Cost and outcome of liver transplantation

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Chapter 1

Introduction

This introduction is meant to inform the reader of some basic aspects of liver transplantation and to provide information regarding the health care environment in which liver transplantations are performed.

1 LIVER TRANSPLANTATION

1.1 Definition

Liver transplantation is the replacement of a diseased liver with another, healthy liver either from a deceased donor or a living donor. The replacement is performed with a whole liver or part of a liver, the so-called partial liver transplantation. After transplantation the donated liver takes over the function of the native liver. The vast majority of recipients of a donor liver need to take immunosuppressive medication for the rest of their lives to make sure the liver is not rejected by their immune system.

Liver transplantation is a life-saving procedure because, unlike dialysis in terminal kidney failure, there is no alternative treatment for patients with end-stage liver disease.

Liver transplantation is one of the most complex medical procedures. It involves practitioners from over 20 medical specialties working in integrated teams. Furthermore the procedure uses substantial resources from the hospital. A liver transplantation operation may last for 6 to 18 hours, often followed by a prolonged period of intensive treatment and subsequent rehabilitation.

1.2 History

Thomas E. Starzl performed the first liver transplantation in the United States in 1963. Unfortunately the patient died during the procedure due to uncontrolled bleeding[1]. In the Netherlands, the first attempted liver transplantation was performed in the Leiden University Medical Center (LUMC) in 1966. This patient also died during the procedure. After a worldwide voluntary moratorium related to poor results in several centers[2-4], the first one-year survivor after liver transplantation was reported in 1968 by Dr. Starzl[5]. A strictly protocolled liver transplant program was started in the University Medical Center Groningen (UMCG) in 1979[6]. Initially this concerned only adult patients but in 1982 the first pediatric liver transplantation was performed. Up till 1983, liver transplantation was regarded as an experimental procedure due to its low one-year survival rate reported to be less than 30%[7,8]. A consensus document of the National Institutes of Health (NIH) was published in 1983, based on the combined improved results of four liver transplant centers: Denver (US), Cambridge (UK), Hannover (Germany) and Groningen (the Netherlands). This document stated that liver transplantation could be recognized as an accepted treatment modality for patients with end-stage liver disease[9]. In the Netherlands, the Erasmus Medical Center and LUMC started their liver transplant programs in 1986 and 1992 respectively.

Since the start of liver transplantation as a medical intervention, important developments have taken place. The surgical technique underwent several important adaptations, such as the introduction of the veno-venous bypass[10,11], the piggyback technique[12-14], reduced-size[15,16], split liver transplantation[17], domino liver transplantation[18,19], and living related liver transplantation[20,21]. Also better immunosuppressants became available, such as cyclosporin A in 1983[22] and tacrolimus in 1994[23], which enabled more tailored immunosuppression for patients. The preservation solution for storage and transport of the liver from the donor to the recipient improved with the introduction of University of Wisconsin (UW) solution[24]. Anesthesia techniques and control of hemostasis improved as well. Knowledge and experience broadened in every aspect of the transplant process. Due to all these combined factors, one-year and five-year patient survival nowadays is 86% and 72% respectively, one-year and five-year graft survival is 82% and 65% respectively (www.unos.org, www.eltr.org, both accessed June 22, 2016). The longest surviving patient after liver transplantation in the Netherlands has been transplanted in the UMCG in 1980. Annually, the global number of liver transplantations exceeded 21 000 in 2010 according to the Global Observatory on Donation & Transplantation (GODT) produced by the WHO[25]. Approximately 14% was performed with an organ from a living donor.

1.3 Indications

A variety of indications may lead to end stage liver disease. Prevalence of transplantation indications varies greatly between countries and between adults and children. In adults, cholestatic liver cirrhosis, such as primary biliary cirrhosis or primary sclerosing cholangitis and post viral (hepatitis B or C) liver cirrhosis, is highly prevalent (Figure 1). In children, biliary atresia and metabolic diseases are more prevalent (Figure 2)[26,27].

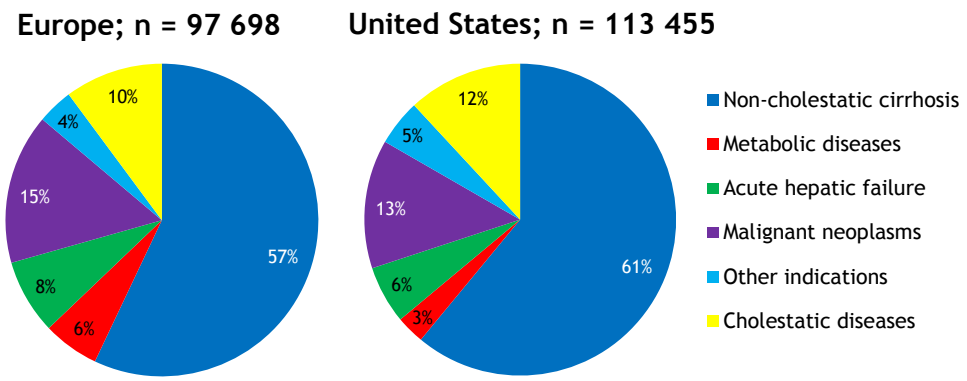

Figure 1. Indications for adult liver transplant recipients in Europe (ELTR) and the United States (UNOS)[26,27].

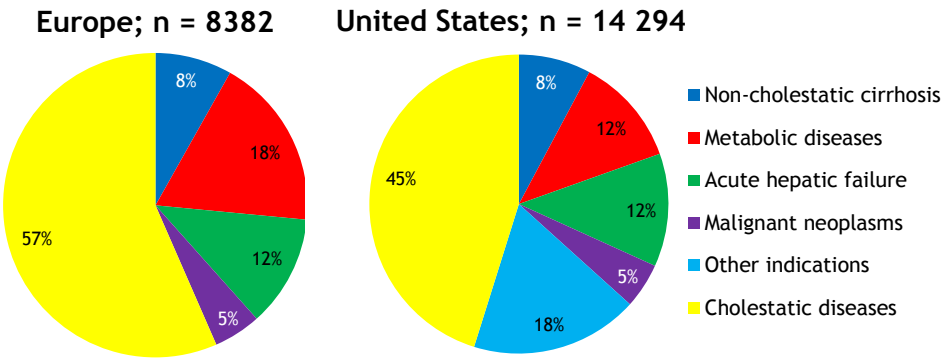

Figure 2. Indications for pediatric liver transplantation in Europe (ELTR) and the United States (UNOS)[26,27].

1.4 Selection of recipients

The selection of candidates eligible for liver transplantation is a complex process. Most patients are referred from other hospitals with acute or chronic liver disease. Their diagnosis has to be confirmed and sometimes more precisely specified. The next step is to determine the stage of the disease. This needs additional laboratory tests and radiological imaging studies. Even invasive procedures like a liver biopsy are sometimes needed. Frequently the assessment is repeated several times in order to judge the speed of progression of disease. This point is of pivotal importance for the timing of placement on the waiting list. Also the general condition of the patient in terms of cardiac, pulmonary, and renal functions needs to be assessed to see whether a major operation such as liver transplantation is possible. Extensive screening and when indicated treatment for bacterial, viral and fungal colonization or infections is mandatory in the light of the post-transplant immunosuppression. The assessment of the psychosocial status of the patient completes the screening process.

1.5 Timing of the liver transplantation

The right timing for liver transplantation is the crossing point of two lines. One line represents the disease progression of the native liver resulting in a declining survival chance. The other line represents the prognosis after liver transplantation with a transplanted liver. When the survival chance with liver transplantation is higher than the survival chance without liver transplantation, it is the right time for liver transplantation.

The disease progression is not a straight line. Intercurrent events can happen as a result of complications inherent to chronic liver disease. Examples are: infections (cholangitis), portal vein thrombosis or hepatorenal- and/or pulmonary syndromes. The optimal timing of LTx belongs to the expertise of experienced hepatologists in cooperation with transplant surgeons (Figure 3). It is further complicated by scarcity of suitable donor organs for given recipients and the absence of extracorporeal liver function replacement devices.

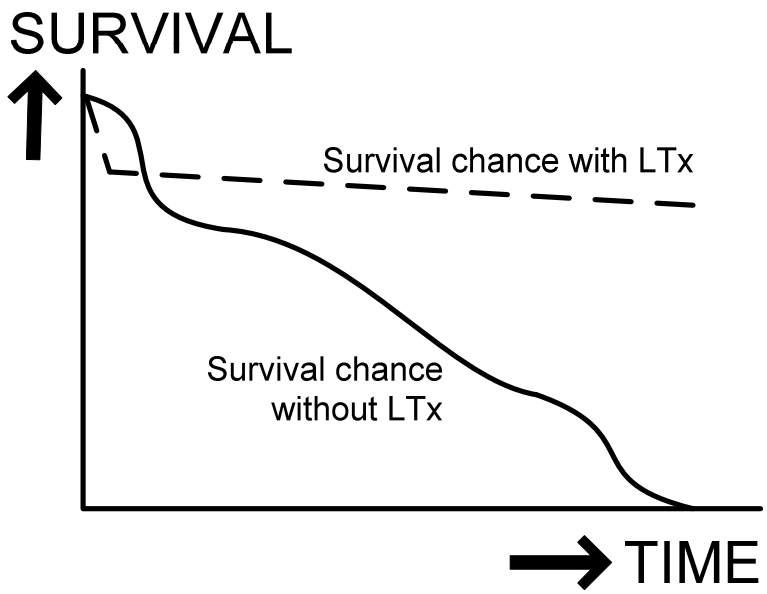

Figure 3. Optimal timing between waiting and receiving a transplant.

1.6 Waiting lists

In most countries a waiting list for liver transplantation has been present for decades. From an ethical perspective, allocation of scarce donor organs is a difficult balance between utility (utilizing the scarce organs as best as possible for the entire group of critically ill patients), equity (justice, sicker patients before healthier patients or patients with long waiting time before patients with short waiting time), and respect for personal autonomy (right to refuse or accept to donate organs or receive organs)[28]. This leads to a variety of allocation systems in different countries. In the Netherlands, the government decided on one national waiting list for all patients from the three liver transplant centers. Placement on this waiting list is done according to nationally agreed selection criteria. The Netherlands is a member of Eurotransplant International Foundation (Eurotransplant). Eurotransplant plays a key role in the allocation and distribution of donor organs for transplantation. The Netherlands participates in the Eurotransplant region together with Germany, Belgium, Luxembourg, Austria, Hungary, Croatia and Slovenia. The allocation of donor livers to patients on the waiting list is based on a MELD score (Model for End-stage Liver Disease) for adults and a PELD score (Pediatric End-stage Liver Disease) for children with standard exceptions as well as non-standard exceptions[29,30,31]. Standard exceptions are applied to all Eurotransplant countries, non-standard exceptions are country specific. These exceptions are based on specific diseases with additional criteria and give additional points to the MELD score. Graft allocation occurs primarily on a national basis. The higher the MELD/PELD score, the higher the place on the waiting list. For high-urgency patients and for organs not accepted by the national transplant centers the allocation is supra-national.

On December 31, 2015 there were 110 patients waiting for a liver or liver-kidney/liver-lung transplantation in the Netherlands[32]. In the last decade approximately 74% of waiting list removals were due to liver transplantation, 5% of patients recovered without transplantation, and 16% died or were too sick for transplantation. The remaining 6% were removed for other reasons, such as moving to another country (Figure 4)[32].

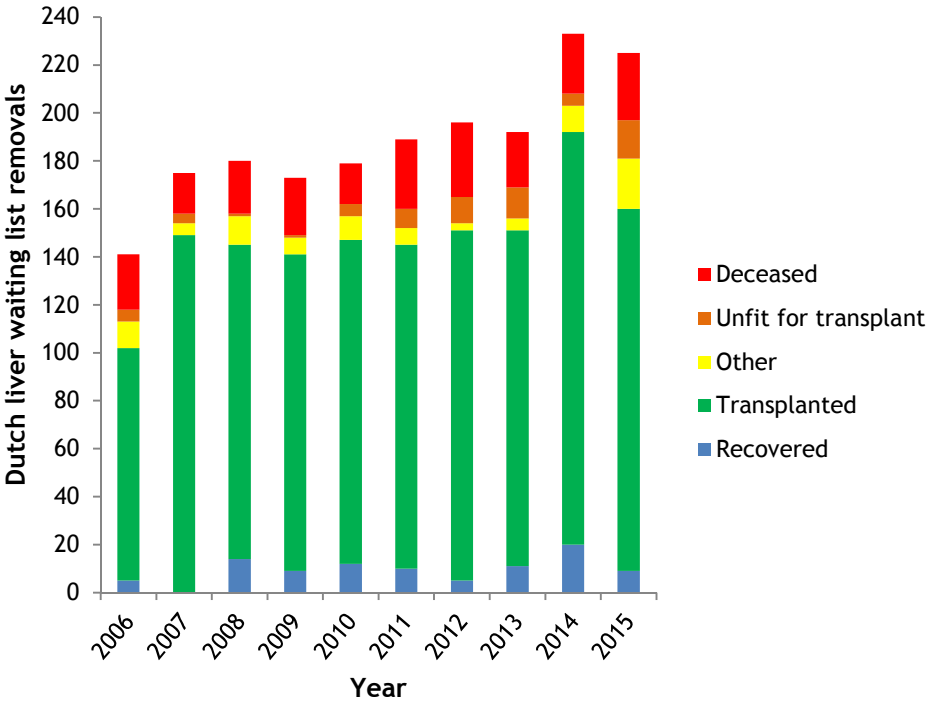

Figure 4. Waiting list removal per year in the Netherlands. Source: Annual report 2015 Nederlandse Transplantatie Stichting (NTS).

1.7 Availability of liver transplantation

The high costs, specific knowledge and medical infrastructure restrict the availability of liver transplantation to wealthier countries or wealthy individuals in countries where this care is not commonly available. In addition, cultural differences may limit the availability of post-mortem donor organs in certain parts of the world, i.e. Japan. Therefore, liver transplantation centers are not evenly distributed in the world. Most liver transplantations are performed in North-America and Europe (Figure 5).

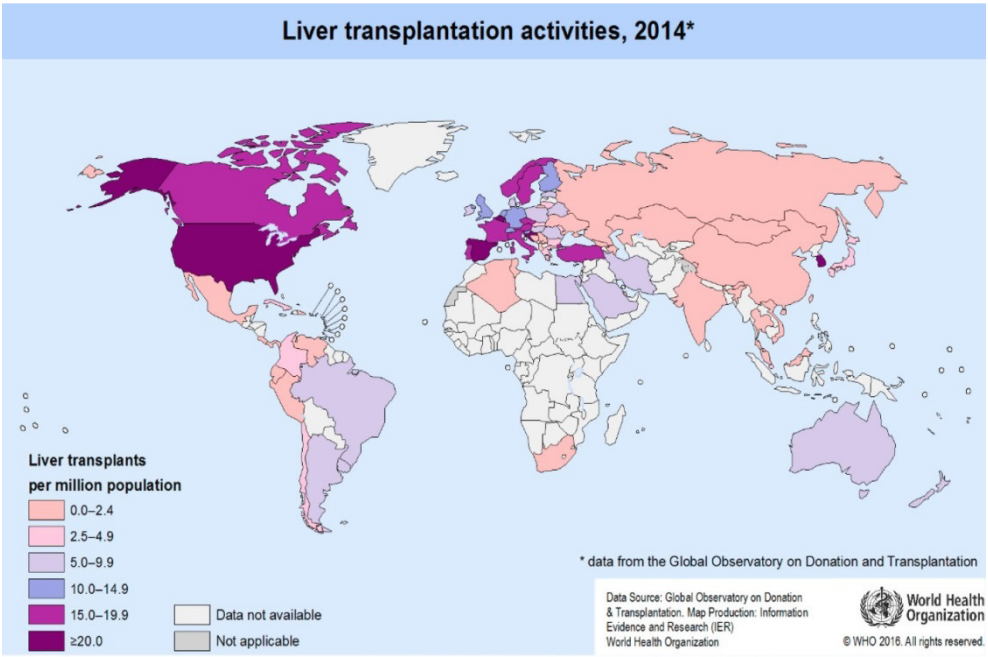

Figure 5. Liver transplants per million population (WHO-GODT 2015).

1.8 Availability of donor organs

The available number of donor organs limits the number of organ transplantations because in most countries the demand for donor organs exceeds the supply, resulting in waiting lists. Worldwide approximately 25% of patients on the waiting list die or are unfit for transplantation and die within a couple of months (Figure 6)[32,33].

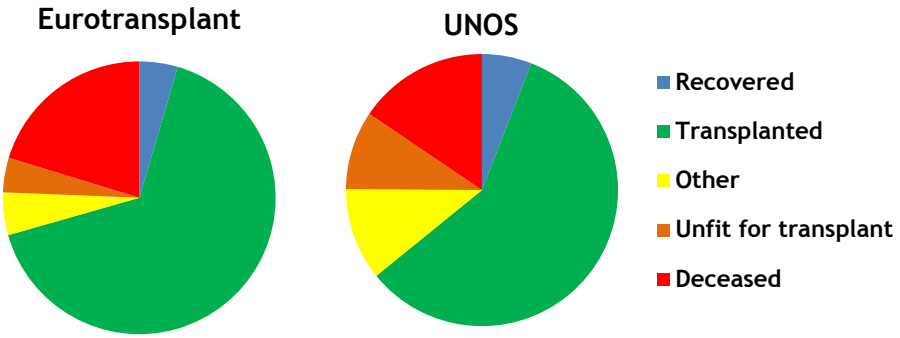

Figure 6. Removals from the waiting list 2004 - 2013 (Eurotransplant (n=25 640) and UNOS (n=106 093)[30,31].

To increase the number of donor organs, a lot of initiatives have been employed, professional, governmental as well as private. This thesis focuses on the professional initiatives. One of the measures was the utilization of less-restricted criteria for organ acceptance, so called extended criteria donors. Nowadays, donors over 65 years of age, higher thresholds for steatosis and organs from non-heartbeating donors are accepted. In order to use these organs with suboptimal function, cold ischemia time is kept as short as possible to prevent further damage. In addition, the donor pool was expanded by the use of technical variant grafts. Different techniques, such as reduced-size, split, and domino liver transplantation, have been developed by professionals. In order to increase the number of donor organs, living donor liver transplantation was introduced as well.

Concurrently, the number of potential optimal donor organs in the Netherlands is decreasing due to improved traffic safety and better diagnosis and treatment of cerebrovascular disease (Figure 7). This trend is comparable to the Spanish situation[34] even though the incidence of both causes of death is lower in the Netherlands.

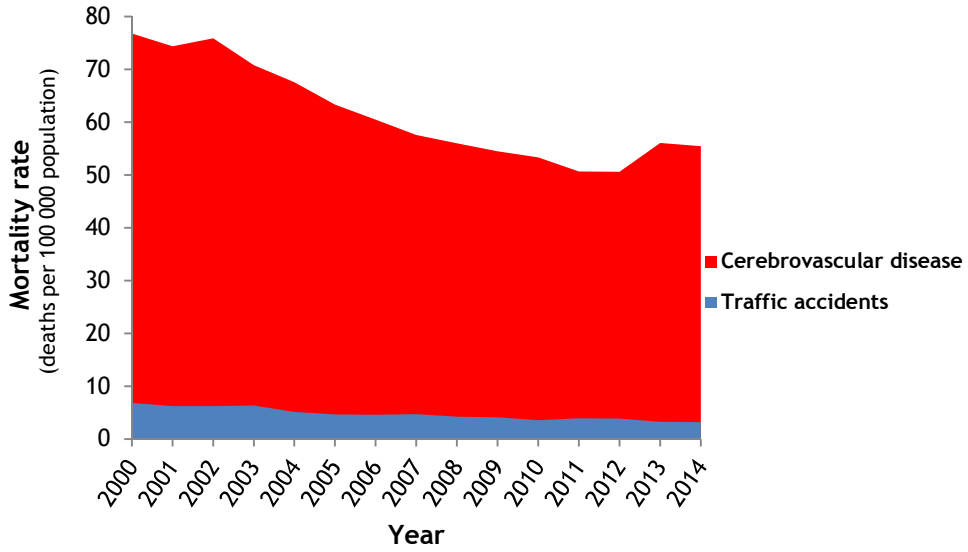

Figure 7. Mortality rate from cerebrovascular disease and traffic accidents (CBS Statline, accessed 2 June, 2016).

Governments have developed legislation to set ethical standards (e.g. establish brain death criteria), enable people to become a living donor (e.g. insurance) and also to increase and influence public awareness[35]. Also excellent examples of private initiatives have been shown, such as the International Emmy awarded Big Donor Show broadcasted in the Netherlands by BNN. Despite all these actions and initiatives the gap between supply and demand of donor organs is still present[36].

1.9 The operation

For the recipient a liver transplantation operation consists of three phases; the first phase concerns the explantation of the native liver. This can be done in the conventional way with removal of the retro hepatic segment of the inferior caval vein together with the liver. To accommodate the interruption of caval and portal flow during the anhepatic phase of the operation some centers still use a veno-venous bypass. This bypass combines the flows of portal and caval vein and transports the combined flows via a centrifugal pump to the axillary vein in order to deliver blood to the heart. Nowadays, many centers prefer to use a 'cava-sparing' technique in which the native liver is peeled off the inferior caval vein. With this technique the continuity of the inferior caval vein is preserved and a veno-venous bypass is not needed during the second phase of the operation: the anhepatic phase[37]. The third phase is the implantation phase. Two different liver transplantation techniques exist. In the commonly used piggyback method the liver graft is connected to the caval system by a side-to-side cavacavostomy, or anastomosing the supra hepatic caval cuff of the donor to the in situ caval vein or hepatic vein orifices of the recipient. In the classic method, the new liver is implanted with the donor retro hepatic inferior vena cava interpositioned in the bed of the native inferior vena cava. In both techniques the portal vein, arterial and biliary anastomosis are made after the caval anastomosis.

A distinguishing feature of liver transplantation is peri-operative blood loss and the use of blood products. Contributing factors to blood loss are disturbed hemostasis due to end stage liver failure, portal hypertension and surgical technique. Blood loss has a direct relation to the number and severity of post operative complications and survival[38]. Increased experience and continuing research in the field of hemostasis have contributed to an important decrease of perioperative blood loss over the years[39].

1.10 Immunosuppression

The immune system of the human body rejects foreign tissue as a means of self-protection. This also occurs in organ transplantation with a donor organ from another person. Immunosuppressive drugs like cyclosporin (CyA) and tacrolimus (FK-506) are used to suppress the reaction of the immune system. After organ transplantation lifelong immunosuppression is needed, even though the dose can often be reduced gradually over time. Because the immunosuppression is active in the entire body, a variety of long-term complications may occur as a result. Cardiovascular disease, impaired renal function, diabetes mellitus, metabolic disorders and opportunistic infections and malignancies may occur[40]. Therefore after a successful transplantation regular medical checkup with physicians specialized in liver transplantation is necessary for early identification and treatment of immunosuppression-related complications.

1.11 Follow-up

After liver transplantation the patient stays a period of time on the intensive care unit. The length of this period is determined by the severity of the liver disease, the pre-operative condition of the patient, and the occurence of per- or postoperative complications. After the intensive care the patient is rehabilitated on the ward until discharge. The length of this period is determined by the same factors as mentioned earlier. In the first year after transplantation regular outpatient visits are planned and in subsequent years annual checkups are performed. The primary care physician is also important for early identification of complications and quick referral[41].

Most complications after liver transplantation occur during the first post-operative year. The frequency diminishes in subsequent years[42].

Immediate post-operative complications are bleeding, biliary, vascular, and graft-related, such as life-threatening primary non-function. These complications need to be treated with a variety of reinterventions or even retransplantation. During hospitalization rejection of the graft, cardiopulmonary and bacterial, viral or fungal infections may occur which need medical treatment, sometimes for a prolonged period. After discharge other complications occur like recurrent disease, chronic rejection or side effects of the immunosuppressive therapy.

Despite these mentioned complications long-term survival after liver transplantation is excellent. However, many liver transplant recipients develop secondary health problems due to side effects of their medication (i.e. skin cancer, diabetes, overweight) or their life style (insufficient return to normal physical activity). In addition many patients continue to struggle with mental and psychological issues or have difficulty in finding a job[43]. These secondary health and social problems are not unique for liver transplant recipients as they can be seen in other solid organ transplant recipients as well. For the UMCG this has been a reason to start a multidisciplinary outpatient clinic for transplant recipients with the aim to improve quality of life and reduce the incidence of secondary events.

2 HEALTH CARE ENVIRONMENT

2.1 Participating medical centers

In the Netherlands, three centers are licensed to perform liver transplantations; Erasmus Medical Center in Rotterdam (adult), Leiden University Medical Center (adult) and University Medical Center Groningen (adult and pediatric). The three centers have a jointly agreed national selection protocol for placement of patients on the waiting list, one national waiting list and nationally agreed allocation criteria. Representatives of the centers meet regularly to adapt or modify existing rules, to discuss shared problems and initiate collaborative research projects.

2.2 Dutch health system

Improving health by the government was already part of the first Dutch constitution in 1814. Since 1983, the text in article 22 of the constitution is: "The government takes measures to improve health of the population". Healthcare in the Netherlands can be divided in two parts: 'care'(Exceptional Medical Expenses Act (AWBZ)) and 'cure' (Health Insurance Act (Zvw)). The 'cure' part of the Dutch healthcare system is financed from private obligatory insurance. As of 2013 there are seven insurance companies with a multitude of labels, which are obliged to provide a basic coverage package which insures a wide range of diagnostics and treatments, including organ transplantation and follow-up. Individuals have to be accepted regardless health status, age, gender, behavior or race and premiums may not be differentiated. The basic package covers approximately 94% of all 'cure' costs in the Netherlands. Additional coverage, with medical selection, may be purchased for dental care, physiotherapy and complementary care.

In the organization of Dutch healthcare the first echelon, mainly consisting of general practitioners, has a prominent place. Apart from acute care patients everyone has to be referred by their general practitioner in order to get access to hospital care. This way the first echelon plays an important role as gatekeeper. The first echelon is well developed and the vast majority of Dutch inhabitants have their own general practitioner.

Prices for Dutch healthcare are regulated for a small part by the government. This concerns low volume care with an inhomogeneous cost structure. The majority of prices have to be negotiated annually between the hospital and the health care insurance companies. University Medical Centers get additional funds for their last resort function. Outlier financing is limited.

In the last decades the Netherlands has been one of the richest countries in the world. With an estimated gross domestic product (GDP) per capita of $ 48 253 (purchasing power parity) in 2014 the country was ranked 14th (http://databank.worldbank.org, accessed: June 2, 2016). In 2014 approximately 10.9% of GDP was privately and publicly spent on healthcare, both care and cure (http://databank.worldbank.org, accessed: June 2, 2016). That is one of the highest expenditures per capita in the world. However, this is well behind the country with the highest spending per capita, the United States with 17.1% (Figure 8). There is a mutual relationship between wealth of a country and health of the population of a country[44].

Figure 8. Visualization from Gapminder World, powered by Trendalyzer from www.gapminder.org, retrieved June 2, 2016.

In the Netherlands, most treatments are available regardless of costs. New treatments and diagnostics are assessed by the National Health Care Institute (Zorginstituut Nederland; ZiN). Quality, accessibility and affordability are the pillars of the Dutch health insurance system[45]. ZiN must guard three conditions:

- The basic package must include all necessary high-quality care (care obligation).
- Insurers must accept everyone for basic insurance (obligation to accept all applicants).
- Everyone must take out health insurance and must therefore pay contributions (obligation to take out insurance).

ZiN has four criteria for assessing what should be included in the basic insured package: necessity, effectiveness, cost-effectiveness and feasibility. For new pharmaceutical products the cost per Quality Adjusted Life Year (QALY) ranged from € 10 000 per QALY for low-impact diseases to approximately € 80 000 for high-impact diseases[46]. For some very rare diseases expensive medication, which cost well over € 1 000 000 per QALY, remain part of the basic insured package[47,48]. For non-pharmaceutical innovations cost-effectiveness is sometimes applied, but not structurally[46].

In international benchmarks the Dutch healthcare system usually performs very well. According to the European Health Consumer Index the Netherlands has been consistently ranked first among 28 European Countries[49]. This benchmark compares health systems on patient rights and information, waiting time for treatment, outcomes, range and reach of services, prevention, and pharmaceuticals.

2.3 Costs and reimbursement

Due to the fact that liver transplantation is a complex treatment with lifelong follow-up and with involvement of a lot of different professionals, the associated costs are high as well. It is one of the most costly medical procedures. On the other hand, the treatment is effective with most recipients adding over 10 years to their life expectancy with good quality of life.

On a national level, the liver transplantation program including follow-up of transplanted patients has a minor budget impact (approximately 0.6‰ of 'cure' expenditures) because the number of liver transplantations is limited to approximately 140 per year due to organ scarcity[32,50].

For liver transplantations in the Netherlands there is separate reimbursement for the donor procedure, the transplantation and the regular follow-up. Also intensive care and reinterventions not directly related to the transplant procedure are reimbursed separately. Because of the inhomogeneous cost structure and the low prevalence the Dutch Healthcare Authority (Nederlandse Zorgautoriteit; NZa) determines the average reimbursement based on costs of the three centers. Hospitals get a fixed amount reimbursed for all liver transplants without regard to the severity of disease of the patient or the type of donor.

REFERENCES

1. Starzl TE, Marchioro TL, Von Kaulla KN, Hermann G, Brittain RS, and Waddell WR. Homotransplantation of the liver in humans. Surg Gynecol Obstet. 1963;117:659–676.
2. Moore FD, Birtch AG, Dagher F, Veith F, Krisher JA, Order SE, Shucart WA, Dammin GJ, and Couch NP. Immunosuppression and vascular insufficiency in liver transplantation. Ann N Y Acad Sci 1964;120:729-738.
3. Starzl TE, Marchioro TL, Rowlands DT Jr, Kirkpatrick CH, Wilson WEC, Rifkind D, and Waddell WR. Immunosuppression after experimental and clinical homotransplantation of the liver. Ann Surg 1964;160:411-439.
4. Demirleau J, Noureddine M, Vignes C, Praverman A, Reziciner S, Larraud P, and Louvier M. Tentative d'homogreffe hepatique [Attempted hepatic homograft]. Mem Acad Chir (Paris) 1964;90:177-9. French.
5. Starzl TE, Groth CG, Brettschneider L, Penn I, Fulginiti VA, Moon JB, Blanchard H, Martin AJ, and Porter KA. Orthotopic homotransplantation of the human liver. Ann Surg 1968;168:392-414.
6. Krom RAF, Gips CH, Houthoff HJ, Newton D, van der Waaij D, Beelen J, Haagsma EB, and Slooff MJH. Orthotopic liver transplantation in Groningen, The Netherlands (1979-1983). Hepatology 1984;4:S1:61S-65S.
7. Starzl TE, Porter KA, Putnam CW, Schroter GPJ, Halgrimson CG, Weil R III, Hoelscher M, and Reid HAS. Orthotopic liver transplantation in ninety-three patients. Surg Gynecol Obstet 1976;142:487-505.
8. Calne RY and Williams R. Orthotopic liver transplantation: the first 60 patients. Br Med J 1977;1:471-476.
9. National Institutes of Health. National Institutes of Health Consensus Development Conference Statement: liver transplantation - June 20-23, 1983. Hepatology 1984;4:S1:107S-110S.

10. Shaw BW Jr., Martin DJ, Marquez JM, Kang YG, Bugbee AC Jr., Iwatsuki S, Griffith BP, Hardesty RL, Bahnson HT, and Starzl TE. Venous bypass in clinical liver transplantation. Ann Surg 1984;200:524-533.
11. Griffith BP, Shaw BW Jr., Hardesty RL, Iwatsuki S, Bahnson HT, and Starzl TE. Veno-venous bypass without systemic anticoagulation for transplantation of the human liver. Surg Gynecol Obstet 1985;160:270-272.
12. Tzakis A, Todo S, and Starzl TE. The anterior route for arterial graft conduits in liver transplantation. Transpl Int 1989;2:121.
13. Belghiti J, Panis Y, Sauvanet A, Gayet B, and Fékété F. A new technique of side to side caval anastomosis during orthotopic hepatic transplantation without inferior vena caval occlusion. Surg Gynecol Obstet 1992;175:270-272.
14. Cherqui D, Rotman N, Duvoux C, Dhumeaux D, Julien M, and Faqniez PL. Orthotopic liver transplantation with preservation of the caval and portal flows. Technique and results in 62 cases. Transplantation 1994;58:793-796.
15. Bismuth H, Houssin D. Reduced-sized orthotopic liver graft in hepatic transplantation in children. Surgery 1984;95:367-370.
16. Broelsch CE, Emond JC, Thistlethwaite JR, Rouch DA, Whitington PF, and Lichtor JL. Liver transplantation with reduced-size donor organs. Transplantation 1988;45:519-523.
17. Pichlmayr R, Ringe B, Gubernatis G, Hauss J, and Bunzendahl H. Transplantation einer Spenderleber auf zwei Empfanger (Splitting-Transplantation) - Eine neue Methode in der Weiterentwicklung der Lebersegmenttransplantation [Transplantation of one donor liver to two recipients (splitting transplantation) - A new method for further development of segmental liver transplantation]. Langenbecks Arch Chir 1988;373:127-130. German.
18. Furtado A, Tomé L, Oliveira FJ, Furtado E, Viana J, and Perdigoto R, Sequential liver transplantation. Transpl Proc 1997;29:467-468.
19. Hemming AW, Cattral MS, Chari RS, Greig PD, Lilly LB, Ashby P, and Levy GA. Domino liver transplantation for familial amyloid polyneuropathy. Liver Transpl and Surgery 1998;4:236-238.
20. Raia S, Nery JR, and Mies S. Liver transplantation from live donors. The Lancet 1989;334:497.
21. Strong RW, Lynch SV, Ong TH, Matsunami H, Koido Y, and Balderson GA. Succesful liver transplantation from a living donor to her son. New Eng J Med 1990;322:1505-1507.
22. Calne RY, Rolles K, Thiru S, McMaster P, Craddock GN, Aziz S, White DJG, Evans DB, Dunn DC, Henderson RG, and Lewis P. Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. Lancet 1979;2:1033–1036.
23. Starzl TE, Todo S, Fung J, Demetris AJ, Venkataramman R, and Jain A. FK 506 for liver, kidney, and pancreas transplantation. Lancet 1989;2:1000-1004.
24. Southard JH and Belzer FO. Organ preservation. Annu Rev Med 1995;46:235-247.
25. Transplant-observatory.org. World Health Organization: Global Observatory on Donation and Transplantation. Liver transplantation activities 2012 [updated 2014, January 7; cited 2016, June 2]. Available from: http://www.transplant-observatory.org/.
26. Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR), Journal of Hepatology, 2012;57:675-688.
27. optn.transplant.hrsa.gov. OPTN/UNOS Statistics: National liver waiting list, organ by diagnosis, by candidates. [updated 2016 July 29, cited 2016 August 3]. Available from: http://optn.transplant.hrsa.gov/.
28. Ethical principles to be considered in the allocation of human organs (Approved by the OPTN/UNOS Board of Directors on June 22, 2010). Available from: http://optn.transplant.hrsa.gov/resources/ethics/.
29. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, and Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464-470.
30. Wiesner RH, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK, Krom RAF, and Kim WR. MELD and PELD: Application of survival models to liver allocation. Liver Transpl 2001;7:567-580.
31. Jung GE, Encke J, Schmidt J, and Rahmel A. Model for end-stage liver disease. New basis of allocation for liver transplantations. Chirurg 2008;79:157–163. German.
32. Statistics.eurotransplant.org. Eurotransplant Statistics: Liver waiting list removals, by year, by country, by reason. [updated 2016 January 4; cited 2016 June 6]. Available from: http://statistics.eurotransplant.org/.
33. optn.transplant.hrsa.gov. OPTN/UNOS Statistics: National liver waiting list removals reasons, by candidates, by year. [updated 2016 July 29, cited 2016 August 3]. Available from: http://optn.transplant.hrsa.gov/.

34. Matesanz R, Domínguez-Gil B, Coll E, De la Rosa G, and Marazuela R. Spanish experience as a leading country: what kind of measures were taken? Transpl Int 2011;24:333-343.
35. Kuiper MA and Jansen NE. Wetswijziging legitimeert de huidige donatiepraktijk [Legislative amendment legitimises current organ donation practices]. Ned Tijdschr Geneeskd. 2013;157:A6456. Dutch.
36. Riemer V, Kirste G, Delmonico F, Noel L, and Miller C. Organ donors still scarce [podcast (mp3)]. Geneva (CH). World Health Organization; 2010.
37. IJtsma AJC, Van der Hilst CS, De Boer MT, De Jong KP, Peeters PMJG, Porte RH, and Slooff MJH. The clinical relevance of the anhepatic phase during liver transplantation. Liver Transpl 2009;15:1050-1055.
38. De Boer MT, Christensen MC, Asmussen M, Van der Hilst CS, Hendriks HGD, Slooff MJH, and Porte RJ. The impact of intraoperative transfusion of platelets and red blood cells on survival after liver transplantation. Anesth Analg 2008;106:32-44.
39. De Boer MT, Molenaar IQ, Hendriks HGD, Slooff MJH, and Porte RJ. Minimizing Blood Loss in Liver Transplantation: Progress through Research and Evolution of Techniques. Dig Surg 2005;22:265–275.
40. McGuire BM, Rosenthal P, Brown CC, Busch AMH, Calcatera SM, Claria RS, Hunt NK, Korenblat KM, Mazariegos GV, Moonka D, Orloff SL, Perry DK, Rosen CB, Scott DL, and Sudan DL. Long-term management of the liver transplant patient: recommendations for the primary care doctor. Am J Transpl 2009;9:1988–2003.
41. Fuchs VR, The gross domestic product and health care spending, New Engl J Med 2013;369:2-4.
42. Jain A, Reyes J, Kashyap R, Dodson F, Demetris AJ, Ruppert K, Abu-Elmagd K, Marsh W, Madariaga J, Mazariegos G, Geller D, Bonham CA, Gayowski T, Cacciarelli T, Fontes P, Starzl TE, and Fung JJ. Long-term survival after liver transplantation in 4,000 consecutive patients at a single center. Ann Surg 200;232:490-500.
43. Saab S, Wiese C, Ibrahim AB, Peralta L, Durazo F, Han S, Yersiz H, Farmer DG, Ghobrial RM, Goldstein LI, Tong MJ, Busuttil RW. Employment and quality of life in liver transplant recipients. Liver Transpl 2007;13:1330-1338.
44. Fogel RW, Economic growth, population theory and physiology, The American Economic Review, 1994;84:369-395.
45. Van Rijen AJG, Westerlaken AA, and Van der Grinten TED. Zinnige en duurzame zorg [Sensible and sustainable care]. Raad voor de Volksgezondheid & Zorg, 2006. Dutch.
46. National Health Care Institute. Van goede zorg verzekerd [Taking care of good health care]. 2014 April. Dutch.
47. College van Zorgverzekeringen. Advies alglucosidase alfa (Myozyme®) bij α-glucosidase deficiëntie (ziekte van Pompe). Dutch.
48. College van Zorgverzekeringen. Advies agalsidase alfa (Replagal®) en agalsidase bèta (Fabrazyme®) bij α-galactosidase-A-deficiëntie (ziekte van Fabry). Dutch.
49. Health Consumer Powerhouse. Euro Health Consumer Index 2015, ISBN: 978-91-980687-5-7. 2015.
50. De Argumentenfabriek. Overzichtskaart: Hoe lopen de geldstromen in de curatieve zorg. Dutch.