

Diploma Thesis

Influence of immunosuppression on de- novo carcinoma in transplanted patients

submitted by

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attaining the academic degree

**Doktorin der gesamten Heilkunde
(Dr. med. univ.)**

at the

Medical University of Graz

conducted at the

Division of Transplantation Surgery

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Graz, August 17th 2009

(signature)

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Danksagungen

An dieser Stelle möchte ich mich ganz besonders bei Ass. Dr. Philipp Stiegler und Univ.- Prof. Dr. Florian Iberer bedanken, da sie diese Diplomarbeit ermöglicht und mich bei deren Erstellung tatkräftig unterstützt haben.

Weiters gilt mein Dank Ass. Dr. Vanessa Stadlbauer- Köllner für die statistische Auswertung der erhobenen Daten.

Außerdem möchte ich mich herzlich bei Lydia und John für die Durchsicht und Korrektur meiner Arbeit bedanken.

Spezieller Dank gebührt natürlich meinen Eltern, die mir nicht nur ein finanziell sorgenfreies Studium ermöglicht haben, sondern auch in jeder Lebenslage für mich da waren und immer an mich geglaubt haben.

Über diese Arbeit hinaus möchte ich mich auch bei meinen Freunden bedanken, die mir immer mit Rat und Tat, während den Höhen und Tiefen des Studiums, zur Seite gestanden sind.

Zusammenfassung

Einleitung: Heutzutage stellt die Organtransplantation vielfach die einzige Möglichkeit dar, um irreversibles Organversagen zu behandeln. Organempfänger haben aufgrund der immunsuppressiven Therapie, die sie ein Leben lang einnehmen müssen, ein erhöhtes Risiko an de- novo Karzinomen (DNC) zu erkranken. Das Ziel unserer Studie war es, Informationen über den Einfluss von immunsuppressiven Therapien auf die Entstehung von DNC nach Transplantationen zu gewinnen.

Methoden: Wir untersuchten retrospektiv alle orthotopen Herz- und Lebertransplantationen (HTX und LTX), die im Zeitraum von März 1983 bis Dezember 2008, an der Medizinischen Universität Graz, Klinische Abteilung für Transplantationschirurgie, durchgeführt wurden.

Für die statistische Auswertung der Daten wurden alle primären HTX und LTX-Patienten eingeschlossen. Organempfänger mit einer Malignomvorgeschichte stellten ein Ausschlusskriterium dar.

Ergebnisse: In unserer Studie konnten wir eine DNC- Inzidenz von 8% beobachten. 12,1% aller HTX- Patienten und 2,4% aller LTX- Patienten entwickelten ein DNC. Dieses Ergebnis zeigte eine statistische Signifikanz ($p < 0,001$). Die häufigste Neoplasie die wir nachweisen konnten, war Hautkrebs (ausgenommen malignes Melanom) mit einem Auftreten von 68,7% aller DNC.

Bezüglich einer Beziehung zwischen einem speziellen Typ von Karzinom und der Behandlung mit einzelnen immunsuppressiven Substanzen, konnte keine eindeutige Korrelation festgestellt werden.

Diskussion: Unsere Beobachtungen, hinsichtlich spezieller Arten von Malignomen, die nach einer Organtransplantation entstehen, insbesondere der Tatsache, dass ausgenommen von Hautkarzinomen, häufig beobachtete Karzinomarten der Normalbevölkerung, wie zum Beispiel Lungen- oder Prostatakrebs, keine Erhöhung der Inzidenz zeigten, sondern sogar eine deutliche Senkung, stimmten mit denen der Cincinnati Transplant Tumor Register überein. Aufgrund der Tatsache, dass verschiedene Transplantationszentren unterschiedliche immunsuppressive Regime führen und eine unterschiedliche Anzahl an Patienten betreuen, ist es schwierig diese zu vergleichen, um aussagekräftige Angaben zu machen.

Abstract

Introduction: In the modern world of 21st century medicine, organ transplantation is still generally regarded as the only serious choice in treating end- stage organ failure. However, it is already known, that solid organ transplant recipients face an enhanced risk of de- novo- carcinomas (DNCs) due to the subsequent obligatory life- long intake of immunosuppressive drugs. The aim of this study was to gather information about the specific influence of immunosuppressive therapy on de- novo malignancies in transplanted patients and then to analyse them statistically.

Methods: We retrospectively reviewed all of the orthotopic heart and liver transplant operations, which were performed at the Medical University of Graz, Austria, Department for Surgery, Division of Transplantation Surgery, between March 1983 and December 2008. This provided us with a combined total of 398 heart and liver recipients for evaluation.

Inclusion criteria were all primary performed heart and liver transplantations (HTX and LTX). Patients with a history of previous malignancy were excluded from the study.

Results: We found that the incidence of DNC in our study amounted to 8%. 12,1% of all HTX recipients and 2,4% of all LTX patients developed a DNC. This difference revealed a statistical significance of $p < 0,001$. The most common cancer in our study was non- melanoma skin cancer (NMSC) with 68,7% of all de- novo malignancies. The relationship between the type of tumor and the treatment with a specific kind of immunosuppressive agent has been inconclusive.

Discussion: Our observations concerning the type of cancer, which occurs after an organ transplantation, were in accordance with the Cincinnati Transplant Tumor Registry (CTTR), namely that apart from skin cancers, commonly observed types of malignant neoplastic diseases in the general population, such as lung or prostate cancers, are not increased, and, in actual fact, even showed some signs of decrease among the transplant recipients in our study.

However, based on the fact that every transplant center has different immunosuppressive regimes and varying numbers of patients, it has proven difficult to either make an accurate comparison between them, or to reach a definitive conclusion.

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List of abbreviations

6- MP	6- mercaptopurine
AK	actinic keratosis
ANZTR	Australian and New Zealand Transplant Registry
AZA	Azathioprine
BCC	basal cell carcinoma
BKV	BK- virus, human polyomavirus 1
BMI	Body Mass Index
CMV	cytomegalovirus
CNI	calcineurin inhibitor
CNS	central nervous system
CRF	chronic renal failure
CSA	Cyclosporine A
CTTR	Cincinnati Transplant Tumor Registry
DCMP	dilatative cardiomyopathy
DM	diabetes mellitus
DNA	desoxyribonucleic acid
DNC	de- novo carcinoma
EBV	Epstein- Barr- virus
ESBL	extended- spectrum b- lactamase
FKBP- 12	FK binding protein 12
GFR	glomerular filtration rate
GN	glomerulonephritis
HAART	highly active antiretroviral therapy
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDV	hepatitis D virus
HHV- 16	human herpes virus, type 16
HHV- 18	human herpes virus, type 18
HHV- 3	human herpes virus, type 3
HHV- 6	human herpes virus, type 6
HHV- 8	human herpes virus, type 8

HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPV	human papillomavirus
HSV	herpes simplex virus
HTX	heart transplantation
ICMP	ischemic cardiomyopathy
ICU	intensive care unit
IL	interleukin
IMPDH	inosine- monophosphate dehydrogenase
INR	international normalized ratio
IV	intravenous
JCV	JC virus, human polyomavirus 2
KS	Kaposi sarcoma
KTX	kidney transplantation
LTX	liver transplantation
MDR	multiply drug resistant
MELD	Model for End-Stage Liver Disease
MM	malignant melanoma
MMF	Mycophenolate mofetil
MOF	multi organ failure
MPA	mycophenolic acid
MRSA	methicillin- resistant Staphylococcus aureus
mTOR	mammalian target of rapamycin
NHL	non Hodgkin's lymphoma
NMSC	non- melanoma skin cancer
NODM	new onset diabetes mellitus
NRTR	Nordic Renal Transplant Registry
NYHA	New York Heart Association
OPT	occult primary tumor
PBC	primary biliary cirrhosis
PSC	primary sclerosing cholangitis
PTLD	post- transplant lymphoproliferative disorders
RNA	ribonucleic acid
SCC	squamous cell carcinoma

TAC	Tacrolimus
TB	tuberculosis
TIMP	thio- inosine- monophosphate
TIPS	transjugular intrahepatic portosystemic shunt
TOR	target of rapamycin
TX	transplantation
UBC	urinary bladder carcinoma
UNOS	United Network for Organ Sharing
UTI	urinary tract infection
UV	ultraviolet
VRE	vancomycin- resistant enterococci
VZV	varicella zoster virus
WHO	World Health Organisation

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1 INTRODUCTION

1.1 TRANSPLANTATION

1.1.1 History of transplantation

The idea to transplant organs has always been an object of myths and legends and can be traced back as far as year 500 B. C., although the first scientific organ transplantation was actually documented in the 18th century. (1)

Organ transplantation in the modern age plays an essential role as the treatment of choice in organ end- stage failure. (2)

Three great achievements have paved the way to allow the routine transplant of solid organs. First, the surgery techniques have been perfected; second, more basic cognition of immunology has resulted in supporting optimum performance of HL- antigens (HLA) to decrease the problem of rejection. Third, the application of immunosuppressive drugs has significantly enhanced survival prospects as a result of inhibition of T- cell- activation.

One of the first fundamental milestones in the history of transplantation was reached by the surgeon Emmerich Uhlmann in 1902 in Vienna with the first successful experimental canine kidney transplantation (KTX). Alexis Carrell improved the vascular suture in 1905. (1)

And in fact, those techniques of vascular anastomosis are exactly the same as those still used today. (3)

On December 23, 1954, the first kidney- graft was transplanted successfully from one healthy monozygote twin to his twin who was dying of chronic glomerulonephritis. The surgery was performed at the Peter Bent Brigham Hospital in Boston under the direction of Joseph Murray. (2)



(1)

Fig.: 1: First kidney transplantation, 1954

The recipient lived eight years with his new kidney before the same renal disease destroyed it. Joseph Murray later won the Nobel Prize in 1990 for his pioneering work. (1)



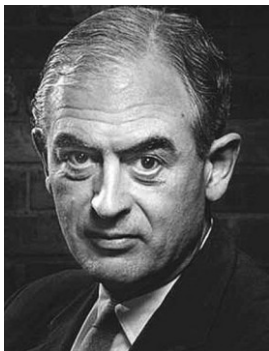
(1)

Fig. 2: Joseph E. Murray

In many animal experiments and also operations on humans, it was not possible for the transplanted organ to survive longer than a few weeks.

The main cause of these failures was the ignorance of the problems of rejection at that time.

Peter Medawar, an immunologist in Oxford, showed in 1945, that rejection is a result of active immunization, a discovery which led to another Nobel Prize award in this field, this time in 1960. (1)



(1)

Fig. 3: Sir Peter Brian Medawar (1915- 1987)

A few years earlier in 1958, the French researcher Jean Dausset had detected several antigens on the surface of nearly all cells, a piece of work which led to the first ever description of the HLA- system in 1958. (1)

After Medawars discovery that rejection was an immunological occurrence, many attempts were made to protect the transplanted organ by weakening the immune system with total body irradiation combined with cortisone. (4)

Although this irradiation suppressed the immune system, it was soon clear that total body irradiation was not the answer. (3)

In 1961, Azathioprine, a derivate of an anticancer agent called 6- mercaptopurine, discovered by Gertrude Elion and George Hitchings of the Wellcome Laboratory, was used as the first immunosuppressive drug to avoid rejections. (1) (3)

The success of kidney transplantations encouraged other surgeons to transplant other organs. For example in 1963 the worldwide first successful lung transplantation took place, followed in 1966 by the world's first successful transplantations of the pancreas (by Richard Lillehei in Minneapolis, Minnesota), the heart (by Christiaan Bernard in Kapstadt) and the liver (by Thomas E. Starzl in Pittsburgh, Pennsylvania). (1)

Partly driven by the replacement of Azathioprine by Cyclosporine in the year 1983, the rate of one- year graft survival increased from 70 percent to more than 80 percent. (1) (2)

During the last decade other more powerful immunosuppressive agents became available, e.g. Tacrolimus, Mycophenolate Mofetil or Sirolimus although each have their own specific side effects. (2) (3)

However, whenever society develops a growing need for something, like the increasing demand for organs, there will often be a growth in related criminal activity driven by money.

In some developing countries for instance poor families suffer from such enormous economic pressures that it is becoming increasingly common for one of the family members to sell an organ out of financial desperation.

In China, where capital punishment is allowed, organ donation from prisoners facing the death sentence, has been common, and people who live in countries where this is against the law but urgently need an organ, often travel there as recipients for an all inclusive- offer.

Certainly this kind of behavior in the area of organ transplantation is illegal, but up to now it has still not been stopped. (5)

Over the years, there have been strategies to solve the problem of the increasing demand for organs, like using tissues and organs from animals, but to date there have been only disappointments.

In the 1960s Reemstma removed a kidney from a chimpanzee and transplanted it into a patient. The new organ worked immediately, but only for 10 months.

These days chimpanzees are ineligible as donors for humans, pigs are more admissible, but there are still many challenges in the future of xenografting. (5)

1.2 LIVER TRANSPLANTATION

1.2.1 General considerations

The moment of transplantation (TX) plays a critical role, because the date has an important impact on lethality and mortality after LTX.

The well- established Child- Turcotte- Pugh Classification provides the following set of clinical criterion which can be used to determine optimum timing for transplant surgery. (6)

Table 1: Child- Turcotte- Pugh- Score

	1 point	2 points	3 points
Bilirubin (mg/dL)	< 2	2- 3	> 3
Ascites	Absent	Slight	Moderate
Prothrombin time (seconds prolonged)/ INR	< 4/INR < 1.7	4-6/ INR 1.7- 2.3	< 6/ INR > 2-3
Encephalopathy grade	None	1- 2	3- 4
Albumin (g/dL)	> 3.5	2.8- 3.5	< 2.8

Class A=5– 6;

Class B=7– 9;

Class C=10– 15 (7)

Over 30% of the patients with a Child C (Child- Pugh- Score >10), are dying within a year while waiting for an organ.

Patients in stage A (Child-Pugh- Score 5- 6) have a 5- year- survival- rate up to 90% without a LTX.

Due to the fact that patients with Child B (Child- Pugh- Score 7-9) have a 5-year- survival- rate of 80%, the indication for TX should be provided, otherwise advanced cirrhosis- specific complications minimize the success of the operation. (6)

Considering the bad prognostic predictive value of the Child- Pugh- Score, UNOS (United Network for Organ Sharing) in the USA use the MELD- Score (Model for End-stage Liver Disease) for allocating liver grafts for TX, since February 2002.

This new prognostic model should reduce the cases of death on the waiting list by a better appraisal of the 3- month- mortality. (6)

Table 2: Model for End- Stage Liver Disease Score

MELD- SCORE	Three- Month Mortality (Hospitalized Patients)
≤ 9	4%
10- 19	27%
20- 29	76%
30- 39	83%
≥ 40	100%

(7)

Actually, the MELD- Score was developed to evaluate short- time prognosis in patients after getting a TIPS (transjugular intrahepatic portosystemic shunt), but soon it turned out that the MELD- Score is a good assessment mechanism for patients with end- stage liver diseases using only laboratory measurements, like serum creatinine, serum bilirubin and INR, to decide which patient has the shortest time of survival. (7) (8)

Compared to the Child- Turcotte- Pugh Classification, the benefit of the MELD- Score is definitively that it is calculating simply with objective values, without using subjective symptoms, such as ascites or hepatic encephalopathy. (7)

Adam and Hoti explained the MELD- Score as follows: “The principle behind using the MELD score is “the sickest first” policy, in which not the time on the waiting list but the risk of mortality is the determining factor in deciding the organ allocation.”

(9)

1.2.2 Indications

The most frequent reasons for making the decision to proceed with a LTX in Europe are viral hepatitis (24%), alcoholic liver disease (20%), cholestatic liver disease (18%) and hepatocellular carcinoma (HCC) (10%). (8)

General indications for LTX are on the one hand benign disorders, such as chronic liver diseases and acute liver diseases, and on the other hand primary malignant diseases. (10)

Liver cirrhosis caused by hepatitis B (HBV), hepatitis C (HCV), hepatitis D (HDV), autoimmune hepatitis, alcohol or cryptogenic, cholestatic liver disorders like primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), secondary sclerosing cholangitis, familial cholestatic syndrome and atresia of the biliary tract, metabolic/ genetic disorders for instance α -1 antitrypsin deficiency, Wilson disease, hereditary hemochromatosis, glycogen storage diseases, Galactosemia, Tyrosinemia, β -Thalassemia, primary oxaluria, urea cycle enzyme deficiency, Mucoviscidosis, familial amyloidotic polyneuropathy, congenital cystic liver, Echinococcosis of the liver and Chronic Budd- Chiari syndrome are all counted among chronic liver diseases. (10) (11)

Also important indications for LTX are complications of cirrhosis, such as ascites, encephalopathy, synthetic dysfunction, refractory variceal hemorrhage and chronic gastrointestinal blood loss due to portal hypertensive gastropathy, and systemic complications of chronic liver disease, like hepatopulmonary syndrome and portopulmonary hypertension. (11)

Fulminant hepatic failure, like drug hepatotoxicity (acetaminophen), acute viral hepatitis; pregnancy- associated liver failure, severe liver trauma and postoperative liver failure following resection or LTX are counting among acute liver diseases. (8) (10)

Primary malignant diseases of the liver are including primary HCC, fibrolamellar hepatocellular carcinoma, liver metastasis of endocrine tumors, hepatoblastoma and epithelioid hemangio endothelioma. (10)

Usually, these patients have to comply with the Milan criteria, namely one up to 5 cm in diameter tumor or till 3 tumors up to 3 cm in diameter. (8)

Liver- retransplantation is performed in cause of irreversible graft failure and in many cases it is the only life- saving therapeutic option. (12)

Early graft loss results from primary nonfunction and hepatic artery thrombosis. (8)

Late graft loss concerns disease recurrence, such as HBV, HCV, autoimmune hepatitis, PBC and PSC; in which HCV is the most common. (11)

In other words, 1/3 biliary tract complications and chronic rejection, 1/3 hepatic artery thrombosis and 1/3 primary nonfunction, acute rejection, portal vein thrombosis, sepsis and HBV and HCV represent the need for liver retransplantation. (12)

On the basis of the facts, that there are some congenital syndromes, e.g. primary hyperoxaluria or familial amyloidotic polyneuropathy, which result in systemic disease, there are also a number of patients, who receive more than just one organ, for example combined kidney/liver, intestine/liver or lung/liver TX. (8)

1.2.3 Contraindications

Contraindications change over the years and between several TX centers. (11)

For example, a short time ago, an infection with human immunodeficiency virus (HIV) was an absolute contraindication for a LTX. Due to the high incidence of co-infections like HBV or HCV, many HIV- infected patients have an increased risk of dying, but after the implementation of the highly active antiretroviral therapy (HAART) the survival rate of these patients improved. Presently, HIV- infection is not any longer an absolute contraindication. (8)

Many TX centers now have their own specialist teams; consisting of hepatologists, transplant surgeons, transplant coordinators, psychiatrists and social workers, to discuss and arrive at a decision. (7)

It is important to distinguish between absolute and relative contraindications.

Absolute contraindications include active extrahepatic malignancy, hepatic malignancy with macrovascular or diffuse tumor invasion, active and uncontrolled infection outside of the hepatobiliary system, active substance or alcohol abuse, severe cardiopulmonary or other comorbid conditions, psychological problems, noncompliance, technical or anatomical barriers and brain death. (11)

Advanced age, cholangiocarcinoma, portal vein thrombosis, chronic or refractory infections, HIV, previous malignancy, active psychiatric illness and poor social support are counted among relative contraindications. (11)

1.3 HEART TRANSPLANTATION

1.3.1 General considerations

The selection procedure for HTX contains the evaluation of patients with end-stage heart disease, which have used up all therapeutic possibilities. (13)

The mortality of patients with NYHA IV averages out to 50% at 6 months. (14)

There is an 80- 90% and 60- 70% probability to survive 1- and 5 years after a HTX, respectively. (15)

From this it follows that any patient with a cardiac constitution with a lower probability of survival would probably benefit from a HTX. (15)

Table 3: New York Heart Association

Heart failure clasification according to NYHA	
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoe (shortness of breath)
ClassII	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoe.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnoe.
Class IV	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

(16)

1.3.2 Indications

Worldwide more than 22 Mio. people suffer from cardiac insufficiency.

The incidence of this disease will regularly effect an additional 2 Mio. new patients per year. About 1/3 of those patients reside in end- stage heart failure, according to NYHA III or IV.

The mortality rate of this patient group adds up to ca. 500 000 per year. (17)

MacDonald defined the indication criteria for HTX in the following way: "The essential indication for heart transplantation is the presence of end- stage heart disease for which no alternative therapy is available." (13)

On the one hand the most common indication is chronic heart failure like dilatative cardiomyopathy (DCMP) and ischaemic heart diseases which account for up to 90% of the patients and some less common types, such as restrictive cardiomyopathy, congenital or valvular heart diseases, which make up 10 %. (13)

On the other hand there are also some less common indications, e.g. giant cell and other forms of myocarditis, infiltrative cardiomyopathies, like cardiac amyloidosis, non- compaction cardiomyopathy and primary cardiac heart tumors. (13)

Although end-stage organ failure usually suspects a chronic disease, there are also some acute heart diseases, which account for up to 5%, such as acute fulminate heart failure, cardiogenic shock, complicating acute myocardial infarction or myocarditis, or after cardiac surgery (postcardiotomy syndrome). (13)

Cardiac retransplantation is the only therapeutic option for patients with irreversible graft failure.

The most frequent reasons for heart- retransplantations are cardiac allograft vasculopathy (55%), acute rejection (19%) and primary graft failure (17%). (18)

The retransplantation outcome can be on a par with the outcome of primary TX. (19)

1.3.3 Contraindications

Generally accepted contraindications are psychiatric or cognitive illness, non-compliance, active abuse of alcohol, cigarettes or other substances, chronic systemic infections, like HIV, malignancies, age > 60 years, morbid obesity (BMI > 30), irreversible secondary organ failure unless considering a combined TX, cardiac amyloidosis, fixed pulmonary hypertension > 5 Wood units, pulmonary embolism < 4 weeks, active gastrointestinal bleeding, chronic neurodegenerative or musculoskeletal diseases that prevent a rehabilitation after TX, diabetes mellitus (DM) with established micro-vascular target organ damage (neuro-, nephro- and retinopathy), severe chronic pulmonary obstructive disease and severe peripheral or cerebrovascular disease, which are not deemed suitable for revascularization therapy. (13) (14) (20)

It is necessary to differ between absolute and relative contraindication, because more and more absolute contraindications have become relative. (13)

Some of the above-mentioned reasons are really relative contraindications, because the ultimate decision whether to transplant or not, depends on the individual situation of the patient and of the different kinds of TX centers. (14)

A case in point is advanced age, where it is not the chronological age by itself that is a contraindications but the general risks which such a situation would present.

“The recently revised National Health and Medical Research Council guidelines regarding organ and tissue donation after death for transplantation includes the statement that ‘there should be no discrimination between potential recipients on the basis of...race, nationality, religious belief, gender, marital status, sexual orientation, social status, disability or age, *except where conditions associated with the patient’s age directly determine the likelihood of a poorer outcome*’. ” (13)

1.4 LONG- TERM COMPLICATIONS

1.4.1 New- onset diabetes mellitus

Diabetes mellitus (DM) in transplanted patients can pre- exist or can develop de novo. (21)

New- onset diabetes mellitus (NODM) is a frequent aggravation after solid organ TX. (22)

De- novo diabetes mellitus is related to a higher incidence of patients death due to infections, cardiovascular complications, like atherosclerosis and coronary heart diseases, and results in a reduced graft survival due to chronic rejection, as well as in a declined quality and quantity of life. (23) (24) (25)

NODM occurs as one of the major metabolic complications after HTX, with an incidence of 20 to 30% in 5 years. (26) In LTX NODM develops in nearly 15%. (27) It is very difficult to define precisely the incidence of NODM, because every study has used different definitions of diagnostic criteria and a varying mix of risk factors. (25) (27)

Fundamental risk factors for the appearance of NODM contain ethnicity, (African American or Hispanics have a greater incidence than white or Asian patients), increased age, obesity, genetic predisposition (a family history of DM in first degree relatives elevates the risk seven- time), immunosuppressive drugs and increased number of transplants. (22) (23)

In the special case of LTX, HCV- related diseases doubled the risk of NODM. (24) In heart transplant cases an ischemic origin of cardiomyopathy is one of the main risk factors of NODM, which is also linked with hypertension, hyperuricemia and renal failure. (26)

Knowing the serious consequences and that patient management of NODM usually is analog to the type II diabetes mellitus, it is important to screen for NODM in transplant recipients to accurately determine the risk profile and to save lives. (22) (28)

1.4.2 Chronic renal failure

Chronic renal failure (CRF) after the TX of nonrenal solid- organs is a frequent complication with multifactorial causes, which can lead in dialysis and KTX, as well as in death. (29) (30) The incidence of CRF ranges from 10 to 80%. (31)

Depending on the kind of organ which is transplanted, the 5- year risk of getting a CRF after TX of a nonrenal solid- organ varies from 7 to 21%. (30)

10 years after the TX, in 12% of the heart- and in 4% of the liver recipients, severe renal insufficiency will occur, from which approximately half of all such cases will result in end- stage renal failure with the need for dialysis or a new renal graft. (32)

Generally, the wide variability of the data is caused by a lack of standard criteria for assessing post- TX renal failure as well as the use of multiple definitions. (30)

CRF often co- exists with various other risk factors, like the pre- and perioperative renal function, that means that the serum creatinine alone is not convincing enough, because poor nutritional status, low muscle mass, weight loss and edema can all lead to an overestimate of renal function, which is vulnerable due to poor effective circulating volume (e.g. low cardiac output in heart- and hepatorenal syndrome in liver potential recipients). (29)

Hyperlipidemia, another common complication, is related to an increased cardiovascular risk. The treatment of hyperlipidemia medicates hypercholesterinemia and hypertriglyceridemia, and may as well decrease the risk of graft rejection. (32) Another special point is that obesity, or, to be precise, an increasing BMI, will also create enhanced risk. (31)

Demographic factors, such as advanced age, female gender, a family history of renal diseases or white patients (the Asian race applies protective), also play an important role in elevating the risk of CRF. (29) (30) (33)

HCV is a significant factor for CRF due to glomerulonephritis (GN). (29)

Proteinuria is related with advanced renal dysfunction, which ordinarily appears many years after the TX. (32)

The best possible close monitoring of hyperlipidemia, proteinuria and hypertension in the post- TX phase, will reduce the risk of CRF. (34)

Other possible points of risk are perioperative renal damage (presence or absence of postoperative acute renal failure), pre- and posttransplant DM, preoperative GFR, dialysis prior to TX as well as the need for short- time dialysis after the operation, the use of nephrotoxic drugs and the TX procedure itself. (35) (36) (30) (37) (38) (39)

In the early 1980s, the development of Cyclosporine- based immunosuppressive agents considerably enhanced the chances of survival. Up to the present time, calcineurin inhibitors (CNIs), like Cyclosporine and Tacrolimus (TAC), form the main basis for posttransplant immunosuppressive therapy. (37)

Both, Cyclosporine A (CSA) and TAC, represent the most important risk factor for the emergence of acute and chronic renal dysfunction after nonrenal solid organ TX. (35) (36)

CNI- nephrotoxicity causes extended vasoconstriction of afferent and efferent glomerular arterioles associated with tubular atrophy, glomerulosclerosis, arteriosclerosis and a striped interstitial fibrosis with nodular arteriolar hyalinosis. (29) (31)

However, only the emergences of CNIs have made the miracle of TX possible. (32)

Nevertheless, despite their inadequacies, CNIs are still widely regarded as the best options for the prevention of graft rejection, because no alternate immunosuppressive agent appears to be either as effective or as reliable. (35)

In comparison with CSA, TAC seems to have less nephrotoxic adverse effects, because it causes less renal vasoconstriction. (29)

Taux et al. demonstrated that the renal plasma flow, GFR and filtration of patients medicated with TAC are less aggrieved than by a treatment with CSA. (32)

Hypertension is a risk factor of CRF, as well as a consequence of a treatment with CNIs. (29) (32)

Especially CSA shows a great incidence of hypertension with an occurrence rate which runs to about 90% of heart patients, and between 65 to 85% of liver recipients. (32)

Anemia also complicates the treatment of a CRF after a nonrenal solid organ TX. Immunotherapies, like AZA or Sirolimus, and erythropoietin deficiency augment anemia and so the quality of life dwindles dramatically, especially in the case of patients with cardiovascular or pulmonary disease. (29)

Due to the fact that the mineral metabolism of patients treated with corticosteroids is disturbed, bone disease is another consequence of CRF. (29)

All in all, the development of CRF is relatively common after TX and complicates the medical management and gives rise to an increasing morbidity and mortality. (30) (37)

Ojo et al. noted that the risk of death of patients with CRF after TX of a nonrenal solid organ is over four times higher. (30)

1.4.3 Infections

Since the implementation of newer and more immunosuppressive agents, the incidences of graft rejection have reduced dramatically, while the susceptibility of infections increased. Recipients of solid organ TX always live with the risk of life-threatening viral, bacterial, fungal and parasitic infections, which have serious consequences on morbidity and mortality. (40) (41) (42) (43)

For example, the most common cause of death in the population of LTX patients is infections. (40)

Table 4: Common Infections in Solid Organ Transplant Recipients

Bacterial:	<i>Gram-pos. cocci</i> : Enterococcus, Staphylococcus, Streptococcus, Escherichia <i>Gram-neg. rods</i> : Pseudomonas, Klebsiella, Serratia, Clostridium diff. <i>Drug-resistant bacterial</i> : MRSA, VRE, MDR Pseudomonas aeruginosa, ESBL producing Klebsiella pneumoniae and E. coli
Fungal:	Candida species Aspergillus fumigatus Pneumocystis carinii
Viral:	Cryptococcus neoformans CMV HSV VZV HHV- 6 Polyomaviruses (BKV, JCV) Adenovirus

(42)

Epidemiologic exposures can be differentiated into 4 classifications, namely donor-derived infections, recipient- derived infections, nosocomial infections and community infections. (43)

In donor- derived infections transplanted organs encourage the communication of infections from the donor, because many infections are latent, such as cytomegalovirus infection (CMV) or tuberculosis (TB), active, like undetected viremia or bacteremia at the time of harvesting organs, or nosocomial, that means that they are resistant to usually antimicrobial prophylaxis, e.g. vancomycin-resistant enterococcus (VRE), and thus transmit the infection in transplanted grafts. (43)

Recipient- derived infections include active infections, which normally should be eliminated before TX, on the basis of immunosuppressive drugs, which aggravate the clinical course of infection. Pathogens, like TB, CMV, Epstein- Barr- virus (EBV), HBV, HCV, HIV, Histoplasma capsulatum, T. cruzi, rank among the most common recipient- derived infections. (43)

Hospitalised patients may get colonized with nosocomial and antimicrobial-resistant organisms, e.g. methicillin- resistant Staphylococcus aureus (MRSA), Clostridium difficile, or aspergillus species, while waiting for a suitable donor organ. (43)

Community infections in immunocompetent persons go relatively well, but in immunodeficient patients such infections may end in fatality. (43)

After solid organ TX, there are 3 general time frames when specific infections occur (the first month, the second through the sixth month and beyond the sixth month), influenced by surgical factors, the level of immunosuppression and environmental exposures. (44) (45)

During the first period most infections are associated with surgical and technical complications, e.g. bacterial and candida wound infection, pneumonia, urinary tract infection (UTI), line sepsis, infections of biliary, chest and other drainage catheters, clostridium difficile colitis and VRE, which are very similar to those infections which occur after operations in non- transplant patients. (44) (45)

Perioperative

|----->|
Pneumonia
Wound
IV catheter
UTI

ICU Related

|----->|
Candida
VRE
C. difficile

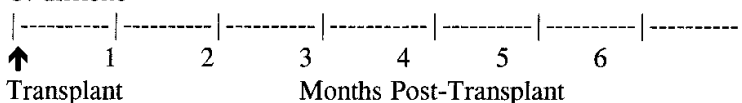


Fig. 4: Timing of infections in relation to organ TX: conventional infections (44)

In the first month post- TX, liver transplant recipients are at elevated risk for hepatic vein occlusion, and portal vein- and hepatic artery thrombosis and also biliary stricture formation and leaks. In the case of heart transplant recipients, mediastinitis and infection at the aortic suture line, with resultant mycotic aneurysm, are among the more common of the severe complications. (44)

Usually, there are no viral infections in this early period, with the exception of reactivated herpes simplex virus (HSV) infection in seropositive patients prior to TX. (44)

The next period, the second through the sixth month post- TX, is the time when pathogens, like CMV, P. carinii, Aspergillus spp., Nocardio spp., Listeria spp. T. gondii, HBV, HCV, human herpes virus, type 6 (HHV-6), HHV- 3, Cryptococcus spp., Histoplasma spp., Coccidioides spp. and Mycobacterium tuberculosis, predominate. (44) (45)

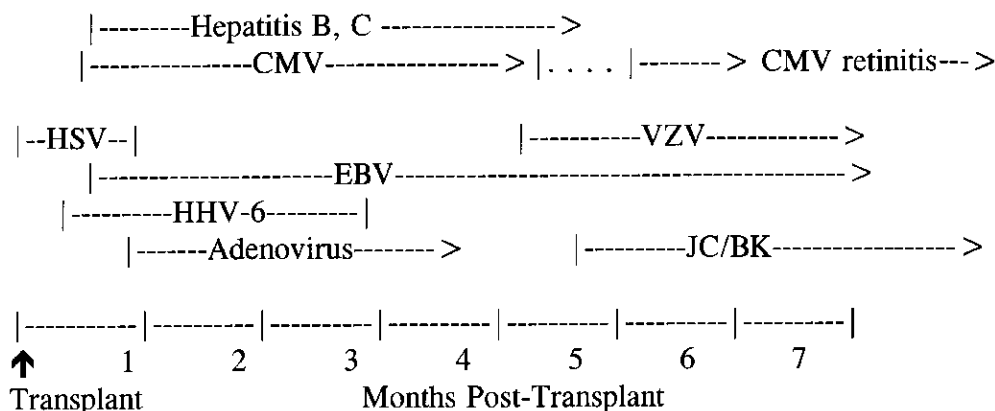


Fig. 5: Timing of infections in relation to organ TX: viral infections (44)

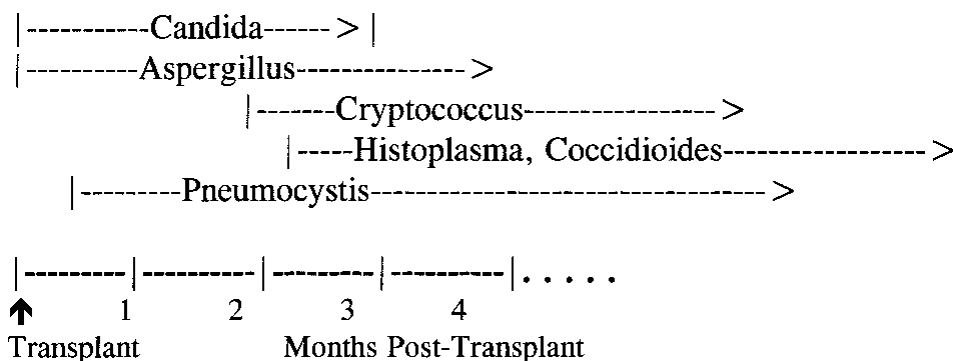


Fig. 6: Timing of infections following organ TX: fungal infections (44)

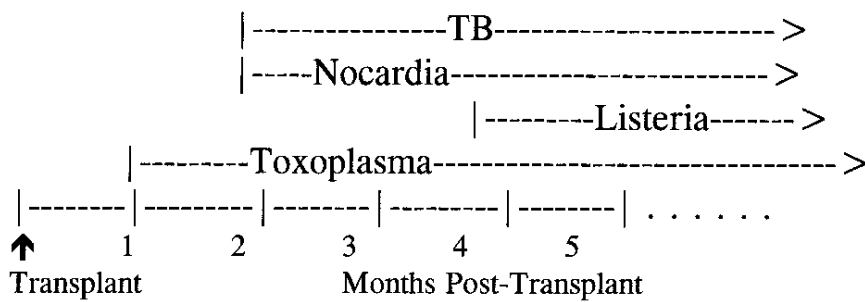


Fig. 7: Timing of infections following organ TX: other organism (bacterial and parasitic)
(44)

From the sixth month and beyond most of the transplant recipients acquire the same infections as the general non transplant patients, including influenza virus, pneumococcal pneumonia and UTI. (44)

Infections in organ transplant recipients are more difficult to identify than in immunocompetent persons, because symptoms are often reduced. (43)

That is why the optimal strategy is prevention, otherwise aggressive and immediate diagnosis and therapy are absolutely necessary. (46)

1.4.4 Malignancies

1.4.4.1 General considerations

Improvements in immunosuppressive therapy make the miracle of TX possible. (47) Newer immunosuppressants reduced the incidence of acute rejection and so lengthen the life of graft recipients. (48)

Unfortunately, these attainments are linked to life- threatening side- effects, namely infections as a main cause of mortality during early years after TX and cardiovascular disease and DNCs as main causes of late mortality. (49) (50)

It is estimated that DNC will top cardiovascular diseases as the most common cause of death in transplant recipients within the next 20 years period. (48)

An increased incidence of DNC after organ TX was first predicted in 1968, by Thomas E. Starzl and colleagues and was affirmed shortly afterwards by others. (51) (52) (53)

The incidence of DNC is estimated as low as 4,1% and as high as 16% with an average of 6%. (52) After 10 years of chronic immunosuppressive therapy the incidence of DNC rise up to 20% and after 30 years post TX 30% of the recipients develop DNC. (48) (54)

In comparison to the general community, transplant recipients are 3 to 4 times more likely to incur malignancy related to chronic immunosuppression, and for specific types of cancer the relative risk increases 100- fold. (48) (47)

The elevated incidence of DNC is also related with high mortality from these cancers. (55)

Post- transplant malignancies can be explained by 3 causes. (56) First, cancer can be transmitted by the donor organ; second, cancer of a previous malignancy of the recipient can occur and finally, cancer can develop de- novo. (49) (56)

DNC are the most common cancers following after TX. (56)

Almost all types of cancers can be found in graft recipients, but the most common are skin cancers, Kaposi's sarcoma (KS), post- transplant lymphoproliferative disorders (PTLD) and some other solid organ cancers. (57) (58)

Although it seems unlikely, the incidence of cancers that occur most frequently in the general population, such as breast, prostate, ovarian, brain (other than lymphoma), lung and colon carcinomas, is not increased among transplant recipients. (56) (59) (60) (61)

Table 5 presents the Cincinnati Transplant Tumor Registry (CTTR), which lists the largest database from world- wide transplant centers, collected by Dr. Israel Penn (1930- 1999) for over 25 years. (59) (62)

Table 5: De Novo Tumors in Organ Transplant Recipients
Reported to the Cincinnati Transplant Tumor Registry

Type of neoplasm	Number of tumors
Cancer of skin and lips	3393 (36.3%)
Lymphomas	1595 (17.1%)
Carcinoma of lung	521 (5.5%)
Kaposi sarcoma	380 (4.1%)
Carcinoma of the uterus (cervix 313, body 54, unspecified 3)	370 (4.0%)
Carcinoma of the colon and rectum	324 (3.5%)
Carcinoma of the kidney (native kidney 278, allograft 31, unspecified 13)	322 (3.5%)
Carcinoma of the breast	294 (3.1%)
Carcinoma of the head and neck (excluding thyroid, parathyroid, and eye)	267 (2.9%)
Carcinoma of the vulva, perineum, penis, and scrotum	230 (2.5%)
Carcinoma of the urinary bladder	205 (2.2%)
Metastatic carcinoma with primary site unknown	203 (2.2%)
Leukemias	173 (1.9%)
Carcinoma of the prostate gland	163 (1.7%)
Hepatobiliary carcinomas	158 (1.7%)
Sarcomas (excluding Kaposi sarcoma)	117 (1.2%)
Carcinoma of the thyroid gland	114 (1.2%)
Carcinoma of the stomach	110 (1.2%)
Testicular carcinoma	74 (0.8%)
Carcinoma of the pancreas	73 (0.8%)
Ovarian cancers	63 (0.7%)
Miscellaneous tumors	175 (1.9%)
Total	9324 (100%)

(59)

The etiology of DNC is multifactorial, including demographic factors, like older age, white race, male gender, environmental and genetic factors, chronic viral infections and the intensity, duration and cumulative dose of immunosuppression, e.g. induction agents, CNIs and AZA are strictly related to both, the incidence and the type of cancer that occurs. (48) (63) (64) (65) (66)

Cyclosporine, for instance may encourage the development of skin cancers and PTLD, and combinations of antirejection medications, like monoclonal antibody against the interleukin-2 (IL- 2) receptor, TAC, and Mycophenolat mofetil (MMF) are estimated to increase the frequency of DNC. (64)

Generally, all immunosuppressive agents induce a state of iatrogenic depression of immune surveillance, so that as a result, the development of DNC is more likely. (51) There is some evidence that the differences in DNC risk is depending on the type of organ a patient received, because varying kinds of grafts need different dosage of immunosuppressants, e.g. heart recipients sustain more likely higher levels of immunosuppressive drugs than other recipients. (60)

The majority of DNC are linked to potentially oncogenic virus infections, like PTLD (non Hodgkin's lymphoma and Hodgkin lymphoma) related to the Epstein- Barr virus, Kaposi sarcoma associated with the HHV-8, liver cancer correlated with the HBV and HCV, and carcinomas of the cervix, vulva/vagina, penis, anus and oral cavity and pharynx linked to the human papillomavirus (HPV). (52) (59) (60) (65)

1.4.4.2 Skin cancer

As in the general population, skin cancer is the most frequent malignancy in transplant recipients and can lead to significantly morbidity and mortality. (67) (68) After solid organ TXs carcinomas of the skin arise at a younger age, they occur more frequently, multiple and have a tendency to be more aggressive than the matched controls. (68)

Risk factors for skin cancer post- TX are nearly the same as in the former group, including increased age, extended ultraviolet (UV) radiation exposure, presence of HPV infection, genetic susceptibility, and easily burned skin and a long duration and high dosage of immunosuppressive agents. (68) (69)

Otley and Pittelkow showed that the prevalence of skin cancer is related to the UV exposure index, e. g. 30% of the Dutch and 70% of the Australian transplant recipients develop cutaneous carcinomas within 20 years. (69)

The allocation seems to be age- related, because patients under the age of 40 get the lesions to 80% on the dorsum of the hands, forearms and upper trunk; whereby older recipients get the lesion to 80% on the head. (67)

There are 3 major types of skin cancer, namely basal cell carcinoma, squamous cell carcinoma and melanoma. (69)

Otley and Pittelkow described the appearance of basal cell carcinomas (BCCs) the following way: “Basal cell carcinoma often appears as a translucent, pink papule with telangiectasia; a pink, scaly patch; or a crusted ulcer or erosion.” (69)

The risk of getting this kind of skin cancer in immunosuppressed patients is 10 times higher. (67)



(69)

Fig. 8: Basal cell carcinoma

Basal- cell- and squamous- cell carcinomas class among for more than 90% of all skin DNC. (67)

The squamous- cell carcinoma (SCC) is the most common skin cancer in immunodeficient patients, occurring 65 to 250 times as frequently as in the general community. (67) (69)

It can appear very similar to the BCC, but it is specifically marked by a nodule with central erosion.

About 5 to 7% of those SCCs tend to metastasize. (69)

SCCs seem to grow quickly and turn up to be more aggressive than in the general population. (67)



(69)

Fig. 9: Advanced squamous cell carcinoma

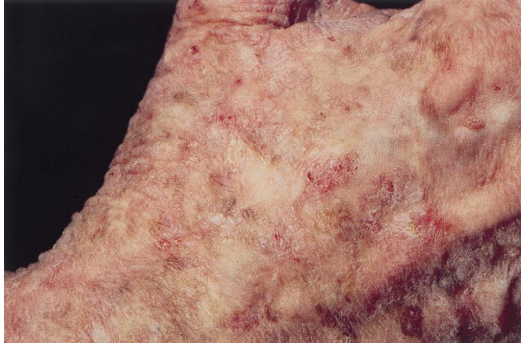
Malignant melanoma (MM) are less likely to occur in transplant recipients than other skin cancers, but potentially fatal. (67) (69) In Europe the risk factor is 1,6 to 3,4 times, and 2 to 4 times higher compared with the matched controls. Usually, such tumors arise in fair- complexioned persons with light eyes and hair. MM add up to 6,2% of skin cancers after TX in adults and 35% of those immunosuppressed patients with MM generate other kinds of cancer as well. (67) Generally, they look like pigmented, asymmetric, black, red or blue colored lesions, but there are also amelanotic MM, which appear pale or weakly red. (69)



(69)

Fig. 10: Malignant melanoma

Actinic keratoses (AK) are precursor lesions for SCCs and that is why they should be treated sharply in immunodeficient persons. AK are scurfy pink- colored papules, usually developing on sun- exposed areas. (69)



(69)

Fig.:11: Multiple actinic keratoses on a "transplant hand"

Neuroendocrine skin carcinomas (Merkel- cell carcinoma) develop mostly in male graft recipients, particularly on the arms, head and neck, with an asymptomatic nodular growth. (67) 46% of those patients die 5 years after the occurrence of a Merkel- cell carcinoma. (48)

The frequency of Kaposi sarcoma (KS) post- TX is 84 to 500 times higher than in the general population. (59) (67) (70)

Euvrard et al. reported that: "Most cases occur in transplant recipients of Mediterranean, Jewish, Arabic, Caribbean, or African descent; the reported incidence ranges from 0.5 percent in most Western countries (including the United States) to 5.3 percent in Saudi Arabia." (67)

90% with KS post- TX get cutaneous and /or mucosal lesions and about 50% of the patients, getting a heart or a liver graft develop visceral contribution. (67)

The pathogenesis of KS is strongly linked to a viral infection, namely HHV-8. (58)

The prognosis for patients with a visceral participation is generally poor, because 46% of them die from this illness. (59)

First and Peddi suggested that: "Kaposi's sarcoma should be suspected whenever a transplant recipient presents with reddish- blue macules or papules in the skin or oropharyngeal mucosa or with apparently infected granulomas that fail to heal."
(59)



(67)

Fig. 12: Kaposi's sarcoma lesions on the leg of a man with a liver TX

Other cutaneous types of sarcoma, including angiosarcomas, fibroxanthomas, leiomyosarcomas, and dermatofibrosarcoma protuberans, are mentioned only in a small number of case reports, so that there is no definite statement possible, whether the incidence is higher in comparison with the general community or not.
(67)

1.4.4.3 Post- transplant lymphoproliferative disorders

PTLD are a very common complication after organ TX, concerning up to 5% of all post- transplant patients. (67) (50) Especially for liver and heart transplant recipients the incidence accounts for 2,8% and 6,3%, respectively. (58)

Penn et al. first, detected the relationship between the increased incidence of PTLD and immunosuppressed graft recipients. (50)

PTLD are mostly EBV-related and B-cell predominant.

B-cell PTLD are differentiate in 4 morphologically types, namely reactive plasmacytic hyperplasia, polymorphic PTLD, monomorphic PTLD and others including plasmacytolike PTLD. (50)

T-cell PTLD develop very seldom in Western countries, but not so in Japan, where the incidence is higher and shows a dramatically clinical course in comparison to B-cell PTLD. (50)

Natural killer/T-cell PTLD are very rarely reported, but they always indicate an aggressive clinical course. (50)

The World Health Organization (WHO) morphologically categorized the PTLD into 4 groups. (58)

Table 6: World Health Organisation categories of PTLD

Classification	Description
Early lesions	Reactive plasmacytic hyperplasia Infectious mononucleosis- like
Polymorphic PTLD	
Monomorphic PTLD (classify according to lymphoma classification)	<u>B- cell lymphomas:</u> Diffuse large B- cell lymphoma (immunoblastic, centroblastic, anaplastic) Burkitt's/ Burkitt's- like lymphoma Plasma cell myeloma Plasmacytoma- like lesions <u>T- cell lymphomas:</u> Peripheral T- cell lymphoma, not otherwise categorized Other types
Hodgkin's lymphoma and Hodgkin's lymphoma- like PTLD	

(58)

The expression PTLD presents a spectrum of diseases, ranging from infectious mononucleosis to the often regressive hyperplasia, to polymorphic lesions to malignant lymphomas. (58) (60)

There are two essential risk factors developing PTLD: EBV sero- negativity and a too high dosage of immunosuppressive drugs. (66)

The mortality of PTLD is ranging between 30 and 60%. (48)

Zafar et al. described the clinical presentation of PTLD as follows: "As with nontransplant- related lymphoma, the most common symptoms are nonspecific, including fever, lymphadenopathy, weight loss, abdominal pain, and splenomegaly." (58)

First and Peddi reported that: "The most common extranodal sites are the central nervous system (CNS) (27%), liver (23%), lungs (22%), kidney (21%), intestines (20%), and spleen (13%)." (59) The worst prognostic factor is a contribution of the CNS. (48)

In the chronological sequence of PTLD there exist two overlapping schemas. The first occurs early usually < 90 days after TX with wide- spread lesions. The second appears several years post- TX after a long duration of immunosuppression, with lesions limited to a single organ. (59)

Actually, only cutaneous lymphomas are uncommon, but when they occur it is normally later, approximately 5 years after TX.

70% of cutaneous lymphomas are related to B-cell lymphomas, the other 30% are T-cell in basis, and demonstrate as mycosis fungoides, erythroderma, or hemorrhagic lesions with generalized lymphadenopathy.

The prediction for cutaneous T-cell lymphomas is worse than for B-cell lymphomas. (67)

The occurrence of cancer in immunosuppressed organ transplant recipients has become an unfortunate complication of a successful operation. (52) (71)

2006, Kauffman bared his thoughts relevant to the question of a new opportunity in the following way: "Because the immunosuppressed organ recipients develop malignancies much more frequently than their age, sex, and race matched controls, and because these malignancies develop within relatively short time spans as compared to controls, these recipients serve as a human laboratory model for analyzing the etiology, epidemiology, genetics, and treatment of cancer. Post- transplant malignancies are a major problem but they also represent a unique opportunity to study the neoplastic process." (66)

1.5 IMMUNOSUPPRESSIVE AGENTS

1.5.1 General considerations

For some well- chosen persons with end-stage organ disease, TX is the only treatment of choice. (72) To protect the graft of rejection, it is essential that those patients receive a life- long immunosuppressive therapy. (73)

The key task of immunosuppressive agents is to blockade the own immune response by pointing both B- and T-cell response through inhibition of cellular proliferation. (73)

Although, over the years immunosuppressive drugs have considerably improved, it is a well- known fact that their side effects result in a significant increase of morbidity and a worsening of quality of life. (74)

“Most of the immunosuppressants used in organ transplantation are characterized by a narrow therapeutic index, whereby underdosing is associated with increased risk of rejection episodes and overdosing may exacerbate drug- related toxicity.” (75) As a result, the principal goal of these drug regimes is to equilibrate the immunosuppressants between over- and underimmunosuppression. (76)

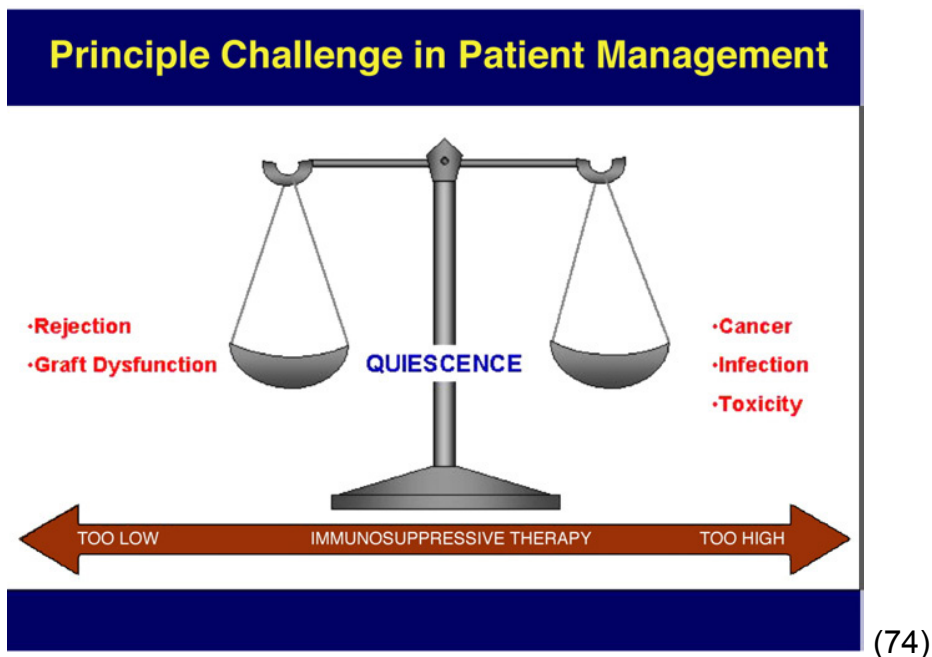


Fig. 13: Principle Challenge in Patient Management

1.5.2 Corticosteroids

1.5.2.1 Mechanism of action

Corticosteroids are powerful immunosuppressive and anti-inflammatory agents, which diffuse across cell membranes and bind to cytoplasmic glucocorticoid receptors. These specific complexes translocate to the nucleus, where they annex to DNA and so inhibit the synthesis of cytokines (IL- 1, IL- 2, IL- 6, tumor necrosis factor and interferon- γ). (73) (76) (77) (78)

Steroids influence all kinds of leucocytes (B- and T-cells, macrophages, granulocytes and monocytes), and endothelial cells. (78)

1.5.2.2 Adverse effects

Because of their potent actions on various target issues, steroids are linked with the largest number of long-term side effects and are generally dose- dependent: Cushing syndrome, e.g., moon face, buffalo hump, weight gain with central obesity, hirsutism, acne, skin fragility, hypertension, diabetes mellitus, emotional lability, cataracts, gastric ulcer and gastrointestinal bleeding, pancreatitis, poor wound healing, , hyperlipidemia, salt and water retention, and osteoporosis with avascular necrosis of bone. (76) (77) (78)

1.5.3 Azathioprine (AZA)

1.5.3.1 Mechanism of action

AZA is a prodrug that is commuted by plasma esterase or by glutathione to the antimetabolite, 6- mercaptopurine (6- MP), which is transformed to thio- inosine- monophosphate (TIMP). TIMP is further converted into a purine analog, which inserts into nucleic acids where it blocks synthesis of DNA, RNA, profactors, nucleozides and proteins. Through these processes AZA inhibits most T- cell functions and decreases the numbers of circulating monocytes and granulocytes. (76) (78)

1.5.3.2 Adverse effects

The main side effect is of AZA is bone marrow depression, including leukopenia, anemia and thrombocytopenia. Other adverse effects contain gastrointestinal afflictions, such as nausea, vomiting, diarrhea, pancreatitis, hepatitis and hepatic veno- occlusive disease, as well as an elevated risk of neoplasia. (76) (77) (78)

1.5.4 Mycophenolate Mofetil (MMF)

1.5.4.1 Mechanism of action

MMF, a product derived of *Penicillium brevicompactum*, is a morpholinoethyl ester and a prodrug of mycophenolic acid (MPA), which is a noncompetitive inhibitor of inosine- monophosphate dehydrogenase (IMPDH), which is an important enzyme in the de novo synthesis of guanine nucleotides. (48) (78) (79) MMF is able to blockade both B- lymphocyte and T- lymphocyte function. Mycophenolate mofetil initiates and enhances apoptosis in antigen- activated T lymphocytes. MPA diminishes the amplification of monocytes to the location of graft rejection and elevates their apoptosis. Additionally, MPA has a direct effect on the function of endothelial cells. (79)

1.5.4.2 Adverse effects

MMF is generally well tolerated; the most common side effects include gastrointestinal symptoms, like diarrhea, abdominal cramps, nausea, vomiting; leukopenia, thrombocytopenia with sporadic pancytopenia and opportunistic infections. (76) (77) (78) (80)

1.5.5 Cyclosporine A (CSA)

1.5.5.1 Mechanism of action

Cyclosporine, a small cyclic peptide initially of fungal origin, inhibits a calcium-activated calcineurin by crossing the cell through diffusion and forming a complex with a cytosolic protein called immunophilin and then CSA binds to a specific receptor group of them, namely cyclophilins. Through the impact with these receptors, calcineurin, a key enzyme in T- cells, is blocked. Further CSA inactivates a calcineurin- calmodulin complex and thus IL- 2 production. (76) (77) (78) (81)

1.5.5.2 Adverse effects

The major side effect of CSA is nephrotoxicity with an incidence raging between 40 and 70%. Acute nephrotoxicity is reversible and dose- related, whereas the chronic form causes arteriolar sclerosis and tubule- interstitial fibrosis and is irreversible.

Other secondary effects contain gingival hyperplasia, hypertrichosis, hypertension, hyperlipidemia, DM, cholestasis, cholelithiasis, nausea, vomiting, osteoporosis and neurological complications, e.g. tremor, paresthesias, headache, mental status change, visual symptoms, insomnia and convulsions. (76) (77) (78)

1.5.6 Tacrolimus

1.5.6.1 Mechanism of action

Tacrolimus, well- known as FK 506, is a macrolide antibiotic and produced from the fungus *Streptomyces tsukubaensis*. It is also a calcineurin inhibitor and similar to CSA, TAC binds a complex with immunophilins, called FK 506 binding protein 12 (FKBP- 12). This complex links to the pivotal enzyme calcineurin, which inhibits the cytokine transcription by the CD 4 cell, and as a result of the cytokine-inhibition the T- cell proliferation is blocked. (76) (77) (78)

1.5.6.2 Adverse effects

TAC has nearly the same side effects as CSA, like nephrotoxicity, neurological toxicity, hypertension, hyperlipidemia, hyperglycemia, hirsutism and gingival hyperplasia. Patients receiving TAC have also suffered from cardiomyopathy, anemia, chronic diarrhea and allergies. (76) (77) (78) (80)

1.5.7 Sirolimus

1.5.7.1 Mechanism of action

In the 1970s, a soil specimen from Rapa Nui (new known as Easter Island) was found to contain a strong antifungal metabolite from a macrocyclic antibiotic, *Streptomyces hygroscopicus*, which was named rapamycin, after the place of its discovery. Although the configuration of Sirolimus is similar to that of Tacrolimus, it inhibits T- cell function at a later step. Sirolimus binds to the FKBP- 12, but it does not inhibit the calcineurin phosphatase, but binds and blocks target of rapamycin (TOR). To inhibit the progression of the T- cells from the G1- phase to the S- phase of the cell cycle, Sirolimus inhibits the IL- 2 receptor. Furthermore, Sirolimus also inhibits B-cell proliferation and as specialness it is capable to block growth factor signaling for immune and non- immune cells. (77) (78) (80) (81) (82) (83) (84)

1.5.7.2 Adverse effects

The main side effects of Sirolimus are headache, nausea, dizziness, epistaxis, hyperlipidemia, hypertriglyceridemia, leucopenia, thrombocytopenia, anemia and infections. (76) (78) (80)

1.5.8 Everolimus

1.5.8.1 Mechanism of action

Everolimus is an analog of Sirolimus, a derivate of rapamycin and belongs to the so- called mTOR- Inhibitors (mammalian target of rapamycin). Everolimus binds to the cytoplasmic FK 506 binding protein 12, which interacts with the mTOR- protein, which inhibits the interleukin- guided proliferation from hematopoietic (lymphocytes), as well as from non- hematopoietic cells (e.g. endothelial cells, fibroblasts). As a result, it comes to an arrest of the cell during the G1- phase. (85)

1.5.8.2 Adverse effects

The most frequently reported side effects are myelosuppression, including thrombocytopenia and leucocytopenia; hypercholesterinemia, hypertriglyceridemia and poor wound healing. (85)

Villard et al. claimed that: "The immunosuppressive regimes used after organ transplantation are efficient but, as a result of their non- specific mechanism of action, they fail to prevent chronic graft rejection, life- threatening infections and malignancies." (73)

The "perfect" drug therapy would not only avoid the graft rejection, but also obtain the "normal" immunity to shelter from infections and their dangerous complications. (73)

2 AIM OF THE STUDY

Transplanted patients have to take a life- long immunosuppressive therapy, to avoid graft rejection.

One of the most serious side effects of immunosuppressive agents is the increased incidence of carcinomas.

It is not obvious, which immunosuppressive drugs actually promote the occurrence of these malignancies nor whether there is a dependence on dosage.

After a statistical evaluation of the data, it should be possible to modify or to adapt the actual therapy regimes, in order to reduce the incidence of carcinomas in transplanted patients.

The primary objective of this study was to gather information about the influence of immunosuppression on de- novo carcinoma in transplanted patients.

The secondary goal was to gain knowledge of the distribution of the different types of carcinomas in heart and liver transplanted patients.

3 METHODS

3.1 Data collection

We retrospectively reviewed all orthotopic heart and liver recipients, performed at the Medical University Graz, Austria, Department for Surgery, Division of Transplantation Surgery.

Between March 1983 and December 2008, 398 HTX and LTX were evaluated.

Inclusion criteria were all primary performed HTX and LTX patients. Patients with a history of previous malignancy were excluded from the study.

Data were retrospectively obtained by means of patient's chart review and from openMedocs (a medical data documentation used at the Medical University of Graz). We collected the following data: transplanted organ, de novo- malignancies, primary disease, gender, exitus, cause of death, reception of cancer treatment, the age of TX, the age of the tumor- diagnosis, the length of time to the tumor- diagnosis and the period to exitus, as well as the specific immunosuppressive regime for each recipient.

For data analysis, the Statistical Package for the Social Science (SPSS), version 17 was used. Data are expressed as mean +/- SEM or as absolute numbers and/ or percentages. Data were compared by Pearson's chi- square or Fisher's exact test, for qualitative variables and Student t- test, for quantitative variables.

In all tests used, a p- value of $\leq 0,05$ (two way analysis of variance) was considered statistically significant.

4 RESULTS

4.1 General observations

In this retrospective study, all patients who developed a DNC after TX at the Division of Transplantation Surgery, Medical University Graz, were included.

Out of a total of 398 patients (100,0%), 231 patients (58,0%) received a heart transplant and 167 patients (42,0%) a liver graft.

Due to the fact, that post- transplant treatment is not carried out at the Division of Transplantation Surgery, but at the Division of Nephrology and Hemodialysis, patients receiving a kidney were not included in this study. Moreover, combined pancreas- kidney TX started only 10 years ago at our department and therefore these patients were not included in this retrospective study.

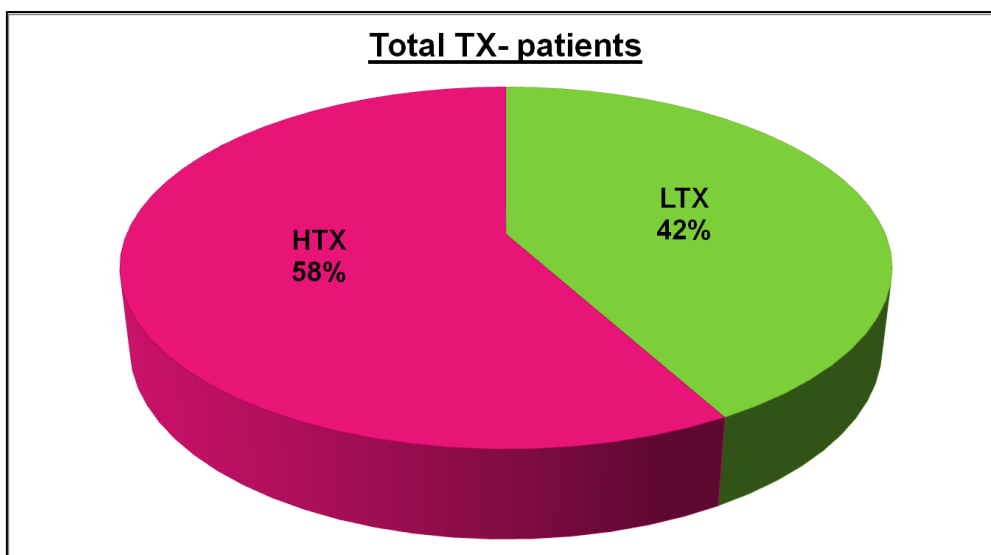


Fig. 14: Distribution of HTX and LTX

Focusing on all 398 patients receiving a heart or liver, the average age at TX was $52,04 \pm 0,54$ years.

The mean age at TX of all 231 HTX patients came to $51,4 \pm 0,8$ years, whereas the median age at TX of all 167 LTX patients added up to $52,9 \pm 0,7$ years.

Statistical analysis showed no significant differences in terms of age between HTX and LTX patients.

Among 398 patients (100,0%), 366 recipients (92,0%) developed no DNC and 32 (8,0%) developed a malignancy, during a follow- up period of over 25 years.

Out of a total of 231 HTX patients (100,0%), 203 recipients (87,9%) developed no DNC and 28 recipients (12,1%) developed a carcinoma during the follow- up period.

Of all 167 LTX patients (100,0%), 163 recipients (97,6%) developed no DNC, whereas only 4 patients (2,4%) developed a post- TX tumor.

The relationship between the kind of TX (HTX or LTX) and the occurrence of cancer revealed a statistical significance ($p < 0,001$).

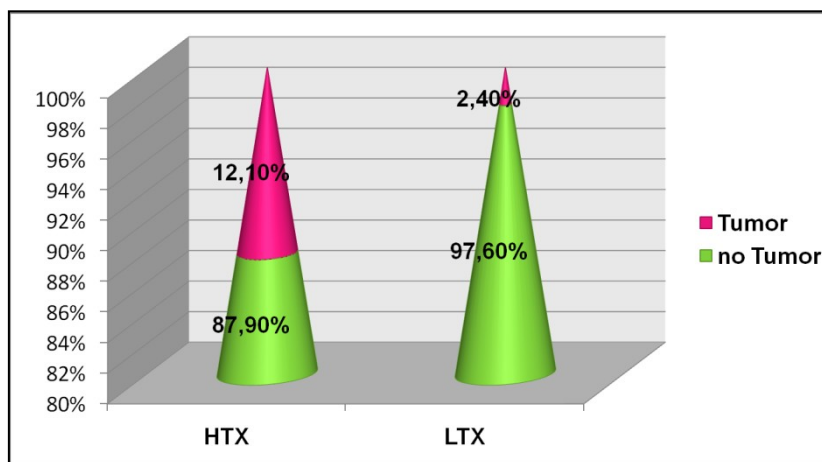


Fig. 15: Distribution of DNCs in HTX and LTX

Concerning sex distribution, it has to be mentioned that among all 398 transplanted patients (100,0%), 80 (20,1%) were female and 318 patients (79,9%) were male.

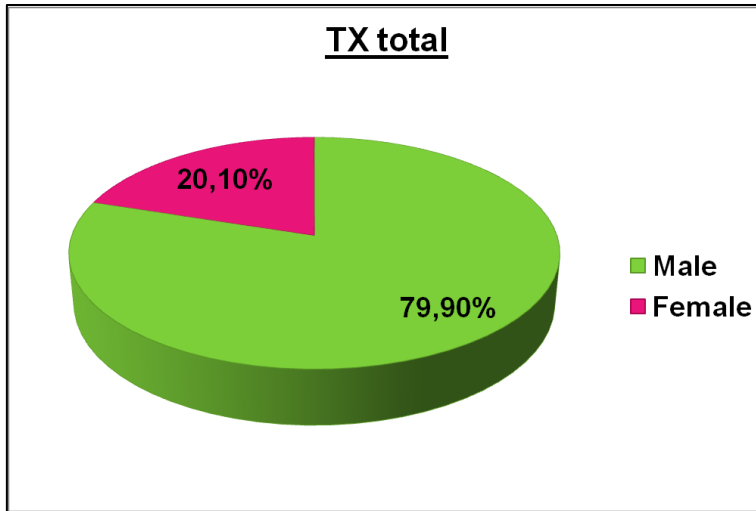


Fig. 16: Distribution of gender: All transplants (HTX and LTX)

Of all 80 transplanted women (100,0%), 39 (48,8%) underwent HTX and 41 patients (51,3%) were liver transplanted.

16,9% of all HTX patients and 24,6% of all LTX patients were women.

Out of 318 transplanted men (100,0%), 192 (60,4%) received a heart and 126 patients (39,6%) underwent LTX.

83,1% of all HTX patients and 75,4% of all LTX patients were men.

The relationship between the gender and the kind of TX (HTX or LTX) showed no statistical significance.

Table 7: Distribution of gender and TX

	HTX	LTX
Female	48,80%	51,30%
Male	60,40%	39,60%

Table 8: Clinical features of patients with DNCs after TX

Patient number	Allograft	Gender (M/F)	Age at TX (years)	Indication	Time to tumor diagnosis (months)	Treatment	Status
1	Heart	M	61	DCMP	101	Yes	Alive
2	Heart	M	58	DCMP	12	No	Deceased
3	Heart	M	67	ICMP	50	No	Deceased
4	Heart	M	58	DCMP	69	Yes	Alive
5	Heart	M	48	DCMP	118	Yes	Deceased
6	Heart	M	53	DCMP	47	No	Deceased
7	Heart	M	46	DCMP	124	Yes	Deceased
8	Heart	M	59	DCMP	93	Yes	Alive
9	Heart	M	51	DCMP	153	Yes	Deceased
10	Heart	M	60	ICMP	32	No	Deceased
11	Heart	M	56	DCMP	106	No	Deceased
12	Heart	M	36	DCMP	59	Yes	Alive
13	Heart	M	63	DCMP	7	Yes	Deceased
14	Heart	M	50	DCMP	87	Yes	Deceased
15	Heart	M	49	DCMP	226	Yes	Alive
16	Heart	M	33	DCMP	176	Yes	Alive
17	Heart	M	49	ICMP	74	Yes	Deceased
18	Heart	F	55	DCMP	85	Yes	Alive
19	Heart	M	58	DCMP	100	Yes	Alive
20	Heart	F	52	Other heart diseases	49	Yes	Alive
21	Heart	M	51	DCMP	37	Yes	Alive
22	Heart	M	59	DCMP	22	Yes	Deceased
23	Heart	M	58	ICMP	40	Yes	Deceased
24	Heart	M	46	DCMP	110	Yes	Alive
25	Heart	M	62	ICMP	98	Yes	Alive
26	Heart	M	50	DCMP	28	No	Deceased
27	Heart	M	64	DCMP	96	Yes	Alive
28	Heart	M	43	DCMP	36	Yes	Deceased
29	Liver	M	47	Nutritive- toxic	76	Yes	Deceased
30	Liver	F	43	Nutritive- toxic	74	Yes	Alive
31	Liver	M	52	Nutritive- toxic	13	Yes	Alive
32	Liver	M	60	Hepatitis	13	Yes	Alive

4.2 Primary disease

The distribution of the kind of primary disease related to all 398 (100,0%) transplanted patients was as follows: 179 recipients (45,0%) suffered from a DCMP, 50 (12,6%) from an ischemic cardiomyopathy (ICMP), 2 (0,5%) from other types of cardiac diseases, 89 (22,4%) from a nutritive- toxic cirrhosis, 35 (8,8%) from a hepatitis, 19 (4,8%) from a HCC, while 24 patients (6,0%) suffered from some other types of liver diseases as a primary cause.

Among the 197 transplanted patients (100,0%), who suffered from a DCMP as primary disease, 22 (12,3%) developed a DNC and 157 recipients (87,7%) did not. 42,9% of all DNC- free transplanted patients and 68,8% of all graft recipients who developed a post- TX tumor, suffered from a DCMP as primary disease.

Out of a total of 50 transplanted patients (100,0%), who suffered from an ICMP as primary disease, 5 patients (10,0%) developed a post- TX- tumor and 45 (90,0%) did not.

12,3% of all DNC- free recipients and 15,6% of all DNC- patients, suffered from an ICMP as primary disease.

Both of the 2 transplanted patients (100,0%), who suffered from other types of cardiac diseases as primary cause, 1 (50,0%) developed a DNC and 1 recipient (50,0%) did not.

0,3% of all DNC- free patients and 3,1 % of all patients, who developed a post- TX tumor, suffered from other types of cardiac diseases as primary cause.

Among all 89 transplanted patients (100,0%), who suffered from a nutritive- toxic cirrhosis as primary disease, 3 (3,4%) developed a DNC and 86 graft recipients (96,6%) did not.

23,5% of all DNC- free patients and 9,4% of all patients, who developed a post- TX tumor, suffered from a nutritive- toxic cirrhosis as primary disease.

Focusing on the 35 transplanted recipients (100,0%), who suffered from a hepatitis as primary disease, 1 (2,9%) developed a DNC and 34 patients (97,1%) did not. 9,3% of all DNC- free transplanted patients and 3,1% of all patients, who developed a post- TX tumor, suffered from a hepatitis as primary disease.

Of all 19 TX patients (100,0%), who suffered from a HCC as primary disease, none of them (100,0%) developed a DNC.

5,2% of all DNC- free patients suffered from a HCC as primary disease.

Among 24 graft recipients (100,0%), who suffered from other types of liver diseases as primary cause, none of them (100,0%) developed a post- TX tumor. 6,6% of all DNC- free recipients suffered from other types of liver diseases as primary cause.

The relation between the kind of primary disease and the occurrence of cancer revealed a statistical significance ($p= 0,009$).

4.2.1 HTX

Out of a total of 231 HTX patients (100,0%), 179 (77,5%) suffered from a DCMP, 50 (21,6%) from an ICMP and 2 recipients (0,9%) suffered from other types of cardiac diseases as primary cause.

77,3% of all DNC- free HTX patients and 78,6% of all HTX patients, who developed a post- TX tumor, suffered from a DCMP as primary disease.

22,2% of all DNC- free HTX persons and 17,9% of all HTX patients, who developed a post- TX tumor, suffered from an ICMP as primary disease.

0,5% of all DNC- free HTX persons and 3,6% of all HTX patients, who developed a post- TX tumor, suffered from other types of cardiac diseases as primary cause.

Statistical analysis showed no significant differences in terms of primary disease and HTX patients.

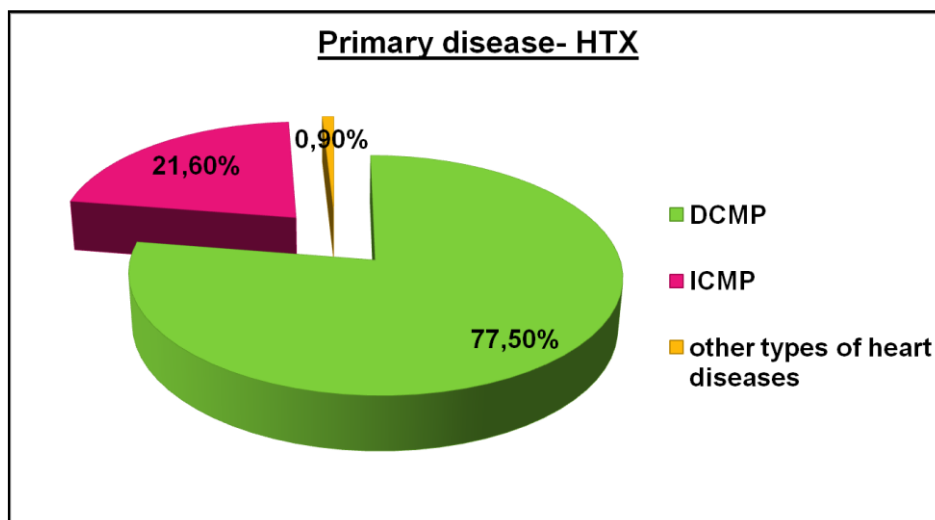


Fig. 17: Primary diseases in HTX- patients

4.2.2. LTX

Concerning the distribution of the kind of primary disease related to all 167 (100,0%) LTX patients it was noted that: 89 recipients (53,3%) suffered from a nutritive- toxic cirrhosis, 35 (21,0%) from a hepatitis, 19 (11,4%) from a HCC and 24 patients (14,4%) suffered from other types of hepatic diseases as primary cause.

52,8% of all DNC- free LTX patients and 75,0% of all LTX patients, who developed a post- TX tumor, suffered from a nutritive- toxic cirrhosis as primary disease.

20,9% of all DNC- free LTX persons and 25,0% of all LTX patients, who developed a post- TX tumor, suffered from a hepatitis as primary disease.

11,7% of all DNC- free LTX patients suffered from a HCC and 14,7% of all DNC- free LTX patients suffered from other types of hepatic diseases as primary cause.

The relationship between primary disease and LTX showed no statistical significance.

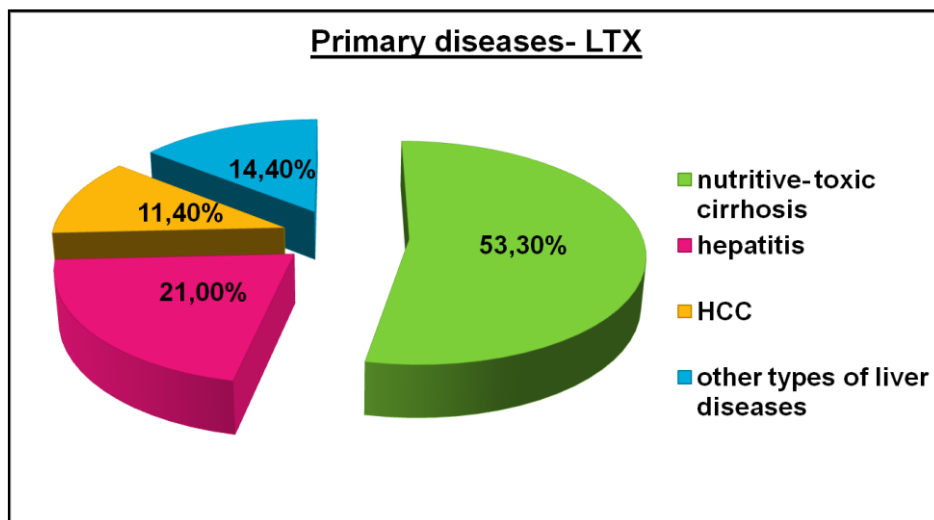


Fig. 18: Primary diseases in LTX- patients

4.3 Tumor distribution

Out of a total of 398 transplanted patients (100,0%), 366 (92,0%) developed no DNC and 32 recipients (8,0%) did.

From the overall total of 231 HTX patients (100,0%), 203 (87,9%) did not develop a post- TX tumor. The breakdown in malignancy type amongst the remainder was as follows: 14 (6,1%) developed a SCC, 2 (0,9%) developed a non- Hodgkin's lymphoma (NHL), 2 (0,9%) developed a bronchogenic carcinoma, 1 (0,4%) developed a prostatic carcinoma, 2 (0,9%) developed a pancreatic carcinoma, 1 (0,4%) developed a urinary bladder carcinoma (UBC), 5 developed a BCC and 1 patient developed an occult primary tumor (OPT).

55,5% of the DNC- free patients, 82,4% who developed a SCC, 100,0% who developed a NHL, 100,0% who developed a bronchogenic carcinoma, 50,0% who developed a prostatic carcinoma, 100,0% who developed a pancreatic carcinoma, 100,0% who developed a UBC, 100,0% who develop a BCC and 100,0% of all graft recipients, who developed an OPT, underwent HTX.

Among all 167 LTX patients (100,0%), 163 (97,6%) developed no DNC, 3 (1,8%) developed a SCC and 1 patient (0,6%) developed a prostatic carcinoma.

44,5% of all DNC- free patients, 17,6% of all persons, who developed a SCC and 50,0% of all patients, who developed a prostatic carcinoma, underwent LTX.

Statistical analysis showed no significant differences between the kind of TX (HTX or LTX) and the occurrence of specific types of cancer.

Focusing on the 32 transplanted patients, who developed a DNC (100,0%), 17 (53,1%) developed a SCC, 2 (6,3%) developed a NHL, 2 (6,3%) developed a bronchogenic carcinoma, 2 (6,3%) developed a prostatic carcinoma, 2 (6,3%) developed a pancreatic carcinoma, 1 (3,1%) developed a UBC, 5 (15,6%) developed a BCC and 1 graft recipient (3,1%) developed an OPT.

Table 9: Type of DNC in 32 patients

Tumor site	Number
SCC	17
BCC	5
NHL	2
bronchial carcinoma	2
pancreatic carcinoma	2
prostatic carcinoma	2
UBC	1
OPT	1

Of the 28 HTX patients, who developed a DNC (12,1%), 14 (6,1%) developed a SCC, 2 (0,9%) developed a NHL, 2 (0,9%) a bronchogenic carcinoma, 1 (0,4%) developed a prostatic carcinoma, 2 (0,9%) developed a pancreatic carcinoma, 1 (0,4%) developed a UBC, 5 (15,6%) developed a BCC and 1 heart recipient (3,1%) developed an OPT. Among the 4 LTX patients, which developed a DNC, (2,4%), 3 recipients (1,8%) developed a SCC and 1 patient (0,6%) developed a prostatic carcinoma.

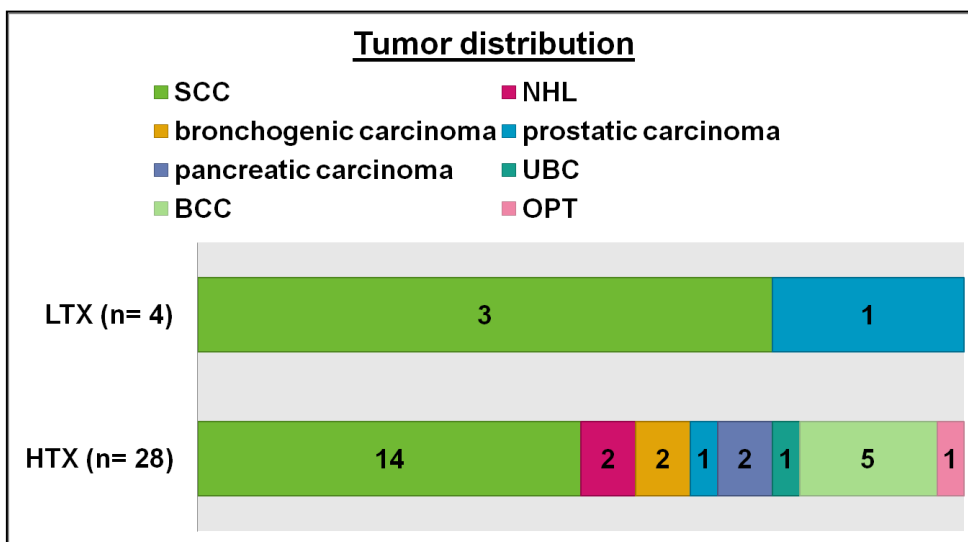


Fig. 19: Distribution of DNCs

Concerning sex distribution, it has to be mentioned that among 32 transplanted patients, who developed a post- TX malignancy (100,0%), 3 persons (9,4%) were female and 29 patients (90,6%) were male.

Out of a total of 80 transplanted women (100,0%), 77 (96,3%) did not develop a DNC and 3 patients (3,8%) developed a post- TX tumor.

21,0% of all DNC- free patients and 9,4% of all recipients, who developed a post- TX tumor, were women.

Among 318 transplanted men (100,0%), 289 (90,9%) did not develop a post- TX tumor although the remaining 29 patients (9,1%) all developed a DNC.

79,0% of all DNC- free recipients and 90,6% of all transplanted patients, who developed a post- TX tumor, were men.

The relationship between the gender and the occurrence of cancer showed no statistical significance.

4.4 Therapy:

Focusing on all 32 transplanted patients (100,0%), who developed a DNC, 26 (81,3%) received a cancer treatment whilst the remaining 6 patients (18,8%) did not.

Among 26 transplanted patients (100,0%), receiving a cancer therapy, 22 recipients (84,6%) underwent HTX and 4 patients (15,4%) were liver graft recipients. 87,6% of all HTX recipients and 100,0% of all LTX patients received a cancer treatment.

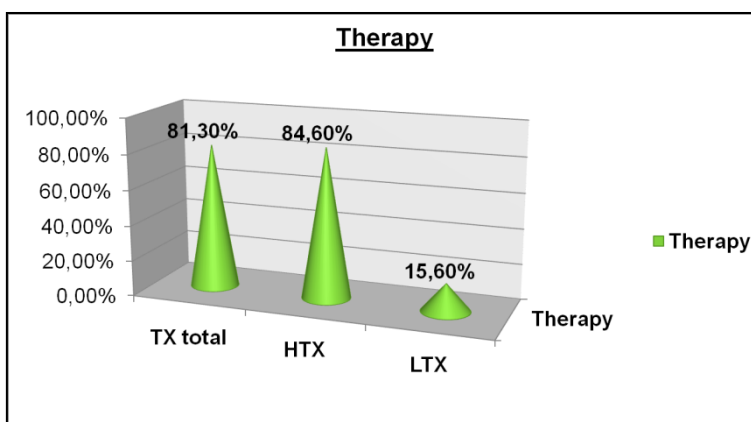


Fig. 20: Distribution of cancer treatment

Out of 6 transplanted patients (100,0%), who did not receive a cancer therapy, all of them (100,0%) underwent HTX.

21,4% of all HTX patients did not receive an appropriate treatment.

Among 3 women (100,0%), who developed a DNC, all of them (100,0%) received a cancer therapy.

11,5% of all transplanted patients, who received a cancer treatment were women.

Focusing on all 29 transplanted men (100,0%), who developed a DNC, 23 (79,3%) received a cancer treatment and 6 patients (18,8%) did not receive an appropriate therapy.

88,5% of all patients, who received a cancer treatment and 100,0% of all patients, who did not receive a cancer treatment, were men.

Statistical analysis showed no significant differences between the gender and the receiving of a cancer therapy.

4.5 Survival:

Out of a total of 398 transplanted patients (100,0%), 195 (49,0%) deceased and 203 recipients (51,0%) are still alive.

Among 32 graft recipients, who developed a DNC (100,0%), 16 (50,0%) passed away and 16 patients (50,0%) are still alive.

Focusing on all 26 TX patients, who received a cancer therapy (81,6%), 10 (38,5%) died and 16 recipients (61,5%) are still alive.

62,5% of all deceased patients and 100,0% of all living patients received a cancer treatment.

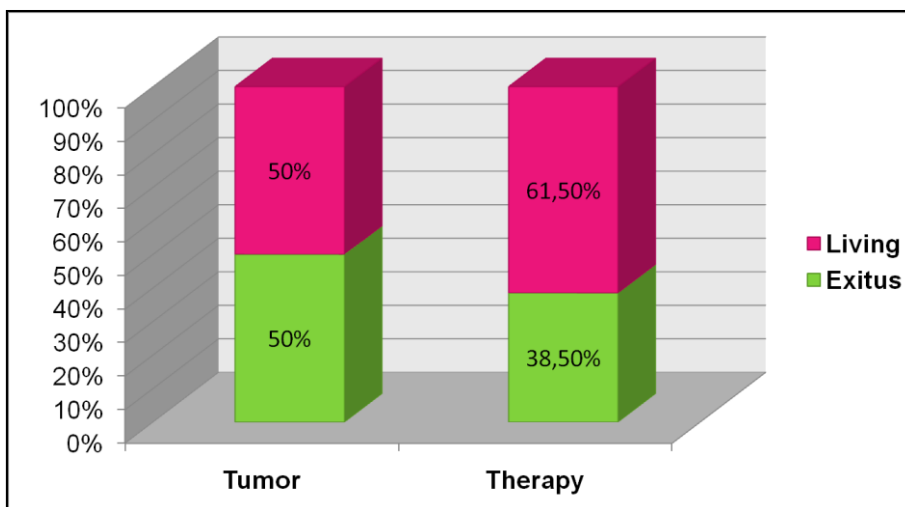


Fig. 21: Relation between cancer therapy and survival

Concerning all 6 transplanted patients (100,0%), who did not receive an appropriate treatment, all of them (100,0%) died.

37,5% of all deceased transplant recipients did not receive a cancer treatment.

The relationship between receiving a cancer therapy and exitus revealed a statistical significance ($p = 0,018$).

The period to exitus, of all 134 HTX patients averaged $41,9 \pm 5,4$ months, whereas the mean timeframe to exitus, of all 57 LTX persons who died, came to $16,4 \pm 3,4$ months.

The relationship between the average period to exitus and the kind of TX (HTX or LTX) was statistical significant ($p < 0,001$).

Among all 80 transplanted women (100,0%), 37 (46,3%) passed away and 43 women (53,8%) are still alive. 19,0% of all deceased patients and 21,2% of all living graft recipients were women.

Of all 318 transplanted men (100,0%), 158 (49,7%) died and 160 men (50,3%) are still alive. 81,0% of all deceased patients and 78,8% of all living graft recipients were men.

The relationship between gender and exitus showed no statistical significance.

4.6 Cause of death:

Among the 367 transplanted patients, from the original sample where there has been detailed follow- up (100,0%), the following is noted: 204 organ recipients (55,6%) are still alive, 73 (19,9%) died because of cardio- vascular failure, 21 (5,7%) passed away due to infections, 11 (3,0%) died because of cerebral complications, 31 (8,4%) passed away due to multi organ failure (MOF), 7 (1,9%) died because of rejection, 1 (0,3%) passed away due to hepatic failure, 4 (1,1%) died because of obstructions of the hepatic artery or portal vein, 9 (2,5%) passed away due to a HCC, 5 (1,4%) died due to other causes of death and 1 patient (0,3%) passed away due to an unknown cause of death.

Of all 367 transplanted patients within this subgroup (100,0%), 335 persons (91,3%) were DNC- free and 32 graft recipients (8,7%) developed a post- TX tumor.

We found that among 335 DNC- free transplanted patients (100,0%), 188 graft recipients (56,1%) are still alive, 67 (20,0%) died because of cardio- vascular failure, 18 (5,4%) passed away due to infections, 11 (3,3%) died because of cerebral complications, 25 (7,5%) passed away due to MOF, 7 (2,1,%) died because of rejection, 1 (0,3%) passed away due to hepatic failure, 4 (1,2%) died because of obstructions of the hepatic artery or portal vein, 9 (2,7%) passed away due to a HCC and 5 patients (1,5%) died due to other causes of death.

It was noted that the following percentages did not develop a tumor: 92,2% of all living patients, 91,8% of all graft recipients, who died because of cardio- vascular failure, 85,7% who passed away due to infections, 100,0% who died because of cerebral complications, 80,6% who passed away due to MOF, 100,0% who died because of rejection, 100,0% who passed away due to hepatic failure, 100,0% who died because of obstructions of the hepatic artery or portal vein, 100,0% who passed away due to a HCC and 100,0% of all patients, who died due to other causes of death.

The average timeframe to exitus of the 175 DNC- free graft recipients added up to $29,2 \pm 3,8$ months, whereas the mean timeframe to exitus of the 16 patients, who developed a post- TX tumor amounted $89,9 \pm 18,3$ months.

The relationship between the median period to exitus and the occurrence of cancer revealed a statistical significance ($p = 0,005$).

The average period to exitus of all 119 DNC- free HTX recipients came to $35,8 \pm 5,3$ months, whereas the mean period to exitus of all 56 DNC- free LTX recipients was $15,1 \pm 3,6$ months.

The relationship between the median period to exitus and DNC- free HTX and DNC- free LTX patients revealed a statistical significance ($p < 0,001$).

Focusing on all 32 graft recipients, who developed a DNC (100,0%), 16 patients (50,0%) are still alive, 6 (18,8%) died because of cardio- vascular failure, 3 cases (9,4%) passed away due to infections, 6 (18,8%) died because of MOF and 1 patient (3,1%) passed away due to an unknown cause of death.

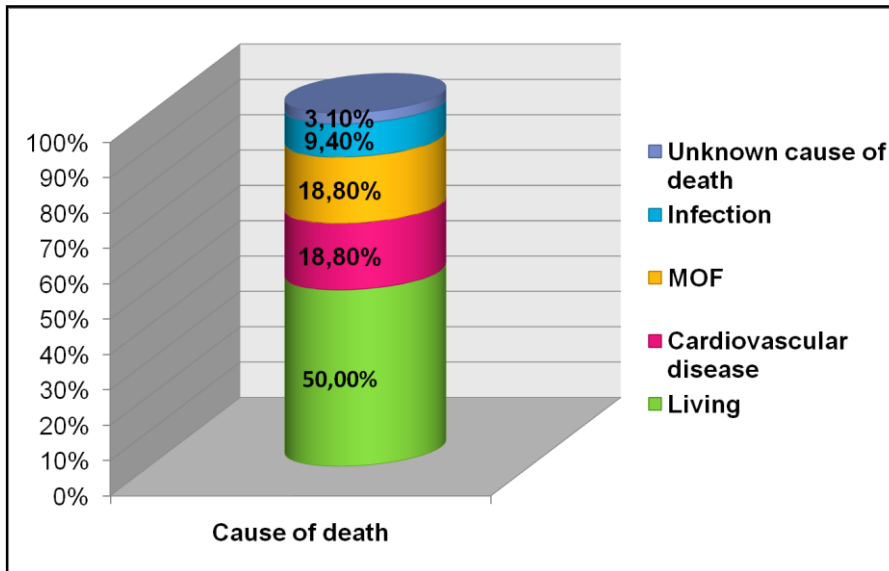


Fig. 22: Outcome after TX

It was noted that the following percentages did not develop a DNC: 7,8% of all living patients, 8,2% of all graft recipients, who died because of cardio- vascular failure, 14,3% who passed away due to infections, 19,4% who passed away due to MOF and 100,0% of all transplanted patients, who passed away due to an unknown cause of death.

The relationship between the cause of death and the occurrence of cancer within this subgroup revealed a statistical significance ($p= 0,035$).

4.7 Immunosuppression

Table 10: Immunosuppressive drugs in relation to the occurrence of DNCs

Immunosuppressive agent	Tumor
Corticosteroids	90,60%
AZA	28,10%
CSA	75,00%
MMF	59,40%
TAC	21,90%
Sirolimus	3,10%
Everolimus	15,60%

4.7.1 Corticosteroids

Out of a total sample size of 32 transplanted patients, who developed a DNC (100,0%), 29 patients (90,6%) were treated with Corticosteroids and 3 recipients (9,4%) were not.

Among 17 transplanted patients, who developed a SCC (100,0%), 15 (88,2%) obtained Corticosteroids and 2 graft recipients (11,8%) did not get Corticosteroids. 66,7% of all Corticosteroid- free treatments and 51,7% of all patients treated with Corticosteroids developed a SCC.

Both of the two transplanted patients, who developed a NHL (100,0%), received Corticosteroids.

6,9% of all patients treated with Corticosteroids developed a NHL.

Focusing on the 2 transplanted patients, who developed a bronchogenic carcinoma (100,0%), all of them (100,0%) obtained Corticosteroids.

6,9% of all patients treated with Corticosteroids developed a bronchogenic carcinoma.

Of the 2 transplanted patients, who developed a prostatic carcinoma (100,0%), 1 (50,0%) received Corticosteroids while the other patient (50,0%) did not get Corticosteroids.

33,3% of all Corticosteroid- free treated patients and 3,4% of all recipients treated with Corticosteroids developed a prostatic carcinoma.

In our study, 2 transplanted patients, who developed a pancreatic carcinoma (100,0%), all of them (100,0%) obtained Corticosteroids.

6,9% of all patients treated with Corticosteroids developed a pancreatic carcinoma.

Of the only 1 transplanted patient, who developed a UBC (100,0%), this 1 patient (100,0%) received Corticosteroids.

3,4% of all patients treated with Corticosteroids developed a UBC.

We found that, of altogether 5 transplanted patients, who developed a BCC (100,0%), all of them (100,0%) obtained Corticosteroids.

17,2% of all patients treated with Corticosteroids developed a BCC.

Of the only 1 transplanted patient, who developed an OPT (100,0%), this 1 patient (100,0%) received Corticosteroids.

3,4% of all patients treated with Corticosteroids developed an OPT.

Statistical analysis showed no significant differences between the type of tumor and the treatment with Corticosteroids.

The mean timeframe to tumor- diagnosis of the 3 transplanted patients, who did not get Corticosteroids amounted to $54,3 \pm 20,7$ months, whereas the average period to tumor- diagnosis of the 29 recipients, who obtained Corticosteroids amounted to $77,5 \pm 9,5$ months.

The relationship between the median timeframe to tumor- diagnosis and the treatment with Corticosteroids showed no statistical significance.

The average age at tumor- diagnosis of the 3 recipients, who did not get Corticosteroids came to $54,3 \pm 3,5$ years, whereas the mean age at tumor- diagnosis of the 29 patients, who received Corticosteroids came to $59,8 \pm 1,4$ years.

The relation between the median age at tumor- diagnosis and the treatment with Corticosteroids showed no statistical significance.

4.7.2 Azathioprine

Out of a total of 32 transplanted patients, who developed a DNC (100,0%), 9 (28,1%) received AZA and 23 recipients (71,9%) did not get AZA.

In our study, of all 17 transplanted patients, who developed a SCC (100,0%), 4 (23,5%) obtained AZA and 13 graft recipients (76,5%) did not get AZA.

65,5% of all AZA- free treatments and 44,4% of all patients treated with AZA developed a SCC.

Among 2 transplanted patients, who developed a NHL (100,0%), none of them (100,0%) received AZA.

8,7% of all AZA- free treated patients developed a NHL.

Focusing on the 2 transplanted patients, who developed a bronchogenic carcinoma (100,0%), 1 (50,0%) received AZA and 1 person (50,0%) did not.

11,1% of all patients treated with AZA and 4,3% of all AZA- free treated patients developed a bronchogenic carcinoma.

Both of the 2 transplanted patients, who developed a prostatic carcinoma (100,0%), 1 patient (50,0%) obtained AZA and 1 (50,0%) did not get AZA.

4,3% of all AZA- free treated patients and 11,1% of all patients treated with AZA developed a prostatic carcinoma.

We found that, among all 2 transplanted patients, who developed a pancreatic carcinoma (100,0%), none of them (100,0%) obtained AZA.

8,7% of all AZA- free treated patients developed a pancreatic carcinoma.

Of the only 1 transplanted patient, who developed a UBC (100,0%), this 1 patient (100,0%) obtained AZA. 11,1% of all patients treated with AZA developed an UBC.

Out of 5 transplanted patients, who developed a BCC (100,0%), 2 (40,0%) received AZA and 3 patients (60,0%) did not get AZA.

22,2% of all patients treated with AZA and 13,0% of all AZA- free treated persons developed a BCC.

Of the only 1 transplanted patient, who developed an OPT (100,0%), this 1 graft recipient (100,0%) did not get AZA. 4,3% of all AZA- free treated patients developed an OPT.

The mean timeframe to tumor- diagnosis of the 23 graft recipients, who did not get AZA amounted $69,2 \pm 10,1$ months, whereas the average period to tumor diagnosis of the 9 patients, who received AZA added up to $91,1 \pm 17,9$ months.

Statistical analysis showed no significant differences between the median timeframe to tumor- diagnosis and the treatment with AZA.

The mean age at tumor- diagnosis of the 23 recipients, who did not obtain AZA came to $59,7 \pm 1,6$ years, whereas the average age at tumor- diagnosis of the 9 transplanted patients, who received AZA came to $58,4 \pm 2,7$ years.

The relationship between the median age at tumor- diagnosis and the treatment with AZA showed no statistical significance.

4.7.3 Cyclosporine A

Out of a total of 32 transplanted patients, who developed a DNC (100,0%), 24 (75,0%) received CSA and 8 recipients (25,0%) did not get CSA.

Focusing on all 17 transplanted patients, who developed a SCC (100,0%), 12 (70,6%) obtained CSA and 5 (29,4%) did not get CSA.

62,5% of all CSA- free treatments and 50,0% of all patients treated with CSA developed a SCC.

Among 2 transplanted patients, who developed a NHL (100,0%), 1 (50,0%) received CSA and 1 (50,0%) did not get CSA.

12,5% of all CSA- free treated patients and 4,2% of all patients, who were treated with CSA developed a NHL.

Both of all 2 transplanted patients (100,0%), who developed a bronchogenic carcinoma, all of them (100,0%) obtained CSA.

8,3% of all patients treated with CSA developed a bronchogenic carcinoma.

Of all 2 transplanted patients, who developed a prostatic carcinoma (100,0%), 1 (50,0%) received CSA and 1 patient (50,0%) did not get CSA.

12,5% of all CSA- free treated patients and 4,2% of all patients treated with CSA developed a prostatic carcinoma.

In our study, both of the 2 transplanted patients, who developed a pancreatic carcinoma (100,0%), received CSA.

8,3% of all patients treated with CSA developed a pancreatic carcinoma.

Of the only 1 transplanted patient, who developed a UBC (100,0%), this 1 patient (100,0%) obtained CSA.

4,2% of all patients treated with CSA developed a UBC.

Focusing on all 5 transplanted patients, who developed a BCC (100,0%), 4 (80,0%) obtained CSA and 1 patient (20,0%) did not get CSA.

16,7% of all patients treated with CSA and 12,5% of all CSA- free treated persons developed a BCC.

Among the only 1 transplanted patient, who developed an OPT (100,0%), this 1 patient (100,0%) received CSA.

4,2% of all patients treated with CSA developed an OPT.

The mean timeframe to tumor- diagnosis of the 8 patients, who did not get CSA amounted to $64,6 \pm 14,3$ months, whereas the average period to tumor- diagnosis of the 24 patients, who obtained CSA added up to $78,9 \pm 10,9$ months.

Statistical analysis showed no significant differences between the median timeframe to tumor- diagnosis and the treatment with CSA.

The mean age at tumor- diagnosis of the 8 recipients, who did not get CSA accounted for $53,8 \pm 2,2$ years, the mean age at tumor- diagnosis of the 24 patients, who obtained CSA came to $61,2 \pm 1,5$ years.

The relation between the average age at tumor- diagnosis and the treatment with CSA showed a statistical significance. ($p= 0,016$)

4.7.4 Mycophenolate mofetil

Focusing on all 32 transplanted patients, who developed a DNC (100,0%), 19 (59,4%) received MMF and 13 recipients (40,6%) did not get MMF.

Of all 17 transplanted patients, who developed a SCC (100,0%), 11 (64,7%) obtained MMF and 6 graft recipients (35,3%) did not get MMF.

46,2% of all MMF- free treatments and 57,9% of all patients treated with MMF developed a SCC.

Both of the 2 transplanted patients, who developed a NHL (100,0%), all of them (100,0%) received MMF.

10,5% of all patients treated with MMF developed a NHL.

Among the 2 transplanted patients, who developed a bronchogenic carcinoma (100,0%), 1 (50,0%) obtained MMF and 1 (50,0%) did not get MMF.

5,3% of all patients treated with MMF and 7,7% of all MMF- free treated patients developed a bronchogenic carcinoma.

Both of the 2 transplanted patients, who developed a prostatic carcinoma (100,0%), 1 (50,0%) was treated with MMF and 1 patient (50,0%) was not.

7,7% of all MMF- free treated patients and 5,3% of all patients treated with MMF developed a prostatic carcinoma.

Of all 2 transplanted patients, who developed a pancreatic carcinoma (100,0%), 1 (50,0%) received MMF and 1 patient (50,0%) did not get MMF.

7,7% of all MMF- free treated patients and 5,3% of all patients treated with MMF developed a pancreatic carcinoma.

Of the only 1 transplanted patient, who developed a UBC (100,0%), this 1 patient (100,0%) did not get MMF.

7,7% of all MMF- free treated patients developed a UBC.

Concerning all 5 transplanted patients, who developed a BCC (100,0%), 2 (40,0%) received MMF and 3 patients (60,0%) did not get MMF.

10,5% of all patients treated with MMF and 23,1% of all MMF- free treated persons developed a BCC.

Of the only 1 transplanted patient, who developed an OPT (100,0%), this 1 patient (100,0%) obtained MMF.

5,3% of all patients treated with MMF developed an OPT.

Statistical analysis showed no significant differences between the type of tumor and the treatment with MMF.

The mean timeframe to tumor- diagnosis of the 13 patients, who did not get MMF amounted to $89,5 \pm 12,6$ months, whereas the average period to tumor- diagnosis of the 19 patients, who obtained MMF added up to $65,6 \pm 12,0$ months.

The relationship between the median timeframe to tumor- diagnosis and the treatment with MMF showed no statistical significance.

The mean age at tumor- diagnosis of the 13 recipients, who did not get MMF came to $61,6 \pm 2,3$ years, whereas the average age at tumor- diagnosis of the 19 patients, who received MMF accounted for $57,7 \pm 1,6$ years.

Statistical analysis showed no significant differences between the average age at tumor- diagnosis and the treatment with MMF.

4.7.5 Tacrolimus

Out of the total number of 32 transplanted patients, who developed a DNC (100,0%), 7 (21,9%) were treated with TAC and 25 recipients (78,1%) were not.

Focusing on all 17 transplanted patients, who developed a SCC (100,0%), 4 (23,5%) received TAC and 13 graft recipients (76,5%) did not get TAC.

52,0% of all TAC- free treatments and 57,1% of all patients treated with TAC developed a SCC.

Both of the 2 transplanted patients, who developed a NHL (100,0%), 1 (50,0%) obtained TAC and 1 person (50,0%) didn't get TAC.

14,3% of all patients treated with TAC and 4,0% of all TAC- free treated patients developed a NHL.

We found that among the 2 transplanted patients, who developed a bronchogenic carcinoma (100,0%), none of them (100,0%) received TAC.

8,0% of all TAC- free treated patients developed a bronchogenic carcinoma.

Of the 2 transplanted patients, who developed a prostatic carcinoma (100,0%), 1 (50,0%) received TAC and 1 patient (50,0%) did not get TAC.

4,0% of all TAC- free treated patients and 14,3% of all patients treated with TAC developed a prostatic carcinoma.

Both of the 2 transplanted patients, who developed a pancreatic carcinoma (100,0%), none of them (100,0%) obtained TAC.

8,0% of all TAC- free treated patients developed a pancreatic carcinoma.

Of the only 1 transplanted patient, who developed a UBC (100,0%), this 1 patient (100,0%) did not get TAC.

4,0% of all TAC- free treated patients developed a UBC.

Concerning on the 5 transplanted patients, who developed a BCC (100,0%), 1 (20,0%) received TAC and 4 patients (80,0%) did not get TAC.

14,3% of all patients treated with TAC and 16,0% of all TAC- free treated persons developed a BCC.

Among the only 1 transplanted patient, who developed an OPT (100,0%), this 1 patient (100,0%) did not get TAC.

4,0% of all TAC- free treated patients developed an OPT.

The mean timeframe to tumor- diagnosis of the 25 patients, who did not get TAC amounted $78,8 \pm 10,4$ months, whereas the average period to tumor- diagnosis of the 7 patients, who received TAC added up to $63,0 \pm 16,4$ months.

Statistical analysis showed no significant differences between the median timeframe to tumor- diagnosis and the treatment with TAC.

The mean age at tumor- diagnosis of the 25 recipients, who did not obtain TAC came to $60,8 \pm 1,5$ years, whereas the average age at tumor- diagnosis of the 7 patients, who received TAC accounted to $53,9 \pm 2,6$ years.

The relationship between the average age at tumor- diagnosis and the treatment with TAC showed a statistical significance. ($p= 0,031$)

4.7.6 Sirolimus

Out of the total of 32 transplanted patients, who developed a DNC (100,0%), only 1 patient (3,1%) was treated with Sirolimus whilst the remaining 31 recipients (96,9%) were not.

We found that of all 17 transplanted patients, who developed a SCC (100,0%), none of them (100,0%) received Sirolimus.

54,8% of all Sirolimus- free treated patients developed a SCC.

Among 2 transplanted patients, who developed a NHL (100,0%), none of them (100,0%) obtained Sirolimus.

6,5% of all Sirolimus- free treated patients developed a NHL.

Both of the 2 transplanted patients, who developed a bronchogenic carcinoma (100,0%), none of them (100,0%) received Sirolimus.

6,5% of all Sirolimus- free treated patients developed a bronchogenic carcinoma.

Focusing on the 2 transplanted patients, who developed a prostatic carcinoma (100,0%), 1 (50,0%) received Sirolimus and 1 patient (50,0%) did not get Sirolimus.

3,2% of all Sirolimus- free treated patients and 100,0% of all patients treated with Sirolimus developed a prostatic carcinoma.

Of all 2 transplanted patients, who developed a pancreatic carcinoma (100,0%), none of them (100,0%) obtained Sirolimus.

6,5% of all Sirolimus- free treated patients developed a pancreatic carcinoma.

Of the only 1 transplanted patient, who developed a UBC (100,0%), this 1 patient (100,0%) did not get Sirolimus.

3,2% of all Sirolimus- free treated patients developed a UBC.

Of altogether 5 transplanted patients, who developed a BCC (100,0%), all of them (100,0%) did not receive Sirolimus.

16,1% of all Sirolimus- free treated persons developed a BCC.

Of the only 1 transplanted patient, who developed an OPT (100,0%), this 1 patient (100,0%) did not obtain with Sirolimus.

3,2% of all Sirolimus- free treated patients developed an OPT.

The relation between the type of tumor and the treatment with Sirolimus revealed a statistical significance ($p= 0,030$).

The mean timeframe to tumor- diagnosis of the 31 patients, who did not get Sirolimus amounted $77,4 \pm 9,0$ months, whereas the period to the tumor- diagnosis of the 1 patient, who received Sirolimus was 13,0 months.

Statistical analysis showed no significant differences between the average timeframe to tumor- diagnosis and the treatment with Sirolimus.

The mean age at tumor- diagnosis of the other 31 recipients, who did not obtain Sirolimus came to $59,3 \pm 1,4$ years, whereas the age at tumor- diagnosis of the 1 patient, who received Sirolimus was 61,0 years.

The relationship between the average age at tumor- diagnosis and the treatment with Sirolimus showed no statistical significance.

4.7.7 Everolimus

Out of the total of 32 transplanted patients, who developed a DNC (100,0%), 5 (15,6%) were treated with Everolimus whilst the remaining 27 recipients (84,4%) were not.

Focusing on all 17 transplanted patients, who developed a SCC (100,0%), 13 (76,5%) did not receive Everolimus and 4 patients (23,5%) did.

48,1% of all Everolimus- free treated patients and 80,0% of all patients treated with Everolimus developed a SCC.

In our study, all 2 transplanted patients, who developed a NHL (100,0%), both of them (100,0%) obtained Everolimus.

7,4% of all Everolimus- free treated patients developed a NHL.

We found that of all 2 transplanted patients, who developed a bronchogenic carcinoma (100,0%), none of them (100,0%) obtained Everolimus.

7,4% of all Everolimus- free treated patients developed a bronchogenic carcinoma.

Both of the 2 transplanted patients, who developed a prostatic carcinoma (100,0%), none of them (100,0%) obtained Everolimus.

7,4% of all Everolimus- free treated patients developed a prostatic carcinoma.

Of all 2 transplanted patients, who developed a pancreatic carcinoma (100,0%), none of them (100,0%) received Everolimus.

7,4% of all Everolimus- free treated patients developed a pancreatic carcinoma.

Of the only 1 transplanted patient, who developed a UBC (100,0%), this 1 patient (100,0%) did not get Everolimus.

3,7% of all Everolimus- free treated patients developed a UBC.

Concerning all 5 transplanted patients, who developed a BCC (100,0%), 4 (80,0%) were not treated with Everolimus and 1 person (20,0%) was.

14,8% of all Everolimus- free treated persons and 20,0% of all patients treated with Everolimus developed a BCC.

Among the only 1 transplanted patient, who developed an OPT (100,0%), this 1 patient (100,0%) did not get Everolimus.

3,7% of all Everolimus- free treated patients developed an OPT.

The mean timeframe to tumor- diagnosis of the 27 transplanted patients, who did not get Everolimus amounted $72,0 \pm 10,4$ months, whereas the average period to

tumor- diagnosis of the 5 patients, who received Everolimus added up to $93,2 \pm 4,5$ months.

Statistical analysis showed no significant differences between the median timeframe to tumor- diagnosis and the treatment with Everolimus.

The mean age at tumor- diagnosis of the 27 transplanted recipients, who did not obtain Everolimus came to $58,1 \pm 1,4$ years, whereas the average age at tumor- diagnosis of the 5 patients, who received Everolimus accounted for $65,6 \pm 3,3$ years.

The relationship between the average age at tumor- diagnosis and the treatment with Everolimus revealed a statistical significance ($p= 0,045$).

Table 11: Immunosuppressive therapy in relation to the occurrence of specific types of de- novo malignancies

Immunosuppressive agent	SCC	NHL	Bronchogenic carcinoma	Prostatic carcinoma	Pancreatic carcinoma	UBC	BCC	OPT
Corticosteroids	+	+	+	+	+	+	+	+
AZA	+	-	+	+	-	+	+	-
CSA	+	+	+	+	+	+	+	+
MMF	+	+	+	+	+	-	+	+
TAC	+	+	-	+	-	-	+	-
Sirolimus	-	-	-	+	-	-	-	-
Everolimus	+	-	-	-	-	-	+	-

5 DISCUSSION

Today, organ TX plays a vital role as the best, maybe the only choice of treatment in organ end- stage failure. (2)

In 1954, the first organ TX was performed by Joseph E. Murray, who later won the Nobel Prize for his pioneering work. (2)

At that time, the main problem of these medical interventions was the impossibility of graft survival longer than a few weeks, this being largely due to ignorance of the fact, that rejection is an immunological occurrence. Peter Medawar, an immunologist in Oxford, discovered that rejection is a result of active immunization, in 1945. (1) (4)

After 1961, when Azathioprine- the first immunosuppressive agent- was discovered by Elion and Hitchings, graft survival became achievable.

Later, other increasingly potent immunosuppressive drugs became available. (1) (2) (3)

However, whenever society develops a growing need for something, like the increasing demand for organs, there will often be a growth in related criminal activity driven by money. For example desperate patients nowadays may consider travelling to countries, like China, where it is possible to access life- saving treatment as a result of the growth of a local black market in organ trade. (5)

Over the years, the increasing demand for organs led to research into solutions for this emerging problem, like xenografting for example. (5)

Before xenotransplantations were imagined, folklore had already presented stories of half- man half- beast chimeras, such as the cave painting in the Lascaux cave in France (15 000 BC), which shows a human being with a head of a bird; the Great Sphinx of Giza, which is a lion with the head of a woman or Anubis, who had the head of a jackal; in Greece, the Minotaur was a man with the head of a bull; and Centaurs, were horses with the heads of men. More recent, legends include half- man half- beast werewolves and vampires for example. However the desire to save lives by exchanging a failing organ for a healthy graft can be traced back to ancient times. (86)

A good early example was Reemtsma in the 1960s, who removed a kidney from a chimpanzee and transplanted it into a patient. The new organ worked immediately, but only for about 10 months. (5) (86)

Although it seems increasingly possible to use animals as a kind of “spare parts depot”, to date there has not been any significant breakthrough in this area. (5)

According to the progression and change over the years in all aspects of TX, indications have widened and contraindications become fewer. (11) (13) (87)

Despite the advanced use of operating techniques to tap the full potential of the donor pool, like splitting of livers, the demand for TX is outstripping the supply of organs. (87) The consequence of this shortage of donors is that an increasing percentage of waiting list patients are dying and those patients on the waiting list become sicker before they receive a graft, and that in turn makes many of them ineligible as they become too sick. (87) (88)

According to UNOS, there are more than 15 patients in the United States, who die on the waiting list each day. (89)

The issue of timing in organ TX is also a crucial factor in the overall success of the operation, and has an important effect of the subsequent outcome.

Patients receiving an organ often have to deal with long- term complications as an ongoing problem after solid organ TX, because of the obligatory subsequent life-long intake of immunosuppressive drugs. (73)

For example NODM occurs as one of the major metabolic complications after HTX with an incidence of 20 to 30% in 5 years and a risk factor of 15 % in liver transplant recipients. (26) (27)

Related to all of its after- effects, NODM is associated to a higher incidence of patients' death. (23) (24) (25)

Chronic renal failure after nonrenal solid organ TX is also a frequent complication with an incidence of 10 to 80%, which can result in dialysis as well as in death. (29) (30) (31)

Although, the etiology of CRF is multifactorial, both, Cyclosporine A and Tacrolimus, represent the most important risk factors for the onset of renal dysfunction. (35) (36)

Since the launch of newer and more potent immunosuppressants, the incidences of graft rejection have reduced dramatically, while the susceptibility of life-threatening viral, bacterial, fungal and parasitic infections increased, all of which have serious consequences on morbidity and mortality. (40) (41) (42) (43)

Epidemiologic exposures can be separated into 4 classifications, namely donor-derived infections, recipient-derived infections, nosocomial infections and community infections. Infections in organ transplant recipients are more difficult to identify than in immunocompetent persons, because symptoms are often reduced. (43)

Evidence seems to support the fact, that the progress in immunosuppressive therapy reduces graft rejection and hence lengthens the patients' life, although that achievement is related to problematic side-effects, like de-novo-malignancy as one of the main causes of late death. (49) (50)

First, in 1968, the enhanced incidence of DNC after organ TX was mentioned by Thomas E. Starzl. (51) (52) (53)

It is estimated that DNC will top cardiovascular diseases as the most common cause of death in transplant recipients within the next 20 years period. (48)

In the literature, the incidence of DNC is estimated between 4% and 16%. (52)

In comparison to the general population, transplant recipients are 3 to 4 times more likely to incur malignancy related to chronic immunosuppression. (47) (48)

The most common DNC is skin cancer, followed by PTDL. (57) (58)

The etiology of DNC is multifactorial, including the presence of environmental (such as tobacco and alcohol) and genetic risk factors common to the general community and the complex interaction well-known between the effect of depressed immunosurveillance, the action of pro-oncogenic viruses, and direct carcinogenic effects of immunosuppressive agents, all of which come together in graft recipients. (62) (90) (91) (92)

The majority of DNCs are linked to potentially oncogenic virus infections, like PTLD (NHL and Hodgkin lymphoma) related to the EBV, KS associated with the HHV-8, liver cancer correlated with the HBV and HCV, and carcinomas of the cervix, vulva/vagina, penis, anus and oral cavity and pharynx linked to the HPV. (59) (52) (60) (65)

As a result of these risk factors, the incidence of post- TX malignancy in organ transplant patients is increased. (62) Another problem is that malignancies occurring during immunosuppressive therapy are much more aggressive than in the general community. (91) (93)

To protect the graft from rejection it is essential that those patients receive a life-long immunosuppressive therapy. These have certainly improved considerably over the years, but it is a fact that their side- effects result in a significant increase of morbidity. (73) (74)

On the one hand most of the immunosuppressive agents are associated with an increased risk of periodic rejection and graft dysfunction as a direct result of underdosing and drug- related toxicity, infections as well as cancer by overdosing. (75)

On the other hand the same therapies applied after organ TX are perfectly effective but, unfortunately, as a consequence of their non- specific mechanism of action, they can often be unsuccessful in averting chronic graft rejection, life-threatening infections and malignancies. (73)

The main theme of our study was to gather information about the influence of immunosuppressive therapy on DNCs in transplanted patients. The secondary goal was to gain knowledge of the distribution of the different types of carcinomas in heart and liver transplanted patients.

Therefore we retrospectively evaluated all 398 HTX and LTX patients, between March 1983 and December 2008, performed at the Medical University of Graz, Austria, Department for Surgery, Division of Transplantation Surgery.

In our study of 398 liver and heart graft recipients, we detected that the incidence of DNC accounted for 8% of the total sample.

This result correlates well with the existing literature, which has noted an incidence of DNC ranging from 4% to 16%. (49)

The most common cancer in our study was non- melanoma skin cancer (NMSC) with 68,7% of all DNC, comprising of 53,1% SCC and 15,6% BCC.

Focusing on the 28 HTX patients, NMSC was diagnosed in 19 recipients (14 SCC and 5 BCC) and in the 4 LTX patients, SCC affected 3 recipients.

Several other studies reported an incidence of NMSC between 39% and 66%. (94) (95) (96) (97)

The findings of the CTTR also confirm the fact, that cutaneous cancer is the most frequent DNC after solid organ TX. (98)

Nonetheless, it should be emphasized, that there are widespread geographical differences. For example in Australia the estimated incidence of skin cancer was 70% after 20 years, of chronic immunosuppressive therapy which contrasted sharply to a study in northern England, where “only” 30% developed skin cancer after the same 20 year period. (97) (99)

NHL as a DNC comprised 6,3% in our study. Our finding deviated to a large extent from data gathered by the CTTR, which cited rates up to 17,1%. (59)

This result, which implies that PTLD is one of the most common DNC, is also in line with data from the literature. (100)

It is noted however that another study during 2008 showed that the incidence of PTLD, especially in liver and heart transplant recipients accounted for 2,8% and 6,3%, respectively, which compares favourably with our outcome. (58)

In Austria, the incidence of NHL in the general population adds up to nearly 3%, which demonstrates an increased incidence after solid organ TXs. (101)

Also with an incidence of 6,3% occurred the pancreatic carcinoma as a DNC in our study. The CTTR vary from our data with an incidence of 0,8%. (59).

In Austria, the incidence of pancreatic carcinomas in the general community accounts for 3,7%, which also shows an enhanced occurrence after an organ TX. (101)

Only 1 patient in our study developed a UBC with an incidence of 3,1%. A similar finding was reported by Israel Penn, who tabulated the CTTR, with an occurrence of 2,2%. (59)

In Austria, the UBC is responsible for 5,1% of all tumor- diagnosis in the general population. (101)

In our study, lung cancer was encountered in 6,3% of cases, which is in close agreement with the results obtained by the CTTR, with an incidence of 5,5%. (59)

In Austria, lung cancer develops in the general community with an incidence of 10%. (101)

Prostatic cancer occurred in 6,3% of all our TX patients, who developed a DNC, which differ from that reported by Israel Penn with 1,7%. (59)

In Austria, 25% of all neoplastic disorders of men in the general population were prostatic carcinomas. (101)

Our results are consistent with those reported by the CTTR. With the sole exception of skin cancer, all the other commonly observed types of malignant neoplastic diseases in the general population, such as lung, prostate, breast and colon, did not increase, but rather decreased among transplant recipients in our study, as well as in the literature. (15) (102) (103) (104)

Contrary to our findings, two other major tumor registries, the Nordic renal Transplant Registry (NRTR) and the Australian and New Zealand Transplant Registry (ANZTR), both cited an enhanced incidence of nearly all types of DNC after solid organ TX. (98)

Although, tumor registries give a good overview, there are always a few problems, when one wants to compare the results, because incidences and types of cancer differ widely from one study to another. For example, while the CTTR is a world-wide gathering of patients, our study- in common with both- the NRTR, and the ANZTR- was based only on a regional population. (98) (103)

Another fact is the total number of transplanted patients, which ranges from a few, (like our study where 32 organ recipients developed a DNC) to thousands of observed patients (CTTR). (98)

Furthermore, the inclusion criteria play a critical role. For instance, the NRTR also covers benign tumors, such as adenomas of the thyroid gland. Therefore, accurate

comparison between different studies is quite difficult although obviously very important for reasons of accurate result interpretation. (98)

In our study the relationship between the kind of TX (HTX or LTX) and the occurrence of cancer revealed an increased risk of HTX patients getting a DNC, in contrast to liver recipients. Because varying kinds of grafts need different dosage of immunosuppressants, HTX patients can probably sustain higher levels of immunosuppressive drugs than other recipients. (60)

The relation between the kind of TX (HTX or LTX) and the occurrence of a specific type of cancer was not significant, based on the fact that skin cancers are the most common DNC in every kind of TX. (57) (58) (67) (68)

Concerning sex distribution, we have not found any relationship, in view of HTX or LTX, between the occurrence of neoplasms, or the receiving of cancer therapy, and exitus.

Focusing on the kind of primary disease in relation to the occurrence of cancer, our study showed a significance when HTX and LTX patients are together in a pool, but there is no relationship, when we split them up into two groups (HTX and LTX). This is readily explained, by the large difference in the number of patients in each group (HTX n=28; LTX n= 4).

Another significant point in our study was that patients who developed a DNC, but received an appropriate cancer treatment, have a longer survival than patients without any treatment. For example, skin cancer as the most common DNC can reduce the quality of life- and even cause the death-, but if it is early diagnosed and treated, the outcome is measurably improved. (69)

Our findings regarding the ultimate cause of death in transplanted patients, who developed a DNC are in line with data from the literature, which reported that cardiovascular diseases are the leading cause of death. (48) (62)

Gutierrez- Dalmau and Campistol noted that the treatment with Corticosteroids enhances the incidence of DNC after TX. (62)

The result of our study, namely that 90,6% of all transplanted patients, who developed a tumor, were treated with Corticosteroids, correlates well with the literature.

AZA causes UV- light related mutagenic oxidative DNA damage, which has a significant consequence for SCCs in organ transplant recipients. (105)

In our study the incidence of DNC under the treatment of AZA adds up to 28,1%.

According to Gutierrez- Dalmau and Campistol MMF is much more potent than AZA, without increasing the risk of cancer. (62)

In our study, the incidence of DNC of MMF amounts to 59,4% and in consideration of the risk of AZA this finding actually differs widely from our study.

CSA and TAC are two CNIs which form a cornerstone of immunosuppressive therapy.

Several comparison studies have proven that Cyclosporine- based regimes compared with Azathioprine- based therapies have cited higher incidences of malignancies. (62)

This observation is in accordance with our study, which shows a malignancy risk of 75% during a treatment with CSA.

Wiesner indicated that TAC is at least as effective as CSA and claimed that Tacrolimus- based therapies have the same incidence of DNC as compared Cyclosporine- based regimes. (106)

In contrast to Wiesner, our result deviates to a large extent, because the incidence of DNC during a treatment with TAC added up to 21,9% unlike the CSA cases which showed a risk rate of 75%.

Sirolimus and Everolimus are both mTOR Inhibitors, which have a dual role as immunosuppressive drug and antitumoral agent. (62)

According to Koehl et al. Sirolimus protects the graft from rejection, while simultaneously controlling cancer progression despite unchanged drug doses. This is in direct contrast to CSA, which is effective in protecting the allograft, while the tumor development is enhanced by continued treatment. (107)

These observations correlate well with the findings in our study. Everolimus has an DNC incidence of 15,6% und Sirolimus shows a frequency of only 3,1%.

Focusing on the median period to tumor- diagnosis in relation to the different kinds of immunosuppressive agents, such as Corticosteroids, AZA, Cyclosporine, MMF, TAC, Sirolimus and Everolimus, our study revealed no significance.

Concerning the age at tumor- diagnosis and the different kinds of immunosuppressants, our study showed no relationship between Corticosteroids, AZA, MMF and Sirolimus, in direct contrast to CSA, TAC and Everolimus. For example, transplanted patients, who received TAC, developed a DNC much earlier, whereas Everolimus apparently prolonged the occurrence of cancer compared to the matched controls. (107)

In our study, with the exception of Sirolimus, all other immunosuppressive drugs did not prefer any type of DNC. In this particular case, our result is not convincing because only 1 patient, who developed a carcinoma, received Sirolimus.

There are a few things to keep in mind, when seeking to compare the different immunosuppressive agents. Generally, immunosuppressive regimes consist usually of different combinations of drugs at various dosages, e.g. Corticosteroids are a crucial part of most immunosuppressive therapies, which is why they are almost always applied in combination with other immunosuppressants throughout different long term follow-ups. (62) (103)

Another important point is that the newer drugs were established at the same time with the intention of delivering better pathology and focus on diagnosis, which were nonstandard in earlier years. (62)

In terms of our study, it is important to mention, that we have a small number of transplanted patients, which makes the comparability with other studies more difficult. Another fact, related to the evaluation of immunosuppressive regimes, is that we did not estimate the different dosages and blood levels, nor the incidence of switching the use of immunosuppressive agents.

Focusing on these patients as human beings, with all their inbuilt deficiencies, we did not assess their compliance concerning the intake of the immunosuppressive medication, or other important risk factors, such as tobacco and alcohol abuse, or alternatively a naturally healthy lifestyle, both of which can obviously play a crucial role in survival and quality of life.

In conclusion, DNC is one of the most serious and well known common occurrences after solid organ TX. (57)

Due to many side effects of chronic immunosuppressive agents, DNC is more aggressive and worsens the prognosis of morbidity and mortality compared to the incidence of which is normally found in the general population. (103) (104)

Although, solid organ TX offers a vision of hope for the future, there remain many unsolved and important challenges. (69)

On the one hand, patients continue to die on waiting lists because of the donor shortage and on the other hand successfully transplanted graft recipients pass away from potentially preventable cancers. (87) (88)

It goes without saying that such fatalities are always tragic, but they may be more avoidable in future thanks to improved management of cancer prevention, continuous and careful investigations, early onset diagnosis and- if necessary- optimized aggressive therapy. (65) (69) (91)

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