and the health authorities for continuous improvement of procedure and the reduction of risks. The surgeon and the patient at first may be unaware of a SAE. As consequences may manifest themselves in a later stage, the surgeon and the patient should be informed as soon as possible. Examples are keratoconus (suspect) and PTK, PRK or Lasik treated corneas. In all cases, this may lead to insufficient visual results but the actual risk is not yet known. Screening methods, OCT and topography have been described to detect the phenomena in the donor eye but routine application of these methods in eye banks is still not possible. Other examples are HLA matching errors between donor and recipient, transplantation of donor tissue, designated for other procedures than the requested, such as a cornea, originally intended for ALKP but later used in a posterior keratoplasty procedure.

**Serious adverse reactions**
A serious adverse reaction (SAR) is defined as: “an unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity”. SAR may include transmission of a severe ocular or systemic viral, bacterial or fungal infection or malignancy possibility attributable to the transplanted tissue; primary failure and delayed epithelial closure (see chapter 2.3.1, 2.3.2, 2.4, 5). A primary failure is defined as a graft failing to clear after surgery. This diagnosis is assessed by the surgeon either, shortly after surgery or at a later point during recovery (see chapter 5). According to the definition technical problems leading to a primary failure and endophthalmitis not transferred by the donor tissue are excluded.

Notifying the eye bank of a SAR is extremely important as investigation of possible causes is then feasible and appropriate measures can be taken. Notification to health authorities is important for the risk assessment and concurrent rules and regulations. The suspicion of transmission of a serious life threatening disease should be reported to the eye bank and health authorities to prevent transplantation of other tissues from that particular donor. Delayed epithelial closure may also be considered a SAR when the trend deviates from normal (see chapter 5) as it might be the first sign of less than optimal donor tissue and impending graft failure.

**Visual disability**
As visual disability is a common indication for corneal grafting, a change in this is a valuable measurement to test the success of the treatment. An accepted outcome is the visual acuity. While visual acuity may be a convenient outcome measurement, the link between visual acuity and visual disability, of interest for the patient, can be tenuous.
The best corrected visual acuity (BCVA), obtained with spectacle or contact lens irrespective of the patient’s preference, is generally registered. The influence of ocular morbidity on visual acuity may be a serious confounder in BCVA. Other visual function tests as parameters for success of the transplantation are studied, i.e. wave front aberrometry, different forms of contrast sensitivity and stray light tests. These tests may play a larger role to assess the benefits of the current lamellar keratoplasty procedures.

**Patient’s satisfaction**

The increased interest for Quality of Life (QOL) as an outcome measure has led to the development of numerous questionnaires to construct this parameter in the field of ophthalmology. For measurement of QOL after keratoplasty the Visual Function Index-14 or modified versions as the Penetrating Keratoplasty Visual Function Questionnaire are used. It has been shown that patient’s satisfaction is correlated with the presence of a clear graft, independence of contact lens correction, and having a better vision in the operated eye than the other eye. It is shown that for the satisfaction of the patient the visual acuity of the non operated eye plays an important role and therefore should be recorded.

**Concluding remarks**

In the literature graft failure and clear graft are often used as outcome measures. The last decades adequate and easy to use equipment is available, objectively assessed outcomes as endothelial cell density and corneal thickness should be included and considered to be more informative. To measure the change in visual disability the BCVA on its own is not sufficient. Currently the applications of additional evaluation methods are explored. The patient’s satisfaction score will be leading in defining relevant outcome results.
Corneal graft registries

General
Data of graft outcome can be collected in various ways. Much of what is reported comes from retrospectively collected data in case series, usually with a relatively short follow-up. There are randomized clinical trials with prospectively collected data. Another way is prospective and protocoled collecting of outcome data in corneal graft registries, together with pre operative and operative data in a uniform way over a prolonged period of time. Those registries offer the possibility to find in a scientific way factors affecting the success of corneal transplantation. Information regarding the effect of general donor parameters, the effect of eye banking procedures on donor tissue and in turn their influence on graft outcome could be obtained by coupling graft registries with eye bank registries. This requires a registration of these data in eye bank systems.

Historical
The first large scale multicentre corneal graft registry was the Australian Corneal Graft Registry, which was established in 1985 and now holds records of more than 20,000 grafts, some of which have been followed for over 20 years. A number of follow-up registries followed, the British register in Bristol, as well as the Dutch (this thesis) and the Swedish registers. In the Netherlands, a single centre registration started in 1976. To this data set, the information about grafts performed between 1939 and 1967 has been added. Detailed information on patients, donors and surgery reported in the theses of Deutman and Kok van Alphen was introduced in the data set.

Since 1980, eye bank data of more than 41,000 corneal donors have been electronically available in the Netherlands. As the Cornea Bank Amsterdam (CBA) was the only national bank till 2004, coupling of these data with the National Corneal Follow-up Registry offered the possibility to analyze the influence of eye banking processes and selecting procedures for donor tissue on graft outcome (see chapter 4,5,6). Results of other corneal graft registries show changing indications over long periods and a different distribution of indications in various parts of the world. For instance in the Netherlands during time a change is observed for the various procedures such as increased graft size and an extended period of corticosteroid treatment after transplantation (Pels, personal communication).
Registration of serious adverse events and reactions

The European Parliament and Council launched in 2004 “the tissue and cells directive” 2004/23/EC and in 2006 directive 2006/17/EC and 2006/86/EC. These directives, in addition to setting standards, require notification of adverse events and adverse reactions to the national authorities.\textsuperscript{144,145,146}

In the Netherlands the organisation “Transfusion Reactions In Patients” (TRIP)\textsuperscript{388} is designated by the Ministry of Health to fulfil this function. TRIP was used to look after the vigilance of blood and blood products.\textsuperscript{388} In 2007 an EU funded project: “Vigilance and Surveillance” was started by EUSTITE (European Union Standards and Training in the Inspection of Tissue Establishments).\textsuperscript{389} This project has the objective to propose common systems for definition, classification and reporting of SAE and SAR that are consistent with vigilant systems elsewhere in the world. A well organised, national and international collection, supported by follow-up registries, of SAEs and SARs data, crucial to define risks, will stimulate and accelerate improvements in eye banking and corneal grafting.
References


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388. TRIP = Transfusie Reacties in Patienten (The competent authority in the Netherlands to notify in case of serious adverse reactions or serious adverse events, according to Commission Directive 2006/86/EC.) www.tripnet.nl