ORGAN TRANSPLANTATION RELATED CANCER

by

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Abstract

Cancer is an important cause of morbidity and mortality among the recipients of solid organ transplantation. Cancer transmitted from the donors often has a poor outcome and the fear of such transmission results in organs from certain donors not being accepted. A study of the transplant recipients in the UK over a period of 10 years identified 15 cases of transmitted cancers. The rate of cancer transmission was 0.05%. The risk of cancer transmission was 9 times higher from donors older than 45 years. Cancer transmission occurred from donors without a history of cancer. A comparison of the organ donor data with the guidelines classifying the donor's risk of cancer transmission showed that a carefully selected cohort of donors, who are classed as a high risk of cancer transmission by the guidelines, could safely donate their organs resulting in valuable additional survival for the recipients, with low risk of cancer transmission. These results provide evidence, based on which the donor classification guidelines can be modified resulting in increased availability of safe organs for transplantation. The risk of recurrence after transplantation of cancers treated before transplantation was low in carefully selected recipients undergoing transplantation after a waiting period of 2 years following the diagnosis of cancer. No association was found between the donor-recipient CMV status and the risk of post transplant cancer. No chronological changes were noted in the incidence of PTLD or in the survival rates after the diagnosis of PTLD. This research estimated the risk of cancer transmission to the organ transplant recipients enabling improved risk assessment in transplantation. This research also explored the ways of increasing the number of safe organs for transplantation whilst reducing inappropriate wastage of donor organs.

Disclaimer

This is to certify that I have, as first author, already published some of the text and the data presented in Chapters 3, 4, 6, and 8 of this thesis. These publications have been used to facilitate the development of evidence-based national guidelines for improving the selection of organ donors. Such content is referenced with their respective publications as follows:

Chapter 3; pages 117 to 143 (paragraphs 3.1 to 3.5) published in: DESAI, R., COLLETT, D., WATSON, C. J., JOHNSON, P., EVANS, T. & NEUBERGER, J. 2012. Cancer transmission from organ donors-unavoidable but low risk. *Transplantation,* 94**,** 1200-7

Chapter 4; pages 145 to 171 (paragraphs 4.1 to 4.5) published in: DESAI, R., COLLETT, D., WATSON, C. J., JOHNSON, P., EVANS, T. & NEUBERGER, J. 2014. Estimated risk of cancer transmission from organ donor to graft recipient in a national transplantation registry. *Br J Surg,* 101**,** 768-74

Chapter 6; pages 192 to 217 (paragraphs 6.1 to 6.5) published in: DESAI, R., COLLETT, D., WATSON, C. J., JOHNSON, P. J., MOSS, P. & NEUBERGER, J. 2015. Impact of Cytomegalovirus on Long-term Mortality and Cancer Risk After Organ Transplantation. *Transplantation,* 99**,** 1989-94

Chapter 8; pages 265 to272 (paragraphs 8.1.2, 8.1.3 and 8.1.5) published in three publications mentioned above

Dedication

I wish to dedicate this thesis to my family, particularly to my wife Seema and children Rahul and Tanya, for their support, patience and encouragement.

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Abbreviations

ARDS	Adult respiratory distress syndrome
AMR	Antibody mediated rejection
AFP	Alpha-fetoprotein
APC	Antigen presenting cell
ALG	Anti-lymphocyte globulin
ATG	Anti-thymocyte globulin
ANZDATA	Australia and New Zealand Dialysis and Transplant Registry
BC	Before Christ
BMI	Body mass index
CNI	Calcineurin inhibitors
CIS	Carcinoma-in-situ
CNS	Central nervous system
CNT	Centro Nazionali di Trapianti
CCL2	Chemokine (c-c motif) ligand 2
CCL5	Chemokine ligand 5
CoE	Council of Europe
CI	Confidence interval

CRP	C-reactive protein
CT	Computerised tomography
CXCL10	c-x-c motif chemokine
CMV	Cytomegalovirus
D	Donor
DNA	De-oxy ribonucleic acid
DCP	Des-gamma-carboxy prothrombin
DBD	Donation after brain death
DCD	Donation after circulatory death
DDC	Donor derived cancer
DOC	Donor origin cancer
DTC	Donor transmitted cancer
EBV	Epstein-Barr virus
GIST	Gastrointestinal stromal tumour
HR	Hazard ratio
HFSS	Heart failure survival score
HBV	Hepatitis B virus
HCV	Hepatitis C virus

HL	Hodgkin’s lymphoma
HHV	Human herpes virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPV	Human papilloma virus
HTLV	Human T-lymphotropic virus
IFN	Interferon
IL	Interleukin
iNOS	Inducible nitric oxide synthetase
IPITTR	Israel Penn International Transplant Tumour Registry
Kg	Kilogram
LAS	Lung allocation score
MRI	Magnetic resonance imaging
MHC	Major histocompatibility complex
mTOR	Mammalian target of Rapamycin
mTORC	Mammalian target of Rapamycin complex
m	Metre
6MP	6-mercaptopurine

MELD	Model for end-stage liver disease
MMF	Mycophenolate mofetil
NCDR	National Cancer Data Repository
NHS	National Health Service
NHSBT	National Health Service Blood and Transplant
NOMDS	National Organ Matching and Distribution Service
NTTRL	National Tissue Typing and Reference Laboratory
NK	Natural killer
NHL	Non-Hodgkin's lymphoma
NMSC	Non-melanoma skin cancer
NS	Not specified
NFAT	Nuclear factor of activated T-cells
OR	Odds ratio
OPTN	Organ Procurement and Transplantation Network
ONT	Organizacion Nacional de Trasplantes
PET	Positron emission tomography
PTLD	Post-transplant lymphoproliferative disorder
PCA	Prostate cancer antigen

PSA	Prostate specific antigen
R	Recipient
SHFM	Seattle heart failure model
SN-OD	Specialist nurses in organ donation
SIR	Standardised incidence ratio
SAS	Statistical analysis software
TCR	T cell receptor
TTS	The Transplantation Society
6TG	6-thioguanine
TGF	Transforming growth factor
TNF	Tumour necrosis factor
UV	Ultraviolet
UK	United Kingdom
UKELD	United Kingdom end-stage liver disease
UNOS	United Network for Organ Sharing
USFDA	United States Food and Drug Administration
USA	United States of America
WHO	World Health Organization

Contents

List of Tables

List of Figures

CHAPTER 1

INTRODUCTION

1.1 Background to this research

One of the major medical advances of the twentieth century is the successful transplantation of solid organs. Within decades, organ transplantation progressed from animal experiments and early human experiments to an established front-line treatment. Developments took place in all aspects of donation and transplantation including assessment and selection of the donors and the recipients, surgical techniques, anaesthetic techniques, intensive care and long-term post-transplant care. At present, transplantation is the most effective treatment for selected patients with end-stage organ failure. Successful transplantation has been shown to improve the length and the quality of life (NHSBT, 2014b). It can be an effective life saving intervention in some cases with acute organ failure and also has a positive impact on the health care economy (NHSBT, 2009).

Cancer, along with infection and cardiovascular disease, is one of the three most common causes of long-term mortality among the recipients of organ transplantation (USRDS, 2012, Pruthi et al., 2001, Rabkin et al., 2001, Jung et al., 2011). The incidence of cancer is higher among the recipients of organ transplantation compared to matched non-transplant population (Collett et al., 2010, Villeneuve et al., 2007, Adami et al., 2003, Hoshida et al., 1997, Kyllonen et al., 1994, Kasiske et al., 2004) and the outcomes of post-transplant cancer are poorer as the disease tends to be more aggressive than in an immunocompetent patient, often resulting in graft loss and death (Barrett et al., 1993, Veness et al., 1999, Martinez et al., 2003).

In this chapter, an overview of organ transplantation is presented, including early and recent history of human organ transplantation, immunological and clinical aspects of graft rejection, immunosuppressive agents and the outcomes after transplantation with emphasis on post-transplant cancer.

1.2 History of organ transplantation

1.2.1 Early history

Successful organ transplantation has only been achieved in recent history but the idea of replacing a human body part in order to improve the function or the appearance has fascinated several ancient human societies in different parts of the world. The oldest references to transplantation are in the ancient Greek, Roman, Indian and Chinese mythology. There are several examples of transfer of a part of the body, often from an animal to a God or a human such as Ganesh, the God with the head of an elephant, Narasimha, the God with the face and claws of a lion, Ox-Head and Minotaur, both examples of men with the head of a bull, Horse-Face and Chiron both of whom were half-horse and half-human. The New Testament describes several accounts of re-implantation of amputated body parts including ears, limbs and breasts.

Archaeological evidence shows that the practice of bone grafting existed in the Bronze Age. The skulls of people treated with trephination to relieve the intracranial pressure were reconstructed using bone autografts (SabistonDCJr, 1981). The earliest scientific documentation of transplantation is in the Sushruta Samhita, a surgical text written by the

Indian surgeon Sushruta who lived in the 6th century before Christ (BC) in the city of Varanasi, in northern India. Sushruta is regarded as the father of modern surgery and several surgical sub-specialties including ophthalmology and neurosurgery. The Sushruta Samhita was written in Sanskrit language, translated to English in 1918 (Bhishagratna, 1963). Sushruta transplanted skin, technically the largest organ in the body. Cutting off the nose or ear lobes was a common social or religious punishment of the time and Sushruta performed skin grafts from the buttocks or forehead (on a vascular pedicle) to the nose or the ears of victims of such punishment.

In the 16th century, Gasparo Tagliocozzi, a professor of anatomy and surgery in Bologna described a procedure to reconstruct the nose using a skin autograft raised from the forearm. Tagliocozzi recognised that allografts suffered with more problems than autografts. He referred to the uniqueness of each individual as 'the force and power of individuality' and warned that anyone who would consider breaching this force would be 'plainly superstitious and badly grounded in physical science' (DuquesnoyRJ, 2005). It was not for another two centuries that the experiments of Gregory Mendel, which planted the seeds leading to the development of Genetics as a specialty.

1.2.2 Xenotransplantation

Transplantation of internal organs from animals to humans was first attempted in the early 20th century. Princeteau inserted slices of rabbit kidney into the failed kidney of a child in 1902 (Reemtsma et al., 1964). The recipient initially experienced improvement in symptoms

and urine production but died on the 16th day after transplantation from pulmonary congestion. Between 1906 and 1966, many surgeons performed transplantation of kidneys from pigs, goats, monkeys, sheep, chimpanzees and baboons. All the recipients died within days or weeks of transplantation (Taniguchi and Cooper, 1997). Starzl noted that his patients who were transplanted with baboon kidneys had developed much more aggressive immunological rejection as compared to the recipients of kidneys from chimpanzees (Starzl et al., 1964a). This experience, although unsuccessful, resulted in recognition of genetic diversity between the species and its correlation to the degree of rejection of the allograft. Xenotransplantation of liver was first performed in 1966 and until 1993, livers from chimpanzees, baboons and pigs and continued to be transplanted into humans. The longest survival of a liver xenotransplantation recipient was 70 days (Taniguchi and Cooper, 1997). Heart transplantation from chimpanzees, sheep, pigs and baboons were performed with recipient survival ranging between 0 and 20 days (Taniguchi and Cooper, 1997). In 1902, Emerich Ullman, an Austrian surgeon, performed the first kidney homotransplantation between two animals (Druml, 2002). He transplanted a kidney from one dog into another, using the neck vessels for anastomosis. Ullman demonstrated the production of urine from the ureter stitched to the skin, to the audience at the meeting of the Society of Physicians in Vienna. This transplant lasted for 4 days.

1.2.3 Early human kidney allotransplantation

In 1902, French surgeon Alexis Carrell described the technique of vascular anastomosis and followed this with pioneering work in attaching severed limbs and transplanting kidneys and hearts in dogs and cats. For this work, Carrell was awarded Nobel Prize in 1912 (Cooper,

2012). Between 1933 and 1936, Russian surgeon Yurii Voronoy performed the first case-series of human kidney allotransplantation in 6 patients with acute renal failure using deceased donors (Matevossian et al., 2009). The first of these recipients was a 26-year-old lady with renal failure secondary to mercury chloride poisoning who was transplanted with a kidney from a 60-year-old donor who died following a skull-base fracture. This recipient died within 48 hours of transplantation. All the grafts in Voronoy's case series failed because of blood group incompatibility and the lack of recognition of the effect of prolonged warm ischemia. Voronoy used anastomosis between donor renal vessels and recipient brachial or femoral vessels and an uretero-cutaneous fistula. Although this method was technically easy and allowed relatively easy access to the graft for biopsy or excision, this was only suitable for patients with acute renal failure who needed the graft for relatively short periods. The technique of placing the kidney graft in the retroperitoneal area with vascular anastomosis using external iliac vessels and ureteric anastomosis to bladder was developed in 1951 in France. This remains the method used today. Between 1936 and 1945, there were isolated attempts at kidney transplantation, all of which were unsuccessful.

1.2.4 First successful kidney transplantation

The kidney transplantation performed in 1945 at Peter Bent Brigham Hospital, Boston by Charles Hufnagel, Ernest Landsteiner and David Hume was the first successful life-saving kidney transplantation. A lady with acute renal failure was transplanted with a deceased donor kidney, which was placed on her forearm, covered with a plastic bag and anastomosed to the ante-cubital vessels. This graft functioned for 4 days by which time the recipient's own kidneys had recovered and she was discharged from the hospital. In 1950 in

Chicago, Richard Lawler performed the first successful intra-abdominal kidney transplantation on a recipient with renal failure due to polycystic kidney disease. This kidney functioned for 54 days and was removed at 10 months. This was followed in 1951 by a series of nine kidney transplantations from deceased donors, performed by a French team of surgeons led by Rene Kuss. The extra-peritoneal approach known as the 'Kuss procedure' was used for the first time in these patients and continues to be used today.

By this time, kidney transplantation from living donors had started. The donor kidneys were usually obtained from healthy relatives of the recipient. Survival beyond the immediate post-transplant period was not achieved until 1954 when David Hume (Hume, 1979) reported a series of nine patients with kidney transplantation. Five of these did not show measurable creatinine clearance. Of the remaining four, three functioned to a degree sufficient to keep the recipients alive for 37, 110 days and 6 months and the survival duration was not specified for one recipient. Two donors in this series were living donors. The failed grafts were examined and the immunological processes involved in rejection of the graft were recognised. However, the only available drug to counter the rejection at this stage was adrenocorticotropic hormone. Some recipients in Hume's series received adrenocorticotropical hormone with or without cortisone, although the longest surviving recipient did not receive these agents. In the longest surviving recipient, the graft was placed in a plastic bag with an intention to avoid contact between the donor and recipient tissues which may initiate graft rejection.

1.2.5 Early human liver allotransplantation

Initial attempts at human liver transplantation were made between 1963 and 1967 in Denver (Starzl et al., 1963, Starzl et al., 1964b), Boston (Moore et al., 1964) and Paris (Demirleau et al., 1964). Some lessons learnt by transplanting kidney were useful but there were unique challenges related to transplanting the liver. The venous return to the heart needed to be maintained during the operation and Starzl achieved this by a veno-venous bypass from inferior vena cava and portal vein into the superior vena cava. Other challenges of liver transplantation included an operative site much closer to vital cardiothoracic organs, a recipient who was generally much sicker with profound coagulopathy than a kidney recipient. All the recipients died following the initial attempts at liver transplantation with longest recorded recipient survival of 23 days. In 1967-68, Thomas Starzl performed first series of 7 successful liver transplantations, of whom, one recipient survived for more than 11 months (Starzl et al., 1968). All the 7 recipients of liver transplantation were matched with their donors for ABO blood groups; human leukocyte antigen (HLA) mismatch was limited to no mismatch in one recipient and 1 or 2 mismatches of the major HLA groups in the remaining recipients. The immunosuppression regimen included anti-lymphocyte globulin, azathioprine and prednisolone. In 1968 in Cambridge, Roy Calne performed the first liver transplantation in the United Kingdom (UK) (Calne et al., 1968). Calne continued to work in the field of transplantation improving the surgical techniques and developing more effective and safer immunosuppression.

1.2.6 Early human allotransplantation of heart and lungs

Alexis Carrel and Charles Guthrie developed surgical technique of heart transplantation in 1905. They performed the first heterotopic canine heart transplantation (Cusimano et al., 1984). Between 1960 and 1965, Norman Shumway in California (Lower and Shumway, 1960, Hurley et al., 1962, Dong et al., 1965) showed the benefits of the cardiopulmonary bypass and cooling of the graft prior to implantation in dogs. In 1967, Christiaan Barnard performed the first human heart transplantation in Cape Town (Barnard, 1968) from a donor with brain injury. This recipient survived the operation but developed a post-operative pneumonia and died after 18 days. In 1968, Donald Ross in London performed the first heart transplantation in the UK, with the recipient survival of 9 weeks. Following this, heart transplantations were performed in several centres worldwide but the initial enthusiasm diminished as a result of poor recipient outcome, resulting in fewer heart transplantations in fewer centres. The advent of ciclosporin in the decade beginning 1980 resulted in resurgence of interest in heart transplantation with more procedure being performed in more centres across the world.

In 1963, James Hardy performed the first human lung transplantation at the University of Mississippi (Hardy et al., 1963). In the following two decades, the results remained poor for lung recipients due to airway complications, infection and other side effects of immunosuppression. In 1981, the cardiovascular team at the Stanford University School of Medicine performed the first successful heart-lung transplantation (Reitz et al., 1982). In 1986, long-term survival following single lung transplantation was reported by the Toronto Lung Transplant Group (Toronto, 1986). Further technical modifications included en-bloc double lung transplantation in 1988 (Patterson et al., 1988) and sequential bilateral double

lung transplantation in 1990 (Pasque et al., 1990) and more recently, lobar transplantation from living donors.

1.3 National transplant programme in the UK

Soon after the first successful kidney transplantation in the UK in 1968, the National Tissue Typing and Reference Laboratory (NTTRL) was started in Bristol. In 1971, the kidney donor card was introduced, which in 1981, was modified to organ donor card to enable donation of multiple organs. In 1972, the National Organ Matching and Distribution Service (NOMDS) was started with a role of maintaining national waiting lists for patients in need of organ transplantation and the first computers were used in the transplant programme for this purpose. The NTTRL and NOMDS were merged in 1979 to form the UK Transplant Support Service. The UK Transplant was created in 2000 and merged with the National Blood Service in 2005 to form the National Health Service Blood and Transplant (NHSBT). The position of Transplant Co-ordinators was created in 1980 to oversee the process of transplantation from the time the donor and the recipient are identified to transplantation operation and continuing through to the long-term post-transplant follow-up. In 1994, the national organ donor register was started as a database of all the individuals in the UK who have signed up to be organ donors.

1.4 Immunology of transplant rejection

1.4.1 Historical background

In the 19th century, the experience of blood transfusion from animals and transplantation of skin from animals and humans resulted in the development of early insight into the immune mechanisms involved in graft rejection. The understanding of humoral immunity developed in the late 19th and early 20th century based on the work of scientists including Louis Pasteur (germ theory of disease, vaccines against anthrax and rabies), Edward Jenner (small pox vaccine), Paul Ehrlich (antibody and auto-immunity), Jules Bordet and Octave Gengou (complement activation), Karl Landsteiner (ABO blood groups), Charles Richet and Paul Portier (anaphylaxis) and Nicolas Arthus (Arthus reaction). The understanding of cell mediated immunity was limited in the early 20th century and the components of humoral immunity including blood group antigens and anaphylaxis were thought to be the cause of the rejection of skin allografts (DuquesnoyRJ, 2005). By the time Yuri Voronoy performed the first human kidney transplantation (donor blood group B, recipient blood group O), he was aware of the problems of ABO mismatch but he believed his recipient (being the universal blood donor) would transfuse the transplanted organ with the universal donor blood and so would not cause agglutination by blood group incompatibility. Medawar and Gibson first described the histological details of the cell mediated graft rejection after studying the victims of firebomb attacks in the Second World War who underwent skin grafting. They described the graft rejection process in human skin graft recipient (Gibson and Medawar, 1943) and subsequently confirmed these findings in animal studies (Medawar, 1944).

1.4.2 Immunological basis of allograft rejection

The most important proteins responsible for the identification of genetic diversity between individuals are histocompatibility antigens. These are coded by the genes located in more

than 40 loci, the most important of which is the Major Histocompatibility Complex (MHC), located on the short arm of chromosome 6. Humans inherit the MHC genes from their parents in two half-sets (haplotypes) and express them co-dominantly, expressing both the alleles. So each individual's MHC is 50% identical to their parent and there is a 25% chance that it will be fully identical to the MHC of one of their siblings. In physiological conditions, the major role of MHC molecules is to present the antigens to T cells, as the T cells only recognise antigens which are presented as a complex with a MHC molecule.

The MHC molecules are divided into two classes (Beck et al., 1999):

Class I: This includes 3 major (A, B and C) and 3 minor (D, E and F) molecules (Marsh et al., 2005). These are expressed on the cell surface of all the nucleated cells and play an important role in presenting intracellular antigens such as viruses and tumour antigens.

Class II: This includes DP, DM, DO, DQ and DR molecules (Marsh et al., 2005). These are expressed on the antigen presenting cells (APCs) such as dendritic cells, macrophages and B cells, and usually present extracellular antigens.

1.4.3 Stages of allograft rejection:

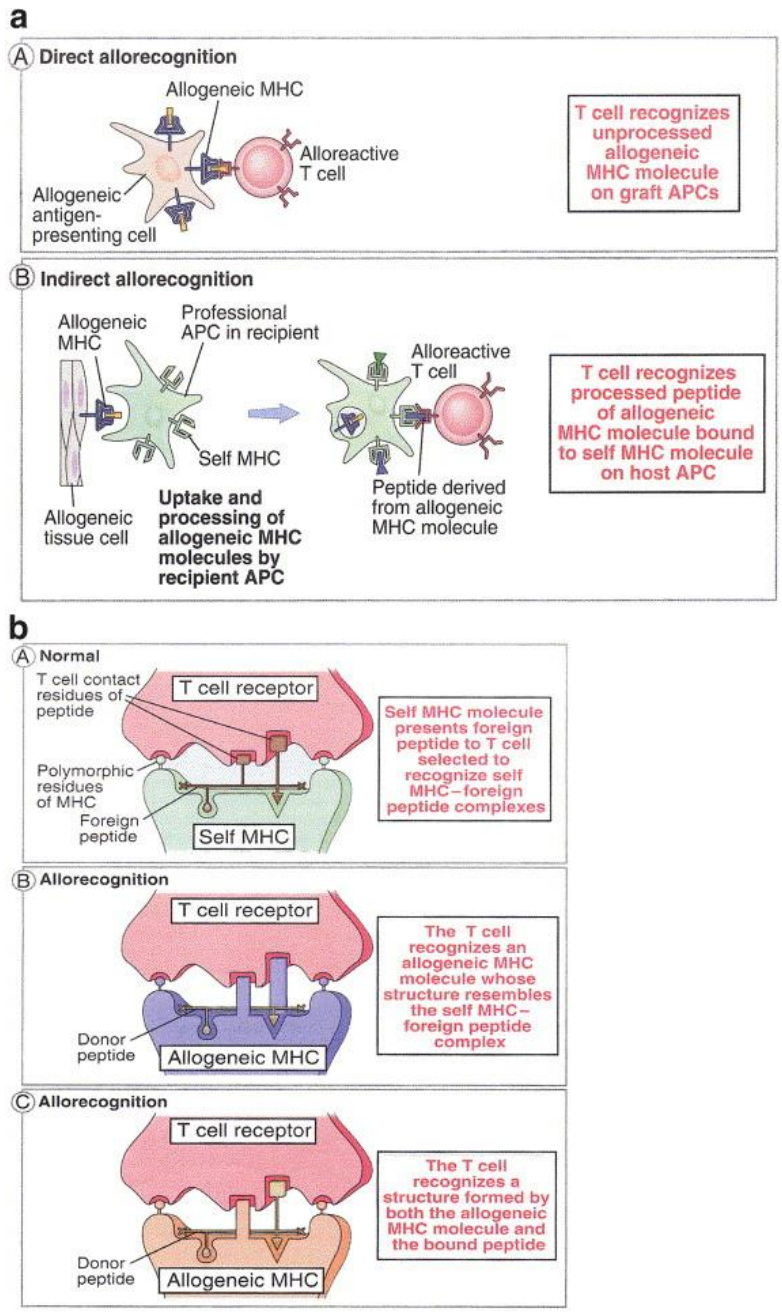
The series of reactions resulting in allograft rejection are divided into two stages: sensitisation stage and effector stage.

1.4.3.1 Sensitisation stage:

This stage involves the recognition of alloantigens and activation of host immune system. This starts as soon as the allograft is placed and blood circulation is established. T cells by themselves, are incapable of recognising alloantigens and reacting to them and only recognise them when they are presented by APCs (Banchereau and Steinman, 1998). APCs express class II MHC molecules on their surface and are specialised in alloantigen recognition and presentation. APCs internalise the alloantigen by phagocytosis or endocytosis and form a complex of MHC with the alloantigen. A part of this alloantigen, to which the T cell has a receptor, is exposed on the cell membrane of the APC. T cell receptor (TCR) binds with the antigen-MHC complex resulting in T cell activation. The donor APCs bind with the alloantigens and present them to CD4 ('helper') and CD8 ('cytolytic') T cells by the direct pathway. The host APCs also bind with alloantigens and present them to the host T cells resulting in their activation via the indirect pathway. Activation of T cells by direct and indirect pathways occurs within the allograft as well as in the host lymph nodes, spleen and other lymphatic organs. The process of alloantigen recognition leading up to T cell activation is shown in Figure 1.1a and b (Abbas AK, 2004).

Figure 1.1 Alloantigen recognition by the host T cell. a. Direct and indirect allorecognition. A. Allogenic APC bound with allogenic MHC is recognised by host T cell. B. Host APC binds with and processes allogenic MHC and presents it to host T cell.

b. The binding of the MHC-antigen complex with the T cell receptor. A. Self MHC binds to foreign peptide and both the MHC and the peptide participate in binding to T cell receptor. B and C. T cell receptor binds with the allogenic MHC – donor peptide complex where the donor peptide may (A) or may not (B) participate in binding with the T cell receptor. Reproduced from Abbas and Lichtman (Abbas AK, 2004).



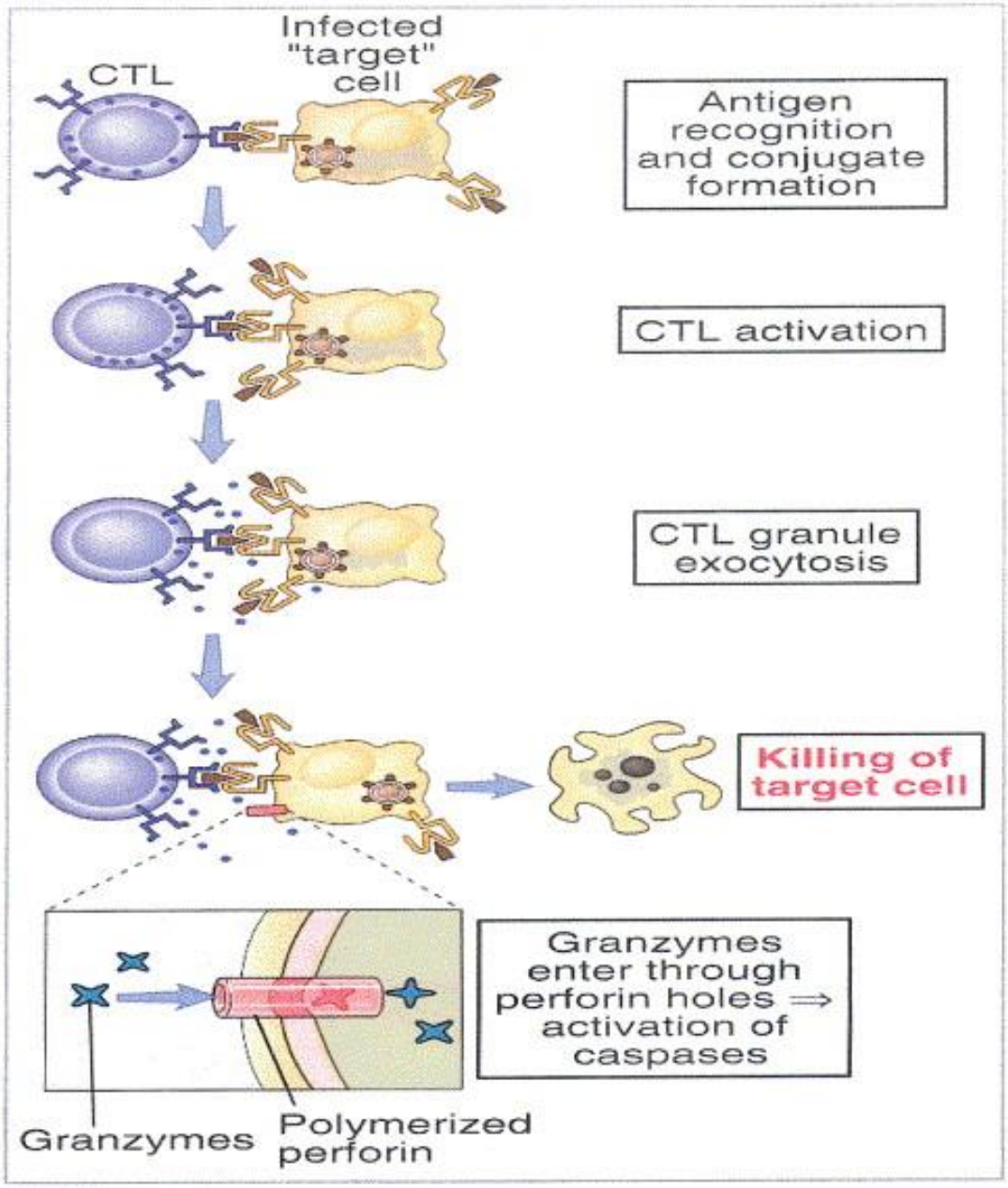
1.4.3.2 Effector stage:

The presentation of alloantigens by direct and indirect pathways results in activation of non-specific inflammatory response with up-regulated expression of adhesion molecules, chemokines and cytokines, including Interleukin-2 (IL2), Interferon gamma (IFN-γ), chemokine ligand 5 (CCL5), C-X-C motif chemokine 10 (CXCL10), chemokine (C-C motif) ligand 2 (CCL2), Interleukin-6 (IL6), tumour necrosis factor-alpha (TNF-α), inducible nitric oxide synthetase (iNOS) and growth factors. These result in further influx of T cells, polymorphonuclear leukocytes and recipient APCs into the allograft. These increase antigen presentation and result in activation of more cytotoxic T cells. B cells are also activated, resulting in production of donor specific antibodies. Activated cytotoxic T cells undergo degranulation to release perforin, granzymes and granulysin. Perforin binds to the plasma membrane of the target cell and forms a pore in the plasma membrane, which facilitates entry of other enzymes into the target cell. Granzymes enter the target cell through the pore formed by perforin and result in activation of caspase and caspase-activated-DNAase. These set off cascades of cleavage of substrates, leading to apoptosis, the programmed cell death (Krupnick et al., 2002). These reactions are shown in Figure 1.2.

Natural killer (NK) cells are a distinct type of cytotoxic T lymphocytes that possess the ability to mount an effector response without prior sensitisation. They can produce cytokines such as IFN-γ and can also effect direct cytotoxicity by perforin-granzyme pathway as well as by fas-Ligand pathway (Kitchens et al., 2006). Another unique characteristic of NK cells, described as the “missing self” hypothesis, is that they can identify foreign cells by the

absence of MHC molecules on their cell membrane. With these features, NK cells play an important role in facilitating the response of other cytotoxic T cells in allograft rejection.

Figure 1.2 Mechanism of cytolytic T cell mediated target cell apoptosis. T cell identifies the target cell by recognising the antigen on the cell membrane. Activated T cell undergoes degranulation to produce perforin, which produces cell membrane pores through which granzymes enter the target cell and initiate caspase mediated target cell apoptosis. Reproduced from Abbas and Lichtman (Abbas AK, 2004).



The role of co-stimulation:

A second signalling mechanism is usually required for effective activation of T cells. This mechanism is called co-stimulation, without which a state of tolerance referred to as clonal anergy (LaSalle and Hafler, 1994) may result. The co-stimulation response is antigen non-specific and is mediated by several proteins on the surface of APC, of which the most important are CD80 and CD86. The full activation of T cell occurs following binding of CD80, CD86 proteins with the CD28 receptor present on the T cell.

1.5 Clinical types of rejection:

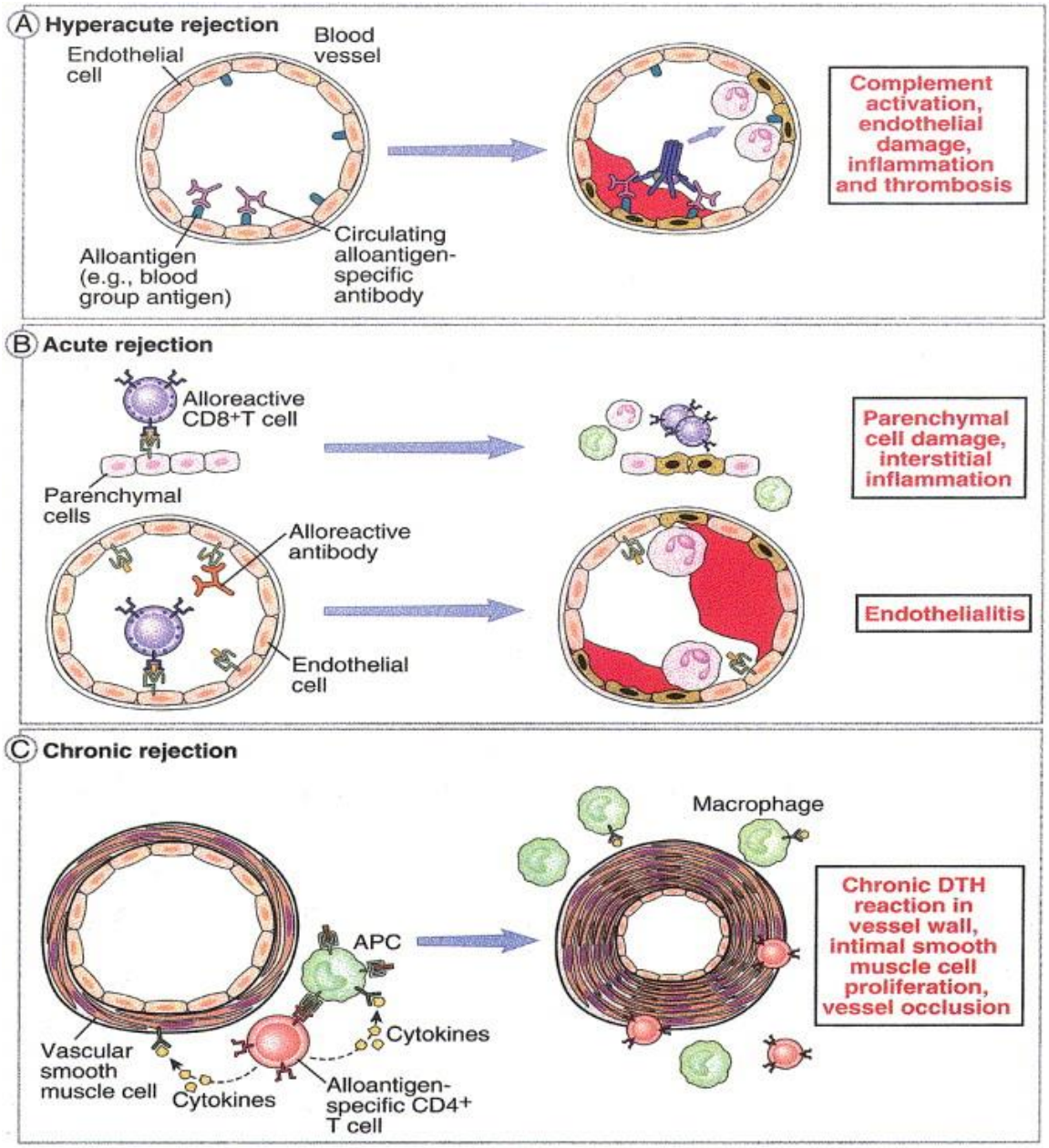
1.5.1 Hyperacute rejection:

Hyperacute rejection is mediated by pre-formed anti-donor antibodies and often develops within minutes to hours after the allograft has been placed. The pre-formed antibodies usually develop as a consequence of previous antigen exposure due to a previous transplantation, blood transfusion or pregnancy. Hyperacute rejection may be delayed by days or weeks in cases where the antigen exposure was in the remote past with very low or absent levels of pre-formed antibody at the time of transplantation (Rosenberg et al., 2004). In such cases, anamnestic reaction results in rapid formation of antibodies against the allograft causing delayed hyperacute rejection. Kidney allografts are most susceptible to hyperacute rejection and the risk is reduced significantly by cross-matching prior to transplantation (O'Rourke et al., 2000). In contrast, liver allografts are least susceptible to hyperacute rejection. Hyperacute rejection of liver is almost exclusively seen in ABO incompatible transplantations and often presents more gradually than kidney, with rise of

serum transaminase levels and impaired coagulation days after transplantation (Hubscher, 2012). The reasons for relative resistance of liver allografts to antibody mediated rejection are not fully understood and have been attributed to dual blood supply, large surface area of and expression of high levels of Fc receptors by the hepatic sinusoidal endothelial cells resulting in absorption of antigen-antibody complexes before they can reach hepatocytes.

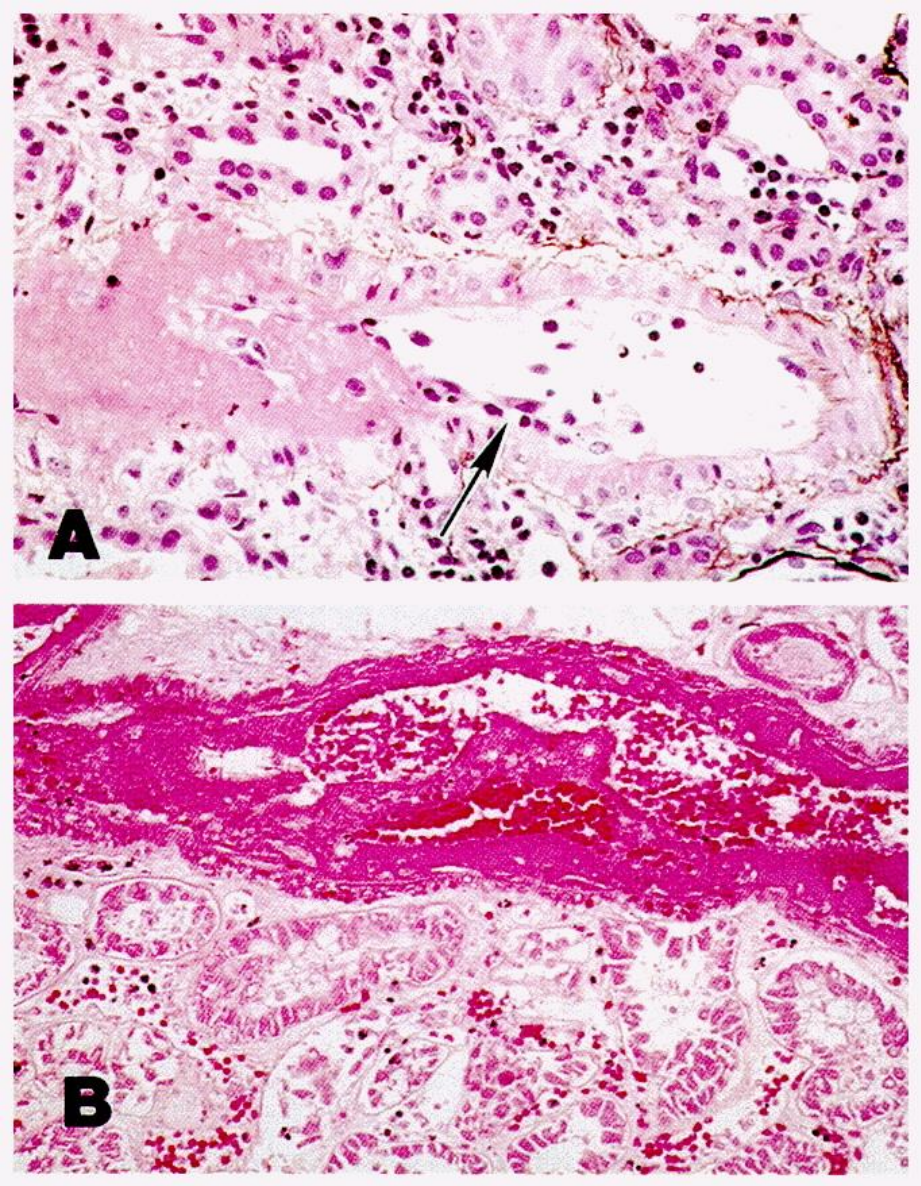
The pathogenesis of antibody-mediated rejection involves formation of complexes between the anti-donor antibodies and the antigens on the allograft vascular endothelium. This results in activation of complement cascade with release of C3a and C5a which act as chemokines attracting inflammatory cells. The inflammation in the endothelium also results in activation of platelets and coagulation cascade resulting in thrombosis. Figure 1.3 shows the pathogenesis of hyperacute, acute and chronic rejection (Abbas AK, 2004).

Figure 1.3 Pathogenesis of rejection: A. Hyperacute rejection, B. Acute rejection and C. Chronic rejection. Reproduced from Abbas and Lichtman (Abbas AK, 2004).



Pathologically, the inflammation is centred on the vascular endothelium with inflammatory infiltration and fibrinoid changes in the early stages followed by thrombosis and necrosis in the later stages. Pathological changes in a kidney allograft biopsy from a recipient who had preformed anti-donor antibodies is shown in Figure 1.4 (Trpkov et al., 1996). Corresponding changes in the liver allografts include severe preservation-reperfusion injury, non-occlusive thrombosis and haemorrhagic necrosis.

Figure 1.4 Kidney allograft biopsy with hyperacute rejection. A. Lymphocytic infiltration in the endothelium (arrow) and fibrin deposition. B. Necrosis and thrombosis of an interlobular artery with tubular infarction. Reproduced from Trpkov (Trpkov et al., 1996).



1.5.2 Acute rejection:

Acute rejection can develop within the first week after transplantation but usually develops in the first year and less commonly later. Acute rejection is more commonly caused by cellular immune response than by antibody-mediated response.

1.5.2.1 Acute antibody mediated rejection (AMR):

Acute AMR is defined based on the presence of four diagnostic features (Colvin and Smith, 2005): clinical (evidence of graft dysfunction), histological (acute graft injury with infiltration of neutrophils, macrophages, fibrinoid necrosis and thrombosis), immunopathological (deposition of complement C4d or C3 in the blood vessels) and serological (anti-HLA or other donor specific antibodies). Acute AMR may be a result of pre-formed donor specific antibodies or antibodies that develop de novo after transplantation (Terasaki and Mizutani, 2006). These combine with donor antigens resulting in activation of complement cascade, recruitment of macrophages and neutrophils resulting in endothelial injury. It is more common in kidney allografts affecting 5-7% recipients (Colvin and Smith, 2005) than in liver, heart and lung recipients (Musat et al., 2011, Takemoto et al., 2004).

Pathological changes in acute AMR are similar to but tend to be less severe than those in hyperacute rejection, discussed in section 1.5.1 and shown in Figure 1.4. Liver allografts undergoing AMR typically present with cholestatic picture, both on biochemical tests and histological examination. Inflammation of bile ducts associated with bilirubinostasis are often seen on biopsy and these have been attributed to ischemia secondary to occlusive

thrombosis of biliary microvasculature by antigen-antibody complexes (Hubscher, 2012). In the lung allografts, the features of acute AMR include inflammatory cell infiltrate and complement deposition in the alveolar capillaries (DeNicola et al., 2013).

1.5.2.2 Acute cellular rejection:

Acute cellular rejection is characterised by graft dysfunction developing within weeks of transplantation along with typical histological features. In the kidney allograft, the histological features include a combination of acute interstitial rejection (referred to as Type I acute cellular rejection) and acute vascular rejection (Type II acute cellular rejection). These develop from different pathogenetic pathways, as shown in Figure 1.3B, but often co-exist. Acute interstitial rejection is characterised by infiltration of cytotoxic T cells, eosinophils, macrophages along with tubulitis and interstitial oedema. Acute vascular rejection is characterised by endothelial inflammation, thrombosis, interstitial haemorrhage and necrosis. These changes are shown in Figure 1.5 (AJKD, 2001).

Figure 1.5 A. Acute interstitial rejection showing severe tubulitis and interstitial infiltration. Periodic acid Schiff, magnification X100. Reproduced from the Atlas of Renal Pathology (AJKD, 2001).

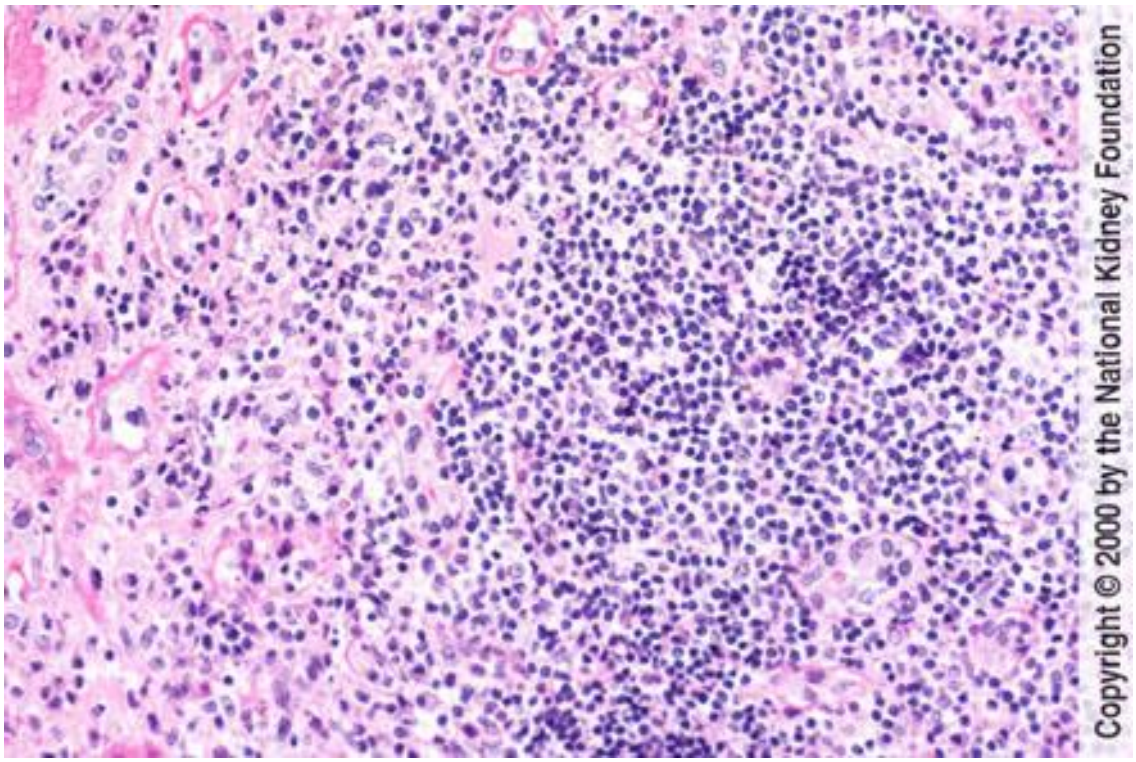
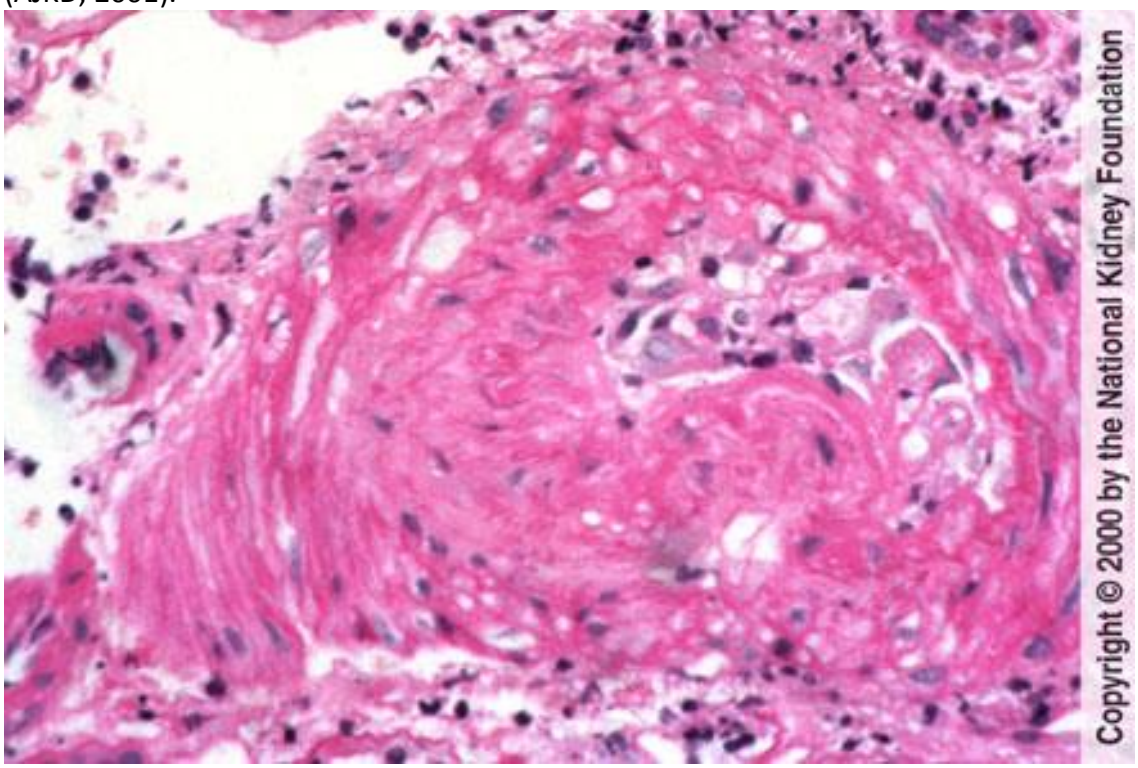


Figure 1.5 B. Acute vascular rejection showing endothelial infiltration and microthrombus. Periodic acid Schiff, magnification X200. Reproduced from the Atlas of Renal Pathology (AJKD, 2001).



1.5.3 Chronic rejection:

Chronic rejection can be mediated by humoral immunity or cell mediated immunity. It results in gradual progressive graft dysfunction, months to years after transplantation. Fibrosis is a common feature but other pathological features vary depending on the organ transplanted: kidney allografts show glomerulopathy, liver allografts show loss of bile ducts, heart allografts develop coronary atherosclerosis and lung allografts develop bronchiolitis obliterans.

There are several contributing factors for the development of chronic rejection including untreated or undertreated acute rejection, ischemia-reperfusion injury, post-transplant cytomegalovirus (CMV) infection, donor factors (age, hypertension) and recipient factors (hypertension, dyslipidaemia, diabetes). Once established, chronic rejection is usually irreversible and the only effective treatment for non-renal recipients is re-transplantation (Chapman et al., 2005).

1.6 Immunosuppression: agents, mechanisms of action and side effects

With the exception of transplantation between identical twins, every allograft develops some degree of rejection. Interventions such as matching the donor and the recipient for blood group and HLA type, lymphocytotoxic assay between the recipient's serum and donor lymphocytes and panel reactive antibody screen help to reduce the risk of rejection. However, to achieve long-term functioning of the allograft, majority of allograft recipients need life-long pharmacological immunosuppression.

Post-transplant immunosuppressive agents can broadly be classified into two groups: biological agents and xenobiotics. Biological agents exert their immunosuppressive action by acting on the receptors present on the cell wall of specific immunologically active cells, whereas, xenobiotics act by interfering with the intracellular mechanisms. Main groups among xenobiotics are corticosteroids, anti-proliferative agents, calcineurin inhibitors and mammalian Target of Rapamycin (mTOR) inhibitors. The mechanisms of action, efficacy and side effects of these agents are discussed below. The effect of immunosuppressive agents on post-transplant cancer is separately discussed in Section 1.7.

1.6.1 Biological agents:

The risk of acute allograft rejection is at its highest in the early post-transplant period and biological agents are often used to reduce this risk. Factors influencing the decision to use these agents include the organ transplanted, estimated risk of rejection, recipient co-morbidities and preference of the transplant team. Commonly used biological agents include polyclonal agents such as anti-lymphocyte globulin (ALG) and anti-thymocyte globulin (ATG), and monoclonal agents and monoclonal human or chimeric antibodies against CD25 (basiliximab, daclizumab), CD3 (OKT3), CD52 (alemtuzumab or Campath 1H), CD20 (rituximab) and adhesion molecules (enlomimab, odulimomab and efalizumab).

1.6.1.1 Polyclonal agents

ALG and ATG are polyclonal antibodies developed by inoculating animals (horses, or more commonly rabbits) with T cell lines or thymocytes followed by extraction of antibodies from the animal serum (Putnam et al., 1976). These are the oldest biological agents, in use since 1960s. In the recent years, rabbit ATG is preferred over the horse ATG or ALG due to a favourable side-effect profile. These exert non-specific immunosuppression by acting on a variety of cell wall receptors causing lysis, apoptosis and depletion of T cells, B cells, plasma cells and NK cells along with inhibition of adhesion and co-stimulation pathways. With a half-life as long as 30 days for rabbit ATG (Bunn et al., 1996), the immunosuppression exerted by these agents is lasting. In comparison to no biological therapy, reduced rates of acute rejection following the use of ATG have been shown in recipients of kidney and heart (Mourad et al., 2001, Charpentier et al., 2003, Zuckermann et al., 2000) but not liver transplantation (Boillot et al., 2009, Bogetti et al., 2005).

Common side effects of ALG and ATG can be grouped into non-specific reactions to animal serum, increased risk of infection and cancer. Non-specific side effects can be mild such as fever, chills and rigors, or as severe as anaphylactic shock, particularly in those with previous exposure to these agents. Some patients experience leukopenia and thrombocytopenia, which are usually dose-dependent. Serum sickness like reaction can also develop, often after a delay of several days with symptoms of fever, maculopapular rash, arthralgia, proteinuria and lymphadenopathy. Local inflammatory reaction following intravenous administration can cause thrombophlebitis or venous thrombosis. Use of these agents is associated with an increased rate and severity of CMV infection (Mourad et al., 2001, Issa and Fishman, 2009) and herpes simplex infection. The association of ATG therapy with an

increased risk of bacterial and fungal infection has been demonstrated (Issa and Fishman, 2009).

1.6.1.2 Monoclonal agents

These are monoclonal human or chimeric antibodies against CD25 (basiliximab, daclizumab), CD3 (OKT3), CD52 (alemtuzumab or Campath 1H), CD20 (rituximab) and adhesion molecules (enlomimab, odulimomab and efalizumab). In contrast to the polyclonal agents, monoclonal antibodies block T cell proliferation by acting on specific receptors resulting in narrow spectrum immunosuppression. Basiliximab and daclizumab are humanised monoclonal antibodies (90% human and 10% murine), which act on CD25 (also called IL2 receptor) resulting in blockage of T cell proliferation rather than T cell depletion. Although pulmonary oedema and adult respiratory distress syndrome (ARDS) are reported following daclizumab administration, both basiliximab and daclizumab have a favourable side-effect profile. Hypersensitivity reactions are less common due to their greater structural similarity with human proteins. Basiliximab has largely replaced daclizumab, leading to cessation of European licence of the latter in 2008 (Krischock and Marks, 2010). Efficacy of basiliximab in reducing the rates of acute rejection is proven by several studies of kidney recipients (Kahan et al., 1999, Nashan et al., 1997, Gralla and Wiseman, 2010, Webster et al., 2004) however none of these studies demonstrated an improvement in graft or patient survival. A meta-analysis of twelve trials assessing the use of IL2 receptor antagonists (IL2RA) in liver recipients showed a significant reduction of rates of acute rejection over 1 year (23% in induction group vs. 28% in no induction group, $p=0.04$) but no significant difference in graft or patient survival, or rates of infection (Wang et al., 2010). Studies of heart recipients

comparing basiliximab against placebo (Mehra et al., 2005) or against ATG (Mattei et al., 2007, Carrier et al., 2007, Carlsen et al., 2005) did not show any difference in the rates of acute rejection between these agents. Results are conflicting among lung recipients with improved survival following IL2RA/ATG induction as compared with no induction in some studies (Hachem et al., 2008) and no difference in rejection rates or in patient survival in some others (Mullen et al., 2007, Brock et al., 2001).

In comparison to no induction or to ATG, the rates of infectious complications are not increased following IL2RA use in heart recipients (Mehra et al., 2005, Beniaminovitz et al., 2000, Mattei et al., 2007, Carrier et al., 2007), kidney recipients (no difference in clinically significant CMV infection) (Lebranchu et al., 2002) and liver recipients (no difference in hepatitis C recurrence rates) (Pageaux et al., 2004, Llado et al., 2008, Otero et al., 2009, Klintmalm et al., 2007).

OKT3, a CD3 murine antibody, was introduced during 1980s. Following recognition of non-superiority when compared against ATG or IL2RA and the side-effects including cytokine release syndrome, ARDS, aseptic meningitis and immunogenicity precluding future use, its use declined resulting in withdrawal in the United States in 2009. Humanised anti-CD3 antibodies might improve the side effect profile but at present no such agents are available for clinical use.

Alemtuzumab is a CD52 humanised antibody. Introduced in 1990s, it was initially used in kidney recipients and subsequently in lung recipients. As CD52 is present on a variety of cells including B cell, T cell, NK cells and macrophages, alemtuzumab results in profound lasting immunosuppression similar to the polyclonal agents. Side-effect profile of alemtuzumab is similar to that of the polyclonal agents, including the first-dose reaction with fever and rash, and rarely anaphylaxis and shock. Its use is limited following recognition of better efficacy and safety of IL2RA.

Rituximab, a CD20 antibody was used as an anti-rejection agent following identification of increased number of CD20+ T cells in kidney recipients with steroid-resistant rejection (Becker et al., 2004) and the association of a higher degree of allograft loss with more dense infiltration of CD20+ T cells (Muorah et al., 2009). Rituximab is shown in small studies to improve the renal function in kidney recipients with steroid-refractory rejection (Becker et al., 2004). With proven superiority of IL2RA in both efficacy and safety, the use of rituximab is limited to a minority of kidney recipients (Hardinger et al., 2013). It also has a potential role in pre-transplant desensitisation of highly sensitised prospective kidney recipients (Vo et al., 2010).

Belatacept is a relatively new agent. This works by blocking the co-stimulation pathways of T cell activation. In kidney recipients, its efficacy and safety are similar to calcineurin inhibitor (CNI) based immunosuppression regimen for maintenance immunosuppression (Larsen et al., 2010) and it has also enabled a CNI-free and steroid-free regimen (Ferguson et al., 2011).

In comparison to CNI, it has a favourable profile in terms side effects such as nephrotoxicity, hypertension and dyslipidaemia. Side effects of belatacept include an increased risk of infection (similar to CNI), anaemia, oedema and diarrhoea. An increased risk of post transplant lymphoproliferative disorders (PTLD), mainly involving the central nervous system (CNS) was seen in patients receiving belatacept and the increased risk was predominantly in Epstein-Barr virus (EBV) negative recipients (Garnock-Jones, 2012). At present belatacept is contraindicated in EBV negative recipients for this reason.

Monoclonal antibodies against leucocyte adhesion molecules have been studied to assess their effect on delayed graft function and acute rejection. None of the published studies assessing enlimomab (Salmela et al., 1999), efalizumab (Kuypers and Vanrenterghem, 2004) and odulimomab (Hourmant et al., 1996) have shown a benefit. ASKP1240, a fully human monoclonal antibody against CD40 is being studied in phase II trials to assess the safety and efficacy when it is used as a replacement for a CNI agent (Hardinger and Brennan, 2013).

1.6.2 Xenobiotics

This group includes agents which are started at the time of or just before transplantation and are continued, in most patients, for as long as the graft continues to function. Factors influencing the choice of immunosuppression regimen include the organ transplanted, primary disease causing the organ failure, perceived risk of rejection, age and co-morbidities of the recipient. In the immediate post-transplantation period, the most commonly used immunosuppressive regimen includes a combination of three agents: an anti-metabolite

(azathioprine, mycophenolate mofetil), a CNI (ciclosporin, tacrolimus) and a corticosteroid. Other immunosuppressants used for long-term immunosuppression include the more recently discovered group of mTOR inhibitors. Often the immunosuppression is more intense in the early post-transplantation period, in accordance with a higher risk of rejection in that period. Transplant recipients are monitored for life, with regular assessment of graft function, co-morbidities, side effects of treatment and all these factors guide the immunosuppressive regimen used in the longer term.

1.6.2.1 Corticosteroids

Prednisolone and its pro-drug, prednisone, along with methyl prednisolone and hydrocortisone are commonly used for prevention and treatment of acute allograft rejection. In the immediate post-transplant period, these are used in nearly all organ recipients but long-term use is avoided or at least minimised in order to reduce the side effects. Corticosteroids exert their immunosuppressive action by regulating gene expression. Glucocorticoid receptor is present in the cytosol of nearly all types of human cells. Corticosteroid molecule forms a complex with the glucocorticoid receptor and this complex binds to the nuclear de-oxy ribonucleic acid (DNA) resulting in regulation of expression of several genes with a role in immune function and inflammation (Bergmann et al., 2012). They also regulate the expression of several other types of genes including those controlling growth and metabolism, some of which mediate the side effects of corticosteroids. In addition, the side effects are also mediated by their action on the mineralocorticoid receptors.

Main side effects of corticosteroids include hyperglycaemia, dyslipidaemia, osteoporosis, avascular osteonecrosis, Cushing's syndrome, fat redistribution, weight gain, skin fragility, acne, mood disturbances, psychosis, cataracts, fluid retention and hypertension. An increased risk of infection among transplant recipients is well known however the relative risk of individual immunosuppressive agents contributing to the increased risk of infection is not well established. Studies comparing corticosteroid-containing regimen and corticosteroid-free regimen have produced conflicting reports with some showing an increased risk of infection with steroid-containing regimen (Griffin et al., 1987, Nematalla et al., 2007, Seydoux et al., 1997, Pelletier et al., 2005, Tan et al., 2006) and others showing no difference (Ko et al., 2007, Ahsan et al., 1999, Li et al., 2009, Tanchanco et al., 2008).

1.6.2.2 Anti-metabolites - azathioprine and mycophenolic acid

Azathioprine was the first potent immunosuppressive agent used in transplantation. Roy Calne led the pioneering work in the development of azathioprine and other immunosuppressive agents, some of which continue to be used today. The era of pharmacological immunosuppression begun following recognition of benefits of azathioprine in animal transplantation (Calne, 1961) followed by human kidney transplantation (Murray et al., 1963). Azathioprine is a pro-drug. Its metabolites, 6-mercaptopurine (6MP) and 6-thioguanine (6TG) inhibit purine synthesis resulting in impaired DNA production. Another metabolite of azathioprine, thioinosinic acid results in inhibition of purine synthesis specifically in T cells. During the decades of 1960 and 1970,

azathioprine along with prednisolone and equine ALG were the mainstay of management of allograft recipients. Side effects of corticosteroids were unavoidable as azathioprine alone was not potent enough to enable rejection-free long-term graft survival. Today, azathioprine is used in nearly all transplant recipients immediately after transplantation and also, in many cases, as a long-term immunosuppressant. Important side effects of azathioprine include bone marrow toxicity resulting in leukopenia, thrombocytopenia and anaemia, gastrointestinal symptoms, hypersensitivity and hepatotoxicity. Bone marrow toxicity is dose-dependent and is often more severe in patients with thiopurine methyl transferase deficiency.

Mycophenolic acid was first extracted from cultures of penicillium in 1893 (Sollinger, 2004). The earliest therapeutic use was in 1970s, when it was used in the treatment of psoriasis (Spatz et al., 1978). The benefits of mycophenolic acid in transplantation were first described in 1991 (Allison et al., 1991) Mycophenolic acid exerts its effect by blocking inositol monophosphate dehydrogenase, an essential enzyme for DNA synthesis in lymphocytes but not in other human cells. The anti-rejection efficacy, short and long-term safety were demonstrated in animal studies (Platz et al., 1991) and in human kidney recipients (Sollinger, 1995). Mycophenolate mofetil (MMF), a synthetic derivative of mycophenolic acid was developed to improve its oral bioavailability and tolerance. MMF is now commonly used for post-transplant immunosuppression, often in combination with either a CNI or a mTOR inhibitor. Although they are not sufficiently potent to be used as monotherapy, antimetabolite agents enable a reduced dosage and hence toxicity of CNI. Diarrhoea is a common side effect of MMF, often needing a dose reduction. Other side

effects include cytopenia related to bone marrow suppression, pancreatitis and increased risk of infections. An increased risk of CMV (Boucher et al., 2006, Jorge et al., 2008, Sarmiento et al., 2000), herpes simplex and varicella zoster (Smak Gregoor et al., 2003) infections have ben shown to be associated with the use of MMF.

1.6.2.3 Calcineurin inhibitors – ciclosporin and tacrolimus

Calne in 1978 (Calne et al., 1978b, Calne et al., 1978a, Calne et al., 1979) and Starzl in 1980 (Starzl et al., 1980) demonstrated beneficial effects of ciclosporin in recipients of kidney transplantation. Calne also demonstrated that steroid-free immunosuppression was capable of maintaining allograft function. Tacrolimus was discovered in 1984 in Japan (Hooks, 1994). Over the next decade, the effects of tacrolimus were tested and confirmed, initially as rescue therapy in human studies involving failing allografts with on-going rejection (Klein, 1999, Woodle et al., 1996) and subsequently as first-line immunosuppressant in recipients of kidney and liver transplantation (Vincenti et al., 2002, Haddad et al., 2006).

Calcineurin is a phosphatase enzyme with a key role in T cell activation initiated by presentation of foreign antigens. Calcineurin dephosphorylates the transcription factor, nuclear factor of activated T cells (NFAT) resulting in transcription of various cytokines including IL2, IL3, IL4, IL5, IFN-γ and TNF-α. Ciclosporin and tacrolimus are activated following binding with intracellular proteins (ciclophilin and immunophilin FKBP12, respectively). They then prevent calcineurin-mediated entry of NFAT into the nucleus and further transcription, resulting in inhibition of expression of inflammatory cytokines.

Another mechanism, independent of calcineurin inhibition, has also been described. Ciclosporin and tacrolimus are able to block Jun N terminal kinase and p38 signalling pathways resulting in supressed activation of transcription factors (Matsuda and Koyasu, 2000). This dual mechanism of action increases the T cell specificity of immunosuppression induced by CNI.

CNI are now the cornerstone of post-transplant immunosuppression (Kapturczak et al., 2004). The benefits of CNI in reducing rejection rates and improving survival after transplantation are well recognised (Isoniemi et al., 1993, Kahan, 1987, Morris, 1981). Studies comparing kidney recipients receiving ciclosporin or tacrolimus have shown fewer episode of acute rejection among recipients receiving tacrolimus but the rates of graft survival are similar (Sonoda et al., 2003, Pirsch et al., 1997).

The most common side effect of CNI is nephrotoxicity. Histological evidence of nephrotoxicity has been observed in 100% recipients after 10 years of CNI use (Nankivell et al., 2004). It is mediated by several mechanisms including vasoconstriction of afferent arteriole, toxic tubulopathy and thrombotic microangiopathy resulting in acute kidney injury, arteriolar hyalinosis and interstitial fibrosis (Krejci et al., 2010). Dose reduction or withdrawal of CNI are more effective in reversing the nephrotoxicity, in the early post-transplant period and less so when chronic renal dysfunction is established. Studies comparing ciclosporin against tacrolimus have shown no significant difference in the degree of nephrotoxicity (Fioretto et al., 2011, Solez et al., 1998) or graft survival (Kaplan et al.,

2003). Post-transplant diabetes mellitus is often multi-factorial, influenced by pre-transplant glucose intolerance, body mass index, genetic factors and post-transplant medications. CNI reduce insulin secretion by a direct inhibitory effect on the β cells of the islets of Langerhans (van Hooff et al., 2004). Insulin resistance mediated by concomitant use of steroids also contributes to diabetogenesis. Epidemiological evidence indicates a stronger association of post-transplant diabetes with tacrolimus than ciclosporin (Heisel et al., 2004, Knoll and Bell, 1999). CNI are also associated with hypertension, dyslipidaemia, alopecia, hirsutism, gum hyperplasia, gastrointestinal symptoms and neurotoxicity. The evidence assessing which CNI agent is more likely to produce these side effects is conflicting (Campos et al., 2002, Montagnino et al., 2002, Kim et al., 2004).

Newer calcineurin inhibitors such as CN585 have shown promise in preclinical in vitro studies (Erdmann et al., 2010) with selective inhibition of calcineurin, which mediates immunosuppression without inhibiting ciclophilin, which is responsible for many side effects of CNI. Voclosporin is a novel CNI agent which is under investigation for use as a maintenance immunosuppressant in recipients of kidney transplantation. Studies comparing voclosporin against tacrolimus, with follow-up up to 6 months post-transplantation have shown non-inferior rates of rejection (Busque et al., 2011). The rates of post-transplant diabetes were lower in low dose voclosporin group but not in medium dose or high dose groups (Busque et al., 2011). Further studies with larger cohorts including patients in all risk groups are underway.

1.6.2.4 mTOR inhibitors – sirolimus and everolimus

Sirolimus was extracted in 1975 from a fungus, *Streptomyces hygroscopicus* from the soil of Easter Island (Sehgal et al., 1975). Originally called Rapamycin, its antifungal, antibacterial and antitumour actions were recognised before its immunosuppressive action. Everolimus is a derivative of sirolimus with improved oral bioavailability. mTOR inhibitors form a complex with FKBP12 (same binding protein used by tacrolimus) and this complex inhibits mTOR pathway. mTOR is a serine/threonine protein kinase with an important role in cell growth and differentiation. Its blockage results in arrested growth of several cell types and in particular, IL2 mediated proliferation of T cells. It is a potent immunosuppressant often being used in cases where CNI dose minimisation or withdrawal is beneficial.

Side effects of mTOR inhibitors include glomerular toxicity causing proteinuria, glucose intolerance, delayed wound healing and pneumonitis. Anti-tumour activity of several other derivatives of sirolimus such as temsirolimus, deferolimus and ridaforolimus is well established. The effect of sirolimus of post-transplant cancer is discussed in section 1.7.5.

1.7 Effects of immunosuppression on post-transplant cancer

There is ample epidemiological evidence confirming the increased risk of cancer following transplantation (Collett et al., 2010, Villeneuve et al., 2007, Adami et al., 2003, Kasiske et al., 2004, Kyllonen et al., 1994, Hoshida et al., 1997). Many factors, relating to both the donor and the recipient, contribute to this increased risk including genetic, environmental, infection-related and socio-economical factors, but a central role is played by the post-

transplant immunosuppression. Immunosuppression increases the risk of cancer by several mechanisms including reduced immune surveillance and increased risk of infection with oncogenic viruses. The effects of immunosuppression not only increase the risk of cancer development but also result in an aggressive disease and poorer outcomes with frequent graft loss and death. Immunosuppressive regimen change continuously as a result of introduction of newer agents, discontinuation of older agents, side effects of a particular agent, comorbidities, personal preferences of the recipient and the medical team and availability of new evidence. As a result of these limitations, it is difficult to tease out the effect of individual agents on the risk of cancer after transplantation. However, there is good evidence demonstrating the association between more intensive immunosuppressive regimen and an increased risk of cancer (Dantal et al., 1998, Vivarelli et al., 2002, Swinnen et al., 1990).

1.7.1 Biological agents

Studies assessing the risk of cancer following the use of biological agents have mainly found an association with PTLD. An increased risk of PTLD in recipients receiving ATG (RR 1.6, compared with no induction) but not in those receiving basiliximab, alemtuzumab or daclizumab was reported by United Network for Organ Sharing / Organ Procurement and Transplantation Network (OPTN/UNOS) in a study of 59560 kidney recipients (Kirk et al., 2007). This is in contrast to a relatively older and smaller study form the same database (Cherikh et al., 2003), which did not show an increase in the risk of PTLD in recipients receiving ATG. A study of Collaborative Transplant Database including 715,000 patient years (approximately 200,000 transplant recipients) from 271 centres in 42 countries also showed

an increased risk of PTLD in patients receiving ATG or OKT3 but not IL2RA (Opelz and Dohler, 2004). In this study, the increased risk of PTLD with ATG or OKT3 was noted in the first year after transplantation only. The evidence for the association of monoclonal agents with PTLD is conflicting with no association in some studies (Kirk et al., 2007) and an increased risk in others (Cherikh et al., 2003, Bustami et al., 2004). Bustami reported the risk of PTLD with individual monoclonal agents for daclizumab (RR 1.92), basiliximab (RR 1.83) and OKT3 (RR 1.71) compared with no induction. The risk of tumours other than PTLD was not increased with either polyclonal or monoclonal agents (Bustami et al., 2004).

1.7.2 Corticosteroids

The scarcity of definitive epidemiological data assessing the use of corticosteroids with the risk of post-transplant cancer is explained by the fact that corticosteroids are seldom used as monotherapy for post-transplant immunosuprression. In the non-transplant population, corticosteroid use is shown to be associated with an increased risk of non-melanoma skin cancer (NMSC) (Karagas et al., 2001) with a standardised incidence ratio (SIR) of 1.5 for basal cell cancer and 2.5 for squamous cell cancer, and non-Hodgkin's lymphoma (NHL) with a SIR of 1.3 (Sorensen et al., 2004). Corticosteroids have been used in the treatment of various cancers for their pro-apoptotic and anti-proliferative action. However, corticosteroids also have anti-apoptotic and proliferative action on cancer cells (Rutz, 2002, Rutz and Herr, 2004), which might explain the increased risk of cancer with these agents.

1.7.3 Anti-metabolites

Mechanism of action of azathioprine includes incorporation of 6TG into DNA. Normal human DNA is relatively resistant to absorption of ultraviolet (UV) - A wavelengths but 6TG-incorporated DNA absorbs UVA, resulting in production of reactive oxygen species. High levels of reactive oxygen species cause oxidation of DNA resulting in DNA damage and genomic instability, facilitating carcinogenesis and proliferation of cancer cells (O'Donovan et al., 2005). Azathioprine is also shown to influence selection of cell clones with deficiencies in DNA mismatch repair, which is associated with development of post-transplant leukaemia (Offman et al., 2004).

In epidemiological studies, azathioprine is shown to be associated with an increased risk of cancer in both immunocompetent and immunosuppressed individuals. A four-fold increase in the incidence of lymphoma was noted in patients on azathioprine for inflammatory bowel disease (Kandiel et al., 2005). A report from the Israel Penn International Transplant Tumor Registry (IPITTR) showed that 93% of the 3,131 transplant recipients developing NMSC were receiving azathioprine (Penn, 1996a). A study assessing the effect of low-dose and high-dose ciclosporin on the risk of post-transplant cancer, along with showing the association of higher dose ciclosporin with an increased risk, also showed that the recipients with higher mean doses of azathioprine had an increased risk of cancer (Dantal et al., 1998).

The risk of cancer in transplant recipients on mycophenolate therapy is increased to a similar degree to those on azathioprine and this is shown by several studies demonstrating no significant difference between these two agents on the risk of post-transplant cancer

(Robson et al., 2005, Wang et al., 2004, Dharnidharka et al., 2002, Funch et al., 2005, Clayton et al., 2012). There are several limitations in interpreting the data assessing the impact of immunosuppression on the risk of cancer. These include incomplete data collection particularly over long term post-transplant follow up, the fact the recipients often receive multiple immunosuppressive agents, each with a different degree of impact on the risk of cancer and the inability of statistical analysis to separate out the impact of individual immunosuppressive agents. Correction for the impact of other confounders influencing the risk of cancer such as oncogenic infections, lifestyle and socioeconomic status of the recipient was also not undertaken in these studies.

1.7.4 Calcineurin inhibitors

CNI increase the risk of development and proliferation of cancer cells by multiple mechanisms. Transforming growth factor (TGF)-β1 has been implicated in the development and spread of cancers (Barrack, 1997, Teicher, 2007). CNI increase the production of TGF-β1 by malignant and non-malignant cells (Prashar et al., 1995, Ohsawa et al., 2006, Khanna et al., 1999). Both ciclosporin (Hojo et al., 1999) and tacrolimus (Maluccio et al., 2003, Khanna et al., 1999) have been shown to increase the number of cancer metastases in animal experiments. CNI also facilitate carcinogenesis by other mechanisms such as increased angiogenesis (Duncan et al., 2007) and inhibition of DNA repair (Herman-Edelstein et al., 2012).

Several epidemiological studies have shown an increased incidence of cancer in transplant recipients receiving CNI when compared with recipients on azathioprine (Hiesse et al., 1997, Marcen et al., 2003, McGeown et al., 2000, Shuttleworth et al., 1989, Kyllonen et al., 2000, Tremblay et al., 2002). Studies comparing the risk of post-transplant cancer between

recipients on ciclosporin and those on tacrolimus have shown variable results depending on the cancer type. In particular, several large retrospective registry-based studies have shown an increased risk of PTLD with tacrolimus immunosuppression. In a study of the United States Renal Data System including 25127 kidney recipients undergoing transplantation between 1996 and 2000, PTLD was diagnosed in 344 patients. In this cohort, among patients without ATG induction the risk of PTLD was higher by 57% among recipients on tacrolimus as compared to ciclosporin, however in recipients receiving ATG there was no significant difference in the risk of PTLD between the two agents (Caillard et al., 2005). Two other large studies have shown an increased risk of PTLD among transplant recipients on tacrolimus: a cohort of 41686 kidney recipients from the Scientific Registry of Transplant Recipients data (Bustami et al., 2004) and a report from the Collaborative Transplant Database studying more than 200,000 recipients (Opelz and Dohler, 2004). However, a meta-analysis of 16 randomised control trials including 3813 liver recipients did not show a significant difference in the risk of PTLD between ciclosporin and tacrolimus (Haddad et al., 2006). With regards to the risk of cancers other than PTLD, several studies have shown no significant difference between ciclosporin and tacrolimus, including a meta-analysis of 30 randomised control trials with a total of 4102 kidney recipients (Webster et al., 2005) and 3 randomised control trials including 413 lung recipients (Penninga et al., 2013). The difference between the two CNI agents with regards to the risks of PTLD and non-PTLD cancers may be explained by the fact that the pathogenesis of PTLD is significantly influenced by the intensity of immunosuppression. The relatively more potent immunosuppression provided by tacrolimus may be one of the reasons which increased the risk of PTLD in the tacrolimus group.

1.7.5 mTOR inhibitors

mTOR is a serine-threonine kinase which plays an important role in the regulation of cell growth and proliferation. mTOR is made up of two sets of proteins, mTOR complex (mTORC) 1 and mTORC2. These two complexes regulate two related aspects of cell growth. In presence of nutrients and other factors favourable for cell growth, mTORC1 regulates the anabolic activity and the rate of protein synthesis by controlling the synthesis of ribosomes, transcription of genes, promoting metabolism and biosynthesis of amino acids and fatty acids whereas, mTORC2 regulates spatial orientation of the cell growth by polarising the actin cytoskeleton in the direction where growth is needed. So, in summary mTORC1 regulates the timing and mTORC2 regulates the direction of cell growth (Wullschleger et al., 2006). mTOR inhibitors inhibit mTORC1 but not mTORC2.

mTOR inhibitors, unlike other immunosuppressive agents used for prevention of allograft rejection, have anti-tumour properties. The anti-tumour effect is mediated by inhibition of different mechanisms including angiogenesis, cell cycle progression and UVB induced DNA damage. These properties have been demonstrated in both murine and human cancer cells (Guba et al., 2002, Luan et al., 2002, Boffa et al., 2004). Epidemiological evidence from several randomised controlled trials confirms a lower cancer risk among recipients on sirolimus immunosuppression in comparison to other immunosuppressive agents. The CONVERT trial (Alberu et al., 2011) included 830 kidney recipients randomly allocated to continue CNI immunosuprression or to switch to sirolimus. At two years following the switch, the risk of de novo cancer was significantly lower in patients on sirolimus therapy at 2.1 cancers per 100 person-years as compared to 6.0 cancers in the CNI group. This difference was mainly due to lower incidence of NMSC in the sirolimus group. In another trial (Mathew et al., 2004) comparing the incidence of cancer following two-year treatment with ciclosporin in combination with sirolimus or with placebo, the incidence of skin cancer

was lower in patients receiving a combination of ciclosporin and sirolimus. This study also reported a lower incidence of cancer in patients on sirolimus monotherapy as compared against patients on a combination of ciclosporin and sirolimus. In another randomised controlled trial (Campistol et al., 2006) of 430 kidney recipients randomised at 3 months post-transplant to continue a combination of ciclosporin, steroids and sirolimus or to have ciclosporin withdrawn, the time to a cancer diagnosis was significantly longer in recipients on sirolimus and steroids as compared to recipients who were also on ciclosporin (1126 and 491 days respectively). The risk of cancer (including both skin and non-skin) was 4.0% and 9.6% respectively. There are several other reports showing an association between sirolimus and a lower incidence on NMSC (Campbell et al., 2012, Euvrard et al., 2012, Gu et al., 2012, Hoogendijk-van den Akker et al., 2013).

These studies demonstrate a reduced risk of cancer, in particular NMSC, among patients on sirolimus immunosuppression as monotherapy or in combination with a CNI. With increasing long-term survival after transplantation and the increased risk of cancer in this group, it is likely that mTOR inhibitors use will increase in a selected sub-group of long-term transplant survivors.

1.8 Current status of organ transplantation in the UK

In the UK, NHSBT in collaboration with other organisations including the Department of Health, transplantation centres and other professional bodies, commissions, regulates and co-ordinates different aspects of organ donation and transplantation. Its remit encompasses

encouraging organ donation, optimising safety of organs, improving the safety, quality, effectiveness and clinical outcomes of transplant services. NHSBT also plays a central role in commissioning and conduct of research in the field of donation-transplantation within the UK as well as offering support, advice and collaboration to international health authorities.

1.8.1 Organ donors: selection and assessment

In 2009, the World Health Organization (WHO) in collaboration with the Transplantation Society (TTS) and the Organizacion Nacional de Trasplantes (ONT), issued a glossary of definitions relating to donation and transplantation (WHO, 2009); these definitions are used here. An actual organ donor is a deceased or living person from whom at least one solid organ or part of it is removed for the purpose of transplantation. A deceased donor can be a deceased donor after brain death (DBD) defined as a donor who was declared dead and diagnosed by means of neurological criteria, or a deceased donor after circulatory death (DCD) defined as a donor who was declared dead and diagnosed by means of cardiopulmonary criteria.

Living donors can be:

A. Related

   A1. Genetically related: 1st degree genetic relative such as a parent, sibling or offspring

   A2. Emotionally related: in-laws, adopted, friend or spouse (who is genetically unrelated)

B. Unrelated: not genetically or emotionally related

A potential deceased donor is a deceased person without absolute contraindication to donation, with brain death or cardiac death diagnosis initiated or completed.

The process of deceased donation starts when a potential donor is identified, such as a patient with a diagnosis of brain death or irreversible process necessitating withdrawal of active treatment. This usually happens in the setting of intensive care or emergency department. In the UK, the Specialist Nurses in Organs Donation (SN-OD) play a key role in facilitating organ donation. The death is explained to the family and careful exploration of the possibility of organ and tissue donation is undertaken, with consideration to the wishes of the potential donor (such as the organ donors' card) and the family. After informed consent, suitability for donation is assessed. This process includes investigation into donor's last illness, past medical history, social history, factors that can affect organ function such as trauma, prolonged hypoxia or hypotension. Donor blood group and the HLA type are determined. The potential donor is screened for transmissible infections and cancers. The screening for transmissible infection includes screening for human immunodeficiency virus (HIV) type 1 and 2, hepatitis B and C (HBV, HCV), human T cell lymphotropic virus (HTLV) type 1 and 2, CMV, EBV, toxoplasmosis, treponema pallidum, Creutzfeldt-Jakob disease, tuberculosis, rabies, malaria, West Nile virus, typhoid, Lyme disease, brucellosis and gonorrhoea. Screening for cancers and the guidelines for stratification of the risk of transmission of cancer are discussed in section 1.13.

Following confirmation of the suitability of the donor, the organ retrieval team is informed and a nationally co-ordinated process identifies the prospective recipients. The factors considered in this process include the priority status of the recipient on the waiting list, geographical location of the donor and the recipient, estimated cold ischemia time and the availability of the local transplantation team.

In order to reduce the ischemia time for the donated organs and the inconvenience of a protracted delay to the family of the deceased, it is an important priority to complete the deceased donation in the shortest possible time. In comparison, the donation from a living donor provides the advantage of a planned non-urgent donation-transplantation process. A majority of the living donors in the UK donate kidneys. In 2013-14, of 2466 donors in the UK, 1146 (46%) were living donors including 1114 kidney donors and 32 donors of a part of liver (NHSBT, 2014b). In addition to screening for transmissible diseases similar to the process in the deceased donor, the living donor assessment would in addition include tests to confirm the anatomical and physiological suitability of the organ for donation, physical fitness of the donor to undergo the donation operation and psychological assessment to assess the donor's preparedness to donate and to confirm that the donation is free from coercion. The risks of donation are explained prior to informed consent of the living donor, including a small risk of wound infection, bleeding and thrombosis. The estimated risk of death from a kidney donation operation is approximately 1 in 3000. Living kidney donors do not experience a significant disadvantage in terms of future kidney dysfunction or life expectancy.

1.8.2 Changing profile of the organ donor

The profile of the organ donors is changing in the UK. Between 2004-2005 and 2013-2014, the number of deceased organ donors in the UK increased by 63%, from 751 to 1320 (NHSBT, 2014b). In the same period, the age and the rate of obesity (defined as body mass index [BMI] of ≥30 kg/m^2 [kilogram per metre squared]) among deceased donors increased; the proportion of the deceased donors aged ≥ 50 years increased from 43% to 59% and the proportion of obese donors, from 16% to 24%. Possible reasons for these changes include increasing longevity and obesity rates in the UK population and also changing criteria for accepting donors. It is possible that influenced by the increasing waiting times for prospective recipients, donors who were previously not accepted due to age or co-morbidities are being accepted for donation in the recent years.

1.8.3 Organ recipients and the waiting list

Organ transplantation is intended to improve the length and/or the quality of life in comparison to continuing without transplantation. The assessment of this benefit is complex and varies for recipients of different organs. When a patient with an organ failure is identified as a potential transplant recipient, assessment is performed to establish the feasibility of transplantation with regards to the recipient's physiological function, psychological status, ability to engage with life-long post-transplant care and family support. Consideration is also given for conditions that would reduce the overall benefit of transplantation such as active or recent cancer, chronic infection like tuberculosis or systemic illness likely to increase the risk of peri-operative or long-term mortality. This

assessment is performed by a multi-disciplinary team involving physicians, surgeons, anaesthetists, transplant co-ordinators and in some cases other specialists such as addiction experts, psychiatrists, social services, nutritionists, radiologists and oncologists. There are several scoring systems designed to help in predicting the benefit of transplantation such as heart failure survival score (HFSS) (Aaronson et al., 1997) and Seattle heart failure model (SHFM) (Levy et al., 2006) for heart transplantation, lung allocation score (LAS) for lung transplantation (Egan et al., 2006), model for end-stage liver disease (MELD) (Wiesner et al., 2003) and the United Kingdom end-stage liver disease (UKELD) (Barber et al., 2011) scoring systems for liver transplantation. These scores are useful in assessing the benefit of transplantation to the prospective recipient and also helpful in prioritising the urgency of the need for transplantation, however no scoring system can cover the complexities of all cases.

Once a decision is made to proceed with transplantation, the prospective recipient is placed on a waiting list and will receive an offer of transplant when a suitable organ becomes available. As a result of the relative shortage of donor organs in comparison to the number of patients on the waiting lists, prospective recipients have to wait for the offer of an organ. In 2013-14 in the UK, the median waiting period for adult patients was 1114 days for kidney, 441 days for heart, 265 days for lung and 145 days for liver transplantation (NHSBT, 2014b). Inevitably, during this waiting period, some patients develop complications and die or become unfit to receive a transplantation. The rates of removal from and death on the waiting list were 4% and 2% for kidney, 10% and 6% for heart, 5% and 10% for lung and 8% and 5% for liver transplant lists respectively (NHSBT, 2014b).

1.9 Benefits of transplantation:

Depending on the indication for transplantation, the recipients can benefit from transplantation in different ways. There can be improvement in the quality of life, relief of specific symptoms or prolongation of life. Of these, the most widely used criterion to measure the success of transplantation is the survival of the recipient after transplantation. In this section, the recipient survival rates following transplantation in the UK are discussed and a comparison is made with the data from the OPTN/UNOS, which includes all recipients of organ transplantation in the United States of America (USA). In these analyses, the recipient survival refers to the duration from transplantation till death, censoring for the recipients who were alive at the end of the study period. Additionally, graft survival rates are shown for recipients of kidney transplantation where graft survival is defined as the duration from transplantation till the time of graft failure, censoring for recipients who died with a functioning graft and also for the recipients who had a functioning graft at the end of follow-up. The UK cohort includes first adult recipients of single organ transplantation and the USA cohort includes all single organ recipients of first or subsequent transplantation.

The survival rates are shown for kidney recipients (Table 1.1), kidney grafts (Table 1.2), liver recipients (Table 1.3) and the recipients of heart or lung transplantation (Table 1.4). The 1-year survival rates are similar in the two countries for all groups of recipients. However the 5-year survival rates are higher for recipients in the UK than the recipients in the USA, particularly for kidney graft survival. A possible explanation for this could be that the UK

cohort was transplanted more recently (2006 to 2008) than the USA cohort (1997 to 2004). With time, the long-term survival rates have improved in both the countries and this is reflected in these results.

Table 1.1 Kidney transplantation: patient survival after transplantation in the UK and USA (percentage survival with 95% confidence interval [CI]) (NHSBT, 2014b, OPTN, 2013)

	UK			USA	
Donor type	DBD	DCD	Living	Deceased*	Living
Period	2006-2008	2006-2008	2004-2006	1997-2004	1997-2004
Number of recipients	2149	888	1317	24140	18306
1-year survival	96 (96, 97)	96 (95, 97)	99 (98, 99)	94.4 (94.2, 94.7)	97.9 (97.7, 98.1)
5-year survival	89 (88, 90)	88 (86, 90)	96 (95, 97)	81.8 (81.3, 82.3)	90.1 (89.6, 90.6)

*including both DBD and DCD

Table 1.2 Kidney transplantation: graft survival after transplantation in the UK and USA (percentage survival with 95% CI) (NHSBT, 2014b, OPTN, 2013)

	UK			USA	
Donor type	DBD	DCD	Living	Deceased*	Living
Period	2006-2008	2006-2008	2004-2006	1997-2004	1997-2004
Number of recipients	2148	887	1317	23078	17901
1-year survival	93 (92, 94)	93 (91, 94)	96 (95, 97)	89.0 (88.6, 89.4)	95.1 (94.8, 95.4)
5-year survival	85 (84, 87)	87 (84, 89)	92 (90, 93)	66.6 (66.0, 67.1)	79.8 (79.2, 80.4)

*including both DBD and DCD

Table 1.3 Liver transplantation: patient survival after transplantation in the UK and USA (percentage survival with 95% CI) (NHSBT, 2014b, OPTN, 2013)

	UK			USA	
Donor type	DBD	DCD	Living	Deceased*	Living
Period	2006-2008	2006-2008	-	1997-2004	1997-2004
Number of recipients	1099	149	-	13080	823
1-year survival	91 (89, 93)	91 (85, 94)	-	86.3 (85.7, 86.8)	90.1 (88.1, 92.1)
5-year survival	80 (78, 83)	-	-	72.0 (71.3, 72.7)	77.7 (74.6, 80.8)

*including both DBD and DCD

Table 1.4 Thoracic transplantation from deceased donors: patient survival after transplantation in the UK and USA (percentage survival with 95%CI) (NHSBT, 2014b, OPTN, 2013)

	UK			USA	
Period	2006-2008			1997-2004	
Organ	Heart	Lung		Heart	Lung
		DBD	DCD*		
Number of recipients	311	334	84	13080	2668
1-year survival	84 (80, 88)	81 (76, 85)	81 (70, 88)	86.3 (85.7, 86.8)	83.3 (82.0, 84.6)
5-year survival	78 (73, 82)	55 (50, 61)	-	72.0 (71.3, 72.7)	47.3 (45.6, 49.0)

* period is 2009 to 2012

1.10 Risks and complications of organ transplantation

As with all medical interventions, organ transplantation has its risks and complications. Table 1.5 shows the complications of organ transplantation divided in three groups depending on when they develop after transplantation. The recipients who develop complications after transplantation are more likely to experience increased risk of graft failure and death.

Table 1.5 Risks of organ transplantation

In the early post-transplant period

1. Risks of major surgery
   - bleeding
   - wound infection
2. Risks of intensive care
   - prolonged organ support such as mechanical ventilation or haemofiltration
   - pneumonia
   - venous thrombosis
   - sepsis related to vascular access
   - cardiovascular or cerebrovascular event
3. Risks relating to transplanted organ
   - non-function or delayed function of the graft, need for re-transplantation
   - acute rejection
   - vascular complications like bleeding or thrombosis
   - anastomotic dehiscence or stricture – ureteric problems in kidney transplants, biliary problems in liver transplants, airway problems in lung transplants

Weeks to months after transplantation

1. Risks relating to immunosuppression
   - acute rejection
   - infections such as CMV, EBV
   - Side effects of drugs such as nephrotoxicity (CNI), cytopenia (azathioprine), hyperglycaemia (steroids, CNI), diarrhoea (MMF)
2. Diseases transmitted from donor
   - infections such as HIV, CMV, HBV, HCV
   - transmitted cancers
3. De novo cancers such as post-transplant lymphoproloiferative disorder, skin cancers

Months to years after transplantation

1. Risks relating to immunosuppression

    - side effects of drugs – diabetes, nephrotoxicity, dyslipidaemia, coronary and cerebrovascular disease

    - de novo malignancy: cancer of the skin, lip, anus, Kaposi's sarcoma, lymphoproliferative disorders, gastrointestinal tract, lung and bronchus, thyroid, bladder, cervix, oral cavity, kidney and liver

    - recurrence of cancer treated prior to transplantation

2. Graft dysfunction

    - chronic rejection
    - recurrence of primary disease

1.11 Cancer after transplantation

Cancer is a common cause of late morbidity and mortality among recipients of organ transplantation. Cancer in the transplant recipient can be one of the following three types (Myron Kauffman et al., 2002):

I. Donor origin cancer (DOC):

   This can be donor-transmitted cancer or donor-derived cancer.

   Ia. Donor-transmitted cancer (DTC): this is the cancer transmitted to the recipient along with the transplanted organ. The presence of cancer may be known or unknown at the time of transplantation.

   Ib. Donor-derived cancer (DDC): this type of cancer develops in the donor cells subsequent to transplantation. The differentiation between donor-transmitted cancer and donor-derived cancer may be possible in cases where the donor is known to have cancer, or the presence of cancer in the allograft is identified at the time of or soon after transplantation. In cases where the recipient develops a cancer of donor origin later during post-transplant follow-up, definitive differentiation between donor-derived cancer and donor-transmitted cancer may be a challenge.

II. De novo cancer:

   This type of cancer develops as a result of a combination of mechanisms including those related to long-term immunosuppression, reduced immune-surveillance and other factors such as infection with oncogenic viruses, environmental factors like exposure to sunlight.

III. Recurrent cancer:

This is the recurrence after transplantation of a cancer treated prior to transplantation. The estimate of the risk of recurrence after transplantation of cancer treated before transplantation can be useful in assessing the overall benefit of transplantation for a patient who has previously been treated for cancer and also in utilising scarce donor organs to those recipients who are more likely to benefit.

1.11.1 Cancer transmission by organ transplantation

Transmission of cancer from organ donors to their recipients is an established complication of organ transplantation (Murray et al., 1965). It was recognised in the early years of human transplantation that organs from donors with cancer at the time of donation or in the past can transmit the cancer to their recipient (McIntosh et al., 1965, Martin et al., 1965, Matter et al., 1970, Barnes and Fox, 1976, Harvey and Fox, 1981). As a result of these reports from the initial years of transplantation, organs from the donors with an active or past cancer were avoided resulting in fewer reports of transmission of cancer in the subsequent period. More recent reports include transmission of cancers from donors who were not known to have cancer at the time of transplantation (Loh et al., 1997, De Soyza et al., 2001, Lipshutz et al., 2003, Snape et al., 2008, Lipshutz et al., 2009). In cases where cancer transmission occurred, it is important to know if the presence of cancer in the donor was known at the time of donation. The significance of the knowledge of cancer in the donor is that the transmission of cancer may be preventable in at least some of these cases. When cancer transmission occurs from a donor, it is also useful to know which organs resulted in cancer

transmission and which organs from the same donor did not, so that the risk stratification can be extended to the individual organs from the donor with a cancer. Table 1.6 shows a list of the cases in the published literature of cancer transmission by organ transplantation. Data regarding whether the presence of cancer was known in the donor and the outcome of all organ recipients from each donor are also included.

Table 1.6 Cancers transmitted by organ transplantation

Type of transmitted cancer	Reference	Donor cause of death	Cancer known in the donor	Organ donated	Recipient outcome	Transplant organ and recipient cancer status	
						With transmission	Without transmission
Breast	(Buell et al., 2004, Penn, 1997)	NS (not specified)	Cancer treated within 10 years of donation	Kidney	Died of sepsis 2 weeks after transplant, cancer noted post mortem in the allograft	Kidney	NS
	(Myron Kauffman et al., 2002)	Living donor	No	Kidney	Bone and brain metastases, improved with chemotherapy, cessation of immunosuppression without graft nephrectomy	Kidney	None
Choriocarcinoma	(Detry et al., 1993)	Cerebral haemorrhage	Autopsy showed haemorrhagic brain metastases and a cancerous nodule in the right kidney which was not accepted for transplant because of difficult anatomy	Left kidney	Cancer in the graft. Remission following transplant nephrectomy and chemotherapy	Kidney, liver	None
				Liver	Cancer in the graft -not excised. Cancer spread and death despite chemotherapy		

Type of transmitted cancer	Reference	Donor cause of death	Cancer known in the donor	Organ donated	Recipient outcome	Transplant organ and recipient cancer status	
						With transmission	Without transmission
Choriocarcinoma	(Braun-Parvez et al., 2010)	Cerebral haemorrhage in pregnancy	Cancer diagnosed in the placenta	Kidney-pancreas	Elevated human chorionic gonadotropin (HCG) levels improved with chemotherapy	Kidneys, liver, heart	None
				Liver	Intestinal metastases, death		
				Kidney	Elevated HCG levels improved following graft excision		
				Heart	Metastatic cancer		
	(Buell et al., 2004, Buell et al., 2001, Penn, 1997)	Six donors, presumed brain tumour/ haemorrhage	Diagnosed at autopsy	Kidney, liver, heart-lung	14 recipients: 1 had no cancer, 9 with disseminated cancer (6 died of cancer and 3 in remission after treatment), 4 with localised cancer	Kidney, liver, heart-lung	NS
	(Baquero et al., 1988)	Cerebral haemorrhage	No	Liver	Death due to cancer	Two kidneys, liver	None
				Kidney 1	Death due to cancer		
				Kidney 2	Metastatic cancer, undetectable HCG following explantation		
				Heart	Well at 10 months		

Type of transmitted cancer	Reference	Donor cause of death	Cancer known in the donor	Organ donated	Recipient outcome	Transplant organ and recipient cancer status	
						With transmission	Without transmission
Choriocarcinoma	(Marsh et al., 1987)	Cerebral haemorrhage - presumed benign	High HCG levels noted in the stored serum retrospectively, after the diagnosis of cancer in the recipient	Liver	Death due to cancer	Liver and kidney	Heart
				Kidney	Prophylactic graft excision showed localised cancer, alive at 5 months		
				Kidney	Metastatic disease and death despite graft excision		
				Heart	Prophylactic re-transplantation. Excised graft showed localised cancer, alive at 5 months		
	(Gokel et al., 1977)	Cerebral haemorrhage	Brain metastases on autopsy, choriocarcinoma excision 2 years prior	Kidney	Prophylactic graft excision showed localised cancer, died of unrelated cause 7 months later	Kidney	None

Type of transmitted cancer	Reference	Donor cause of death	Cancer known in the donor	Organ donated	Recipient outcome	Transplant organ and recipient cancer status	
						With transmission	Without transmission
Choriocarcinoma	(Knoop et al., 1994)	Cerebral haemorrhage 6 months after child birth, presumed benign	No	Lung	Nodule resected before implantation, which was later confirmed to be choriocarcinoma, died of graft rejection	Kidney, liver, heart-lung	None
				Liver	Death due to metastatic cancer		
				Kidney	Metastatic disease-explantation, cancer-free survival of 4 years		
Colon	(Zelinkova et al., 2012)	Cerebrovascular event	No	Liver	Death due to transmitted cancer	Liver	NS
				Kidney	No transmission		
				Kidney	No transmission		
	(Ison and Nalesnik, 2011)	NS	NS	NS	Two cases of confirmed transmission	NS	NS
	(Buell et al., 2004)	Brain death	NS	NS	Two cases of confirmed transmission	NS	NS
	(Kim et al., 2013)	Cerebral haemorrhage	No	Liver	Death due to transmitted cancer	Liver	None

Type of transmitted cancer	Reference	Donor cause of death	Cancer known in the donor	Organ donated	Recipient outcome	Transplant organ and recipient cancer status	
						With transmission	Without transmission
CNS - Astrocytoma	(Kashyap et al., 2009)	Pilocytic astrocytoma	Yes	Liver	Death due to transmitted cancer	Liver	NS
	(Penn, 1997, Buell et al., 2003)	Grade III astrocytoma	Yes	NS	Death due to transmitted cancer	Kidney	NS
CNS – Glioblastoma	(Buell et al., 2003)	Glioblastoma	Yes	Kidney	Graft excision, no recurrence		None
				Kidney	Metastatic disease, death despite graft excision		
				Liver	Confirmed transmission, death		
				5 others	Death due to transmitted cancer		
	(Jonas et al., 1996)	Glioblastoma	Yes	Liver	Death due to transmitted cancer	Liver	Kidneys, heart
	(Val-Bernal et al., 1993)	Glioblastoma	Yes	Kidney	Localised tumour, no recurrence after graft excision		
	(Ruiz et al., 1993)	NS	Yes	2 kidneys	Localised tumour, no recurrence after graft excision in both cases	Kidneys	None
	(Ison and Nalesnik, 2011)	NS	NS	NS, 1 recipient	NS	NS	NS

Type of transmitted cancer	Reference	Donor cause of death	Cancer known in the donor	Organ donated	Recipient outcome	Transplant organ and recipient cancer status	
						With transmission	Without transmission
CNS - glioma	(Morse et al., 1990)	Malignant glioma	Yes	Liver	Death due to transmitted cancer	Liver	Heart, kidneys
				Kidney,heart	No transmission to 3 recipients		
	(Penn, 1997, Buell et al., 2001, Buell et al., 2003)	NS	Yes	2 kidney recipients	Confirmed cancer transmission	Kidney	Not specified
CNS - Medulloblastoma	(Penn, 1997, Buell et al., 2003)	Medulloblastoma	Yes	NS	Metastatic disease in 3 recipients	Kidney	NS
	(Lefrancois et al., 1987)	NS	Yes	Kidney-pancreas	Death due to transmitted cancer despite graft excision	Kidney, kidney-pancreas, heart	None
				Kidney	Transmitted tumour, explant		
				Heart	Death due to transmitted cancer		
Hepatoma	(Matter et al., 1970)	Metastatic hepatoma	Yes	Kidney	Resolved following cessation of immunosuppression	Kidney	None
	(Penn, 1997)	NS	Yes	NS	Metastatic disease	Liver	NS
	(Ison and Nalesnik, 2011)	NS	NS	NS	One case	NS	NS

Type of transmitted cancer	Reference	Donor cause of death	Cancer known in the donor	Organ donated	Recipient outcome	Transplant organ and recipient cancer status	
						With transmission	Without transmission
Kaposi's sarcoma	(Shaheen et al., 1997)	NS	No	Kidney	Two cases of transmission from the same donor	Kidney	NS
	(Penn, 1997) (Penn, 1991)	NS	NS	Liver	Metastatic disease, death due to complication of treatment	Kidney	
Kidney – renal cell carcinoma	(Buell et al., 2004)	NS	Excised ex-vivo before implantation, size 2.1cm, Fuhrman I or II	Kidney	No recurrence in 14 such recipients	Kidney	NS
	(Barrou et al., 2001)	Cerebral haemorrhage	1.7mm tubulopapillary tumour, Fuhrman grade I/II identified in right kidney which was not transplanted	Left kidney	Graft excision, re-transplanted and recurrence-free at 5 years	Kidney, heart	None
				Heart	Death due to transmitted cancer		
				Liver	Death during transplant		
	(Myron Kauffman et al., 2002)	NS	No	Kidney	Transmitted renal cell cancer, treated with graft excision	Kidney	None
	(Ison and Nalesnik, 2011)	NS	No	Kidney	Seven cases of transmission	Kidney	Not specified
		NS	Donors with cancer in one kidney	Other kidney, liver	75 recipients with no cancer transmission		

Type of transmitted cancer	Reference	Donor cause of death	Cancer known in the donor	Organ donated	Recipient outcome	Transplant organ and recipient cancer status	
						With transmission	Without transmission
Kidney – renal cell carcinoma	(Llamas et al., 2009)	NS	No	Kidney 1	Metastatic renal cell cancer, death despite explantation	Kidney	None
				Kidney 2	Localised cancer, recurrence-free after graft excision		
Kidney - oncocytoma	(Myron Kauffman et al., 2002)	NS	No	Kidney	Transmitted renal oncocytoma, treated with graft excision		
Kidney - nephroblastoma	(Knoop et al., 1994)	Cerebral haemorrhage, presumed benign	Tumour confirmed on right kidney which was not transplanted	Lung	Death due to metastatic disease	Lung	Liver, left kidney (right kidney with cancer was discarded)
				Left kidney	2 year cancer-free survival		
				Liver	Death due to graft failure		
				Heart	Lost to follow-up		
Lung	(Barnes and Fox, 1976)	Brain metastases	As described	Left kidney	Transmitted lung cancer, dissemination and death	Kidney	None
				Right kidney	Prophylactic nephrectomy showed no cancer. No recurrence		

Type of transmitted cancer	Reference	Donor cause of death	Cancer known in the donor	Organ donated	Recipient outcome	Transplant organ and recipient cancer status	
						With transmission	Without transmission
Lung	(Buell et al., 2004)	Cerebral event	Lung cancer secondaries	Kidney	Transmitted lung cancer	NS	NS
	(Penn, 1997)	NS	Lung cancer within 10 years before donation	Two kidney	Transmitted lung cancer, death due to another cause	Kidney	NS
	(Ison and Nalesnik, 2011)	NS	NS	NS	Four cases of transmission, death due to cancer in three	Not specified	NS
	(Bodvarsson et al., 2001)	Living donor	Cancer in donor, 10 months after donation	Kidney	Transmitted lung cancer, responded to graft excision and chemotherapy	Kidney	None
	(von Boehmer et al., 2012)	NS	No	Lung	Lung cancer with dissemination causing death	Lung	NS
	(Winter et al., 2001)	Living donor	Cancer in donor, 8 months after donation	Kidney	Metastatic cancer, responded to graft excision and chemotherapy	Kidney	None
	(Forbes et al., 1981)	Head injury	Donor cancer diagnosed week after donation	Right kidney	Transmission of cancer, cause of recipient's death not specified	Kidney	None
				Left kidney	Death due to metastatic cancer		

Type of transmitted cancer	Reference	Donor cause of death	Cancer known in the donor	Organ donated	Recipient outcome	Transplant organ and recipient cancer status	
						With transmission	Without transmission
Lymphoma	(Harbell et al., 2008)	Suspected meningitis	Lymphoma in the donor's brain was diagnosed subsequent to donation	Kidney	Remission of disseminated caner following graft excision	Kidneys, pancreas and liver	None
				Liver	Disseminated lymphoma, death		
				Pancreas	Remission of disseminated caner following graft excision		
	(Schutt et al., 1993)	Cerebral trauma	No	Kidney 1	Remission after graft excision	Kidney	Heart
				Kidney 2	No transmission		
				Heart	No transmission		
	(Penn, 1997)	NS	NS	Kidney	Graft excision, remission	Kidney	NS
	(Ison and Nalesnik, 2011)	NS	NS	NS	Transmission to six recipients, fatal in four	Not specified	NS
Melanoma	(Birkeland and Storm, 2002)	NS	NS	Kidney	Transmitted cancer	Kidney	None
	(Elder et al., 1997)	Cerebral haemorrhage	No	Kidney	Remission after graft excision	Kidney, liver	Heart
				Liver	Fatal transmitted cancer		
				Heart	No transmission		

Type of transmitted cancer	Reference	Donor cause of death	Cancer known in the donor	Organ donated	Recipient outcome	Transplant organ and recipient cancer status	
						With transmission	Without transmission
Melanoma	(Milton et al., 2006)	Subdural haemorrhage	No	Lung	Transmitted cancer, outcome NS	Kidney, lung	Kidney, heart
				Heart	NS		
				Kidney 1	Remission of transmitted cancer following graft excision		
				Kidney 2	Prophylactic graft excision showed no transmission		
	(Kim et al., 2009)	Cerebral haemorrhage	No	Kidney 1	Prophylactic graft excision, no cancer in the graft	Kidney, liver	Kidney
				Kidney 2	Fatal transmitted cancer		
				Liver	Fatal transmitted cancer		
	(Morris-Stiff et al., 2004)	Sub-arachnoid haemorrhage	No	Kidney 1	Fatal transmitted cancer	Kidney, liver	Heart
				Kidney 2	Fatal transmitted cancer		
				Liver	Fatal transmitted cancer		
				Heart	No transmission for 5 years post-transplant		

Type of transmitted cancer	Reference	Donor cause of death	Cancer known in the donor	Organ donated	Recipient outcome	Transplant organ and recipient cancer status	
						With transmission	Without transmission
Melanoma	(Stephens et al., 2000)	Cerebral haemorrhage	No	Kidney 1 and 2	Disseminated transmitted cancer, fatal despite explant in both cases	Heart, liver, kidney	None
				Liver and heart recipients	Disseminated transmitted cancer, fatal in both cases		
	(Ison and Nalesnik, 2011)	NS	NS	NS	Two cases of transmission, one fatal	Not specified	NS
	(Penn, 1997)	NS	NS	NS	Twenty one cases, 13 deaths due to cancer, 5 remissions after graft excision	Kidney	NS
	(Jeremy et al., 1972)	NS	Metastatic melanoma diagnosed on autopsy	Kidney 1	Disseminated cancer, fatal despite graft excision	Kidney	Kidney
				Kidney 2	No transmission		
	(Cankovic et al., 2006)		No	Kidney	Fatal transmission of cancer	Kidney, liver	None
				Liver	Fatal transmission of cancer		
	(Wilson et al., 1992)	NS	No	Kidney	Fatal transmission of cancer	Kidney	None

Type of transmitted cancer	Reference	Donor cause of death	Cancer known in the donor	Organ donated	Recipient outcome	Transplant organ and recipient cancer status	
						With transmission	Without transmission
Melanoma	(MacKie et al., 2003)	Sub-arachnoid haemorrhage	No	Kidney1	Fatal transmission of cancer	Kidneys	None
				Kidney2	Transmitted cancer, explant		
Neuroendocrine carcinoma	(Foltys et al., 2009)	Sub-arachnoid haemorrhage	No	Liver	Fatal transmission of cancer	Liver	Kidneys
				Kidney1	Fatal transmission of cancer		
				Kidney2	Explanted for unrelated reason, no transmitted cancer		
	(Begum et al., 2011)		No	Heart	Post op death, cancer transmission status unknown	Liver	Kidneys
	(Baehner et al., 2000)	NS	No	Liver	Transmitted cancer	Liver, kidney	None
				Two kidney	Prophylactic explantation-transmitted cancer in both cases		
	(Baehner et al., 2000)	NS	No	Kidney 1	Transmitted cancer, explant	Kidney	Liver
				Kidney 2	Lost for follow-up		
				Liver	No transmitted cancer		
	(Ison and Nalesnik, 2011)	NS	NS	NS	NS	NS	NS

Type of transmitted cancer	Reference	Donor cause of death	Cancer known in the donor	Organ donated	Recipient outcome	Transplant organ and recipient cancer status	
						With transmission	Without transmission
Ovary	(Lipshutz et al., 2009)	Cerebral anoxia	No	Two kidney recipients	Transmitted cancer, fatal despite graft excision in both cases	Liver	None
	(Ison and Nalesnik, 2011)	NS	NS	NS	NS	NS	NS
Pancreas	(Gerstenkorn and Thomusch, 2003)	NS	Suspected during bench preparation of kidney	Kidney	Transmitted tumour, death due to unrelated cause	Liver, kidney	None
				Liver	Re-transplanted (cancer in the explant); cancer-free at 1 year		
	(Ison and Nalesnik, 2011)	NS	NS	NS	NS	NS	NS
Pinealoblastoma	(Zhao et al., 2012)	Cerebral trauma	Diagnosed on donor autopsy	Multi-visceral	Fatal transmission of tumour	Liver, pancreas, intestine	None
Prostate	(Loh et al., 1997)	Sub-arachnoid haemorrhage	Diagnosed after heart retrieval, confirmed on autopsy	Heart	Alive on chemotherapy at 18 months	Heart	None
	(Penn, 1997)	NS	Yes			NS	NS

Type of transmitted cancer	Reference	Donor cause of death	Cancer known in the donor	Organ donated	Recipient outcome	Transplant organ and recipient cancer status	
						With transmission	Without transmission
Sarcoma	(Detry et al., 2005)		No	Kidney, liver	Transmitted cancer	Kidney, liver	None
	(Penn, 1997)	NS	No	Kidney	Metastatic transmitted cancer	Kidney	NS
Thyroid	(Penn, 1997)	NS	No	Kidney	Explant, remission	Kidney	NS
Unspecified	(Penn, 1997)	Living donor	Anaplastic cancer at nephrectomy site	Kidney	Metastatic disease and death	Liver	NS
	(Kakar et al., 2002)	NS	NS	Liver	Cancer-free after re-transplant	Liver	None
	(Krapp et al., 2005)	Cerebral haemorrhage	Yes	Kidney	Cancer-free at 8 months following graft excision	Kidney	None
	(Conlon and Smith, 1995)	Cerebral haemorrhage	No	Kidney 1	Cancer-free following explant	Kidney	None
				Kidney 2	Fatal transmitted cancer		
Urothelium	(Backes et al., 2012)	Cerebral haemorrhage	No	Liver	Cancer-free after re-transplant	Liver, kidney	None
				Kidney	Transmitted cancer		
	(Ferreira et al., 2010)	Cerebral haemorrhage	No	Kidney1	Fatal transmitted cancer	Liver, kidney	Kidney
				Kidney2	No transmitted cancer		

The cases summarised in the Table 1.6 showed transmission of twenty two different cancers by solid organ transplantation. It is difficult to draw clinically useful conclusions for the donor selection and recipient management based on this information due to the variations in donor assessment and recipient management.

1.12 Assessment of the risk of cancer transmission from organ donors

The evidence for the assessment of the risk of cancer transmission from organ donors comes from two types of sources – Registry reports and case reports. Data from both these sources have their own advantages and disadvantages. The reports from the transplant registries have the advantage of including a relatively large cohort of cases with a longer follow-up. Such data can be useful for calculating incidence rates and identifying trends in the outcome among different sub-groups. The variations in the detail of the data between cases, censoring of the data, underestimation of the risk due to variable reporting of cases and retrospective nature of the analysis are some of the limitations of the registry data. In comparison, case reports and case series often report greater detail of clinical events of a small number of cases. However, trends cannot be identified from case reports and it can be misleading to extrapolate the findings and conclusions from a small cohort to all the patients.

The major registries providing useful data about the risk of cancer transmission are IPITTR, OPTN/UNOS, ONT, Centro Nazionali di Trapianti (CNT, the Italian registry) and the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA).

Transmission of cancer is a relatively uncommon complication of transplantation. Studies from the transplant registries and the cancer registries have reported rates of cancer

transmission from donors between 0·04% and 0·2%. An analysis of the data from the OPTN/UNOS registry including 108,062 recipients from 34933 donors transplanted over 51 months reported donor origin tumours in recipients of 14 donors (of 34933) at the rate of 0.04% (Myron Kauffman et al., 2002). The Odense University Hospital in Denmark reported one case of transmitted cancer from a cohort of 626 donors (0.2%) (Birkeland and Storm, 2002).

1.13 Guidelines for the estimation of the risk of cancer transmission from organ donors

The Council of Europe (CoE) has issued guidelines for the assessment of the risk of cancer transmission from organ donors (COE, 2010); these are summarised in Table 1.7. These guidelines classify the risk of cancer transmission into three groups based on the cancer type, stage and the cancer-free duration at the time of donation: standard risk, non-standard risk and unacceptable risk. A standard risk donor is an acceptable donor for all the donated organs and for all the recipients, a non-standard donor is acceptable for life-saving transplantation justified by the severity of the recipient's condition and the risk-benefit assessment. An unacceptable risk donor is a contraindication to organ transplantation other than in exceptional and life-saving situations.

The evidence on which the CoE guidelines are based, comes from case series, registry reports and expert opinion. The data showing cancer transmission from donors with a history of cancer is given greater importance in risk stratification than the impact of exclusion of such donors on the morbidity and mortality of the patients on the waiting list for transplantation. A critical assessment of this evidence is included in sections 4.5.

All cancers present at the time of donation are classed as having an unacceptable risk of transmission with the exception of localised NMSC, low-grade (WHO grade I or II) tumours of the CNS and low-grade (Fuhrmann grade I or II) renal tumours identified during organ retrieval of 2.5cm to 4cm size.

The assessment of the risk in a donor with a past history of cancer is more complex and depends on following factors:

A. Cancer-free period

For most cancers, a cancer-free period longer than 5 years is considered to be associated with non-standard risk of transmission. The CoE guidelines (COE, 2010) acknowledge that due to national variations within Europe, some countries would recommend a cancer-free period of at least 10 years for some cancers prior to accepting as non-standard risk donors. All donors with a history of melanoma (including carcinoma-in-situ), lymphoma, sarcoma, chronic leukaemia, choriocarcinoma, cancer of the breast, ovary or thyroid (other than capsulated papillary or minimally invasive follicular type) are considered to have an unacceptable risk of cancer transmission regardless of the cancer-free period at the time of donation.

The evidence for classifying some cancers as having an unacceptable risk in spite of a long cancer-free period is based on reported cases of cancer transmission following transplantation of organs from donors with a past history of cancer (some of the cases in Table 1.6). Some of this evidence is also from the extrapolation of experience from reported cases of late recurrences of cancer in immunocompetent patients, i.e. recurrence rates of cancer in the general population.

The presence or absence of dormant cancer cells in the donated organ cannot be demonstrated conclusively despite a thorough assessment of the donor prior to accepting the organs for transplantation. Therefore, the risk of transmission of cancer from a donor cannot be estimated accurately. So this risk cannot be completely eliminated, and needs to be balanced against the risk to the prospective recipient of not accepting the organ and continuing without a transplant.

B. Stage of cancer in the donor

Stage at which a cancer is detected usually corresponds to the degree of malignant behaviour of the cancer. Early stage cancers have high rates of successful treatment and low long-term recurrence rates. Donors with regional or distant metastases of cancer pose a significant risk of transmission to the recipient, regardless of the duration between the diagnosis of cancer and organ donation. Therefore organs from such donors are usually not accepted for transplantation.

C. Treatment of cancer in the donor

When a donor presents with a history of cancer that has not been treated with curative procedure or when the follow-up information is not available, the risk of transmission of such cancer by organ transplantation cannot be assessed so organs from such donors are not accepted.

Table 1.7 Council of Europe guidelines for stratification of risk of cancer transmission

DONORS WITH UNACCEPTABLE RISK OF TRANSMISSION
Features applicable to cancer of any histological type at any time prior to donation - Presence of metastasis – lymphatic or distant - Absence of curative surgical treatment or missed follow-up (except low-grade prostate cancer under surveillance) - Palliative treatment of cancer **Non-CNS cancer at any time prior to donation** - Breast - Ovary - Choriocarcinoma - Malignant melanoma - Sarcoma - Chronic Leukaemia - Thyroid (except capsulated papillary or minimally invasive follicular type) **Non-CNS cancer diagnosed during organ retrieval:** All cancers, except - Renal cell cancer <2.5 to 4cm (pT1a), tumour free resection margin and Fuhrman grade I or II - Localised low grade (Gleason score≤6) prostate cancer - Small gastrointestinal stromal tumours (GIST) - Localised non-melanoma skin cancer **Cancers of the CNS:** - WHO grade IV cancers - WHO grade III cancers with following features: Presence of ventriculo-peritoneal or ventriculo-atrial shunts Craniotomy

Systemic chemotherapy Radiotherapy
DONORS WITH NON-STANDARD RISK
Carcinoma-in-situ (CIS) other than CIS of breast, lung, choriocarcinoma, melanoma or sarcoma WHO grade III cancers without the features mentioned in ‘unacceptable risk’ group Small localised GISTs
DONORS WITH STANDARD RISK
Donors without a history of cancer Localised non-melanoma skin cancers Localised low grade (Gleason score≤6) prostate cancer Stage pT1 bladder cancer Localised WHO grade I or II cancers of the CNS

1.14 Role of CMV in post-transplant cancer

Viruses such as human papilloma virus (HPV), human herpes virus (HHV) 8, HIV, EBV, HBV and HCV have an established role in the development of cancer both in the immunocompetent population and in the immunosuppressed transplant recipients. But the role of CMV in post-transplant cancer is not well understood. The understanding of the role of CMV in the pathogenesis of post-transplant cancer is particularly important as up to 80% of the adult population is infected with CMV (CDC, 2010) and the dilemma of accepting an organ from a CMV positive donor into a CMV negative recipient, without full understanding of long-term implications, is not uncommon. In the non-transplant population, while CMV antigens have been identified in cells of certain tumours such as cancers of the colon, prostate, lymphoma and glioblastoma (Soderberg-Naucler, 2006), it is not known if the presence of CMV is an epiphenomenon or whether there is a causative association. The published data assessing the impact of CMV on post-transplant cancer are limited to studies with small cohort size which show conflicting opinions with some studies suggesting a reduced risk in CMV infected recipients (Couzi et al., 2010) and others showing an increased risk in CMV infected recipients (Courivaud et al., 2012). Considering the high prevalence of CMV, it will be useful to establish the impact of CMV on the risk of post-transplant cancer using a large cohort with results that are more unequivocal. Such data will have the potential to influence the clinical practice while accepting an organ for transplantation, depending on the CMV status of the donor and the recipient.

1.15 Post transplant lymphoproliferative disease

PTLD is one of the most important complications of transplantation and therapeutic immunosuppression. Along with NMSC, PTLD is one of the two most common cancers after transplantation (Collett et al., 2010). The outcome of the patients with PTLD depends on factors such as the time of diagnosis after transplantation, immunosuppression before and after the diagnosis, the EBV status, the extent and the grade of PTLD and the organ transplanted. Data comparing the incidence of PTLD in different eras of transplantation, correlation with the immunosuppressive agents and HLA type of the donor and the recipient will be useful in understanding the evolution of this disease and to develop guidelines for diagnosis and management of PTLD in future recipients.

1.16 The importance of this thesis

Some donors are excluded from donating their organs as a result of the estimated risk of transmission of cancer. The risk of transmission of cancer determined at the time of accepting the donated organs needs to be balanced against the risk of not accepting these organs and the consequent increased waiting period for the patients on the waiting list. The factors associated with cancer transmission from organ donors are not identified and these factors would be useful in increasing the accuracy of this assessment, further reducing the risk of cancer transmission to the recipients of organ transplantation and also avoiding inappropriate refusal of an organ which may have a low risk of cancer transmission. Some patients with end stage organ failure, who have previously been treated for a cancer, are excluded from transplantation as a result of perceived risk of recurrence of cancer after transplantation. This risk also needs to be balanced against the risk of refusing transplantation to such patients. As the survival rates are increasing for the recipients of all

organs, the risk of cancer is likely to increase due to a combination of advanced age of the recipient and longer duration of exposure to immunosuppression. The incidence of PTLD in different sub-groups of recipients and its relation to HLA status will be useful in improving the understanding of the disease and is likely to influence the outcome for patients with PTLD. The assessment of the impact of CMV on the risk of post-transplant cancer in a large cohort will be useful in producing reliable results and help in resolving the conflict of opinion produced by the existing data, regarding the association of CMV with post-transplant cancer. These factors highlight the importance of the research detailed in this thesis.

CHAPTER 2

AIMS OF THE THESIS

This thesis aims to investigate the risk of cancer transmission from organ donors and explores the scope for increasing the number of safe organ donors. The recipients with donor-transmitted cancer are studied in order to explore measures which can mitigate the risk. The recipients with recurrence after transplantation of a cancer treated before transplantation are studied to assess the risk factors associated with cancer recurrence. The impact of CMV status of the donor and the recipient on the risk of post-transplant cancer are examined. The incidence of PTLD in chronology and its association with the HLA type are explored.

The aims of this thesis are:

1. To investigate the recipients of solid organ transplantation in the UK for donor-transmitted cancers and identify risk factors associated with cancer transmission, assess the outcome of the recipients with donor transmitted cancers, explore the measures to reduce the risk of cancer transmission

2. To examine the actual and potential solid organ donors in the UK with a history of cancer to determine the risk of transmission of cancer from such donors and to provide guidelines for the assessment of risk of cancer transmission from organ donors with past history of cancer

3. To study the recipients of organ transplantation with a history of cancer treated prior to transplantation, assess the risk of recurrence of cancer following transplantation

4. To assess CMV status among organ donors and recipients and its association with the risk of post-transplantation cancer

5. To study the recipients of organ transplantation with PTLD, examine the changes in the incidence of PTLD with time and its relation to the HLA

CHAPTER 3

DONOR TRANSMITTED CANCERS IN TRANSPLANT RECIPIENTS

(Data and text from this chapter have been published

(Desai et al., 2012))

Disclaimer

This is to confirm that some of the text and data included in this Chapter has been published in peer-reviewed journal (Desai et al., 2012). Inclusion of this work has been approved by the Editor of the journal.

The published manuscript is included in the Appendix 3.

I confirm that all the work reported in this manuscript has been done be myself except where stated. This includes designing the study, conducting literature search, data collection, data analysis, interpretation of results and writing the manuscript. Apart from the text referenced to other sources, I wrote all the text in the publication and prepared all the Tables and Figures.

Professor James Neuberger and Professor Philip Johnson supervised this work and helped with the design of the study. Professor Dave Collett supervised the statistical analysis which I performed independently. Professor Christopher Watson helped with facilitating the collection of data from the transplant centres. Dr Tim Evans helped with providing access to the data held by the cancer registries.

All the coauthors read and approved the final manuscript in line with current guidance and suggested minor changes.

3.1 Introduction

A majority of the published cases of DTC are from case reports or small series as shown in Table 1.6. Whilst these are useful, the findings and outcomes reported in small number of cases cannot be generalised to all the recipients with DTC. The most recent and the largest transplant registry report from OPTN/UNOS published in 2002, estimated that the risk of cancer transmission was 0.01% (15 of 108062 recipients) (Myron Kauffman et al., 2002). In this study 0.03% of the donors resulted in cancer transmission (9 of 34993 donors). Since this report, the average age of the donor, obesity rates among the donors and the proportion of DCD donors have all increased (NHSBT, 2014b) and some of these factors are likely to influence the risk of cancer among the donors. Therefore, an assessment of the risk of cancer transmission in a recent cohort of donors and recipients would be useful to understand the impact of the changing donor profile on the risk of cancer transmission.

In this chapter, I present the results of the first comprehensive national survey of transplant recipients in the UK to establish the extent of DTC, DDC, donor characteristics associated with cancer transmission, circumstances of cancer transmission, recipient management and outcome. These data will enable an assessment of the risk of cancer transmission to the transplant recipient in the UK. This information will form an important part of the risk assessment whilst assessing the donors and accepting the organs for transplantation. It will also form an important part of the information provided to the prospective recipient whilst obtaining the informed consent for transplantation.

3.2 Aims

The aims of this chapter are:

1. To assess the risk of cancer transmission from organ donors to their recipients
2. To investigate the donor factors associated with the risk of cancer transmission
3. To study the time of diagnosis of the transmitted cancer and its impact on the management and outcome of the recipients with transmitted cancer
4. To study the impact of the transmitted cancer on the recipient survival

3.3 Methods

The data recorded by the UK Transplant Registry were used to identify all the recipients of solid organ transplantation in the UK. Among these, the cases of DOC could not be identified from the UK Transplant Registry, as the Registry did not routinely record these cases. Individual transplant centres in the UK had recorded these cases on local databases. For the duration between 1st January 2001 and 31st December 2010, complete electronic records of all transplant recipients were available within individual transplant centres, which could be investigated to identify cases of DOC. Therefore, this duration was used for this study. Recipients who had developed DOC were identified by a combination of methods including a database search at the transplant centres, consultation with transplant doctors and coordinators and by searching through clinical governance reports held by NHSBT. To achieve this, I contacted each transplant centre in the UK and visited several of them. I presented the scheme of my research at the departmental meetings and multidisciplinary meetings at the transplant centres and sought their engagement with my project. I worked

with local data managers, transplant co-ordinators, doctors and secretaries to identify the cases of DOC. DOC in the recipients had been confirmed to be of donor origin using histology, molecular genetic techniques or HLA analysis in all cases except one case of donor derived lymphoma (where the donor origin of cancer was suspected).

3.3.1 Classification of DOC as DDC and DTC

The classification of DOC into DDC and DTC is useful but it can often be a challenge to distinguish the two. DTC can be diagnosed with high degree of confidence when the cancer is identified at the time of or soon after transplantation or in those cases where the donor is known to have the same type of cancer. I used the following criteria for inclusion as DTC:

- Cancers identified in the graft at the time of or within six weeks of transplantation
- Metastatic cancer deposit (of donor origin) identified in the allograft without evidence of primary cancer in the recipient (for example, colon cancer deposits in the liver graft with normal colonoscopy and normal colonic computerised tomography [CT] scan)

Other DOC were classified as DDC.

All organ donors for the duration of the study were identified using the data held by the UK Transplant Registry. By matching the data of the recipients who had developed DTC with the donor dataset, the donors whose organs had resulted in cancer transmission were

identified. The donor characteristics available for analysis included age, gender, donor type, smoking history and BMI. These characteristics of the donors resulting in DTC were compared with the donors whose organs did not transmit cancer. Donors with incomplete record of their characteristics (n=20) were excluded. In donors aged over 18 years, obesity was defined using the WHO definition (BMI≥30kg/m^2) (WHO, 2011a). For donors aged between 5 years and 18 years WHO growth charts were used and BMI higher than the 95th percentile for age and gender was considered as obesity (WHO, 2011b).

There are eleven cancer registries in the UK including eight regional cancer registries in England and a national cancer registry each in Scotland, Wales and Northern Ireland. These record all new cases of cancer diagnosed based on clinical data, imaging and histology, including biopsies and post-mortem examination. As a routine and mandatory practice, the information about all new cases of cancer is passed on from the primary care and the hospitals to the cancer registries. The eight cancer registries in England have pooled their data to form the National Cancer Data Repository (NCDR), which contains data relating to the cases of cancer registered by any one of the English registries. When a donation resulted in cancer transmission to one solid organ recipient, all other recipients of organs from this donor were identified using the UK Transplant Registry and their details (NHS number, name, address, gender, date of birth and date of death) were matched with the NCDR to establish if these donors and recipients were recorded to have cancer. Cancer data after 2008 and data for residents of Wales, Northern Ireland and Scotland were not available in the NCDR. For these cases, data were obtained from the UK Transplant Registry and the transplant centres.

For assessment of the incidence, the recipients who received a kidney with or without another solid organ were included in the kidney recipient group. Recipients of a liver with or without another solid organ (except kidney) were included in the liver recipient group. Combined heart-lung transplant recipients were included with the lung recipient group. Recipients of pancreas with or without intestine were included in the pancreas recipients group. Recipients registered with non-NHS transplant centres (n=60) and recipients of intestinal transplant only (n=29) were excluded.

3.3.2 Statistical analysis

All calculations were performed using statistical analysis software SAS, version 9.3 (SAS Institute, Cary).

3.3.2.1 Incidence of transmitted cancer in different recipient groups

As described in section 3.3.1, the recipients were divided into 5 groups, based on the organ transplanted. Each of these categories was further divided into recipients with and without cancer transmission. As this is a comparison of categorical data that are classified in two different ways and there were small numbers in the categories, Fisher's exact test was used to assess the differences in the incidence rates of transmitted cancer between the recipient groups. Unpaired t-test without assuming equal variances was used to compare donor age and BMI between donors resulting and not resulting in cancer transmission.

3.3.2.2 Risk of cancer transmission from donors

The data included independent variables such as donor age, gender, type and obesity status. The dependent variable was a categorical variable with a binary outcome – cancer transmission occurred or did not occur. The outcomes were known for all the donors and there was no censoring of the data. Use of a linear regression model would be unsuitable for this analysis as the dependent variable is binary rather than normally distributed (Tripepi et al., 2008). For these reasons, logistic regression was used to assess the association between donor characteristics and the risk of cancer transmission.

3.3.2.3 Survival of recipients with and without DTC

Post-transplant recipient survival was compared between the recipients with and without DTC. As described above in section 3.3.2.2, linear regression analysis was unsuitable for this analysis as the outcome was binary (alive or dead) rather than normally distributed. At the end of the follow-up period some recipients were alive, resulting in right censoring of the data. Similarly, those recipients who had not been followed-up until the end of the study period and who were alive at their last known follow-up would result in right censoring. In presence of censored data, logistic regression analysis would be inappropriate, since no account could be taken of the data from these patients. Therefore, survival analysis was used for this analysis. Kaplan-Meier survival curves and log-rank test were used to compare unadjusted survival and Cox regression was used for assessment of risk-adjusted hazard of death.

3.4 Results

3.4.1 Recipient groups

In the UK, a total of 30765 recipients underwent solid organ transplantation between 1st January 2001 and 31st December 2010. The kidney recipient group included recipients of kidney only (n=19784), kidney and pancreas (n=1112), kidney and liver (n=119), kidney and heart (n=12) and kidney with liver and pancreas (n=2). The liver recipient group included recipients of liver only (n=6612), liver and pancreas with or without intestine (n=28), liver and heart (n=2) and liver and lung (n=3). The lung recipient group included recipients of lungs only (n=1257) and heart-lung recipients (n=110). The heart recipient group included 1433 recipients.

3.4.2 Donor origin cancers

DOC were identified in 18 recipients (18 of 30765, 0.06%, Table 3.1). Of these, three cases were likely DDC (0.01%). The three cases of DDC are discussed here:

The first case was a transitional cell carcinoma occurring in the recipient of a kidney from a living donor, diagnosed 23 months after transplantation. This was likely to be a DDC because of the interval from transplantation; the donor remained free from cancer 50 months after donation.

The second case was of a renal cell cancer found incidentally in a kidney explanted for benign disease. This was likely a DDC as the tumour was small (not seen on cross sectional imaging) and was diagnosed 38 months after transplantation.

The third case was a lymphoma of suspected donor origin presenting as a mass in the hilum of the transplanted liver 5 months after transplantation. The deceased donor had no evidence of lymphoma at the time of donation.

Table 3.1 Transplant activity in the UK and cases of DOC between 2001 and 2010

Organ recipient group	Number of transplants	Age in years Mean (95%CI)	Sex Male (%)	Follow up in years Median* (95%CI)	Cases of DDC	Follow up in years Median (range)	Incidence of DDC (%)	Cases of DTC	Follow up in years Median (range)	Incidence of DTC (%)	p-value (for DTC incidence)
Kidney	21029	43·9 (43·7, 44·1)	61	3·95 (3·93, 3·98)	2	2.40 (1.90, 2.90)	0·01	12	2.90 (0.02, 8.97)	0·06	0·67
Liver	6645	43·6 (43·1, 44·1)	58	3.71 (3·52, 3·79)	1	0.66	0·02	2	3.32 (0.95, 5.69)	0·03	
Heart	1433	37·6 (36·5, 38·6)	69	4·24 (4·00, 4·81)	0		0	0		0	
Lung	1367	44·5 (43·7, 45·3)	54	2·41 (2·06, 2·79)	0		0	1	0.84	0·07	
Pancreas	291	41·8 (40·7, 42·9)	51	2·18 (1·98, 2·87)	0		0	0		0	
Total	30765	43·7 (43·5, 43·9)	60	3·89 (3·87, 3·92)	3	1.90 (0.66, 2.90)	0·01	15	2.89 (0.02, 8.97)	0·05	

*the median follow up period for transplantations performed between 2001 and 2010 is relatively low. This is explained by the higher number of transplantations in the recent years (who will be censored as they remain under follow up), increasing survival rates for the recipients transplanted in the recent years and improving collection of survival data with time.

3.4.3 Donor transmitted cancers

Fifteen recipients had DTC (15 of 30765, 0.05%) from 13 donors. The details of individual cases of DTC are described in Table 3.2. In none of the cases was the presence of cancer known at the time of transplantation. These 13 donors had donated organs to 19 other recipients, none of whom had evidence of cancer. Cancer was transmitted from one donor to multiple recipients on two occasions: lung cancer and lymphoma.

Table 3.2 Cases of transmitted cancer from organ donors in the UK

	Donor age, gender	Recipient age, gender	Cancer extent: Localised to graft or disseminated	Time of diagnosis (days)	How the cancer was discovered	Explant / excision	Recipient outcome	Death due to DTC	Follow up (months)
Case 1	Donor 1 46 years male	Kidney recipient 1 12 years, M	Transmitted renal cancer, localised	9	Incidental (biopsy to assess graft dysfunction)	Explant	Alive		107
		Kidney recipient 2 69 years, M	Data not available			No	Deceased	No	19
		Liver recipient 52 years, male	No cancer			No	Alive		102
		Heart recipient 58 years, male	No cancer			No	Alive		108
Case 2	Donor 2 51 years male	Kidney recipient 1 58 years, male	Transmitted renal cancer, localised	7	Incidental (biopsy to assess graft dysfunction)	Explant	Deceased	No	34
		Kidney recipient 2 59 years, male	No cancer			No	Deceased	No	86
Case 3	Donor 3 48 years male	Kidney recipient 1 64 years, male	Transmitted renal cancer, localised	0	Incidental (protocol biopsy)	Explant	Alive		82
		Kidney recipient 2 61 years, male	No cancer			No	Alive		85
Case 4	Donor 4 62 years female	Kidney recipient 1 61years, female	Transmitted renal cell carcinoma, localised	7	Incidental (biopsy to assess graft dysfunction)	Excision	Alive		12
		Kidney recipient 2 46 years, male	No cancer			No	Alive		15
		Liver recipient 61 years, male	No cancer			No	Alive		9

	Donor age, gender	Recipient age, gender	Cancer extent: Localised to graft or disseminated	Time of diagnosis (days)	How the cancer was discovered	Explant / excision	Recipient outcome	Death due to DTC	Follow up (months)
Case 5	Donor 5 54 years male	Kidney recipient 1 47 years, male	Transmitted renal cancer, localised	0	Incidental (protocol biopsy)	No	Alive		101
		Kidney recipient 2 51 years, female	No cancer			No	Alive		96
		Liver recipient 53 years, male	No cancer			No	Alive		12
Case 6	Donor 6 53 years male	Kidney recipient 1 64 years, female	Transmitted renal cancer, localised	0	Incidental (protocol biopsy)	Excision	Alive		35
		Kidney recipient 2 55 years, male	No cancer			No	Alive		34
Case 7	Donor 7 45 years male	Lung recipient 30 years, male	Transmitted non-small cell lung cancer, disseminated	192	Lymphadenopathy	No	Deceased	Yes	10
		Kidney recipient 1 35 years, female	No cancer			No	Alive		43
		Kidney recipient 2 52 years, female	No cancer			No	Alive		47
		Liver recipient 69 years, male	No cancer			No	Alive		47
Case 8	Donor 8 57 years female	Kidney recipient 1 47 years, male	Transmitted squamous lung cancer, localised	0	Incidental (protocol biopsy)	Explant	Alive		37
		Kidney recipient 2 52 years, female	No cancer			Explant	Alive		47

	Donor age, gender	Recipient age, gender	Cancer extent: Localised to graft or disseminated	Time of diagnosis (days)	How the cancer was discovered	Explant / excision	Recipient outcome	Death due to DTC	Follow up (months)
Cases 9 and 10	Donor 9 59 years male	Kidney recipient 1 64 years, male	Transmitted small cell lung cancer, localised	0	Incidental (on protocol biopsy)	Explant	Alive		26
		Kidney recipient 2 41 years, female	Transmitted small cell lung cancer, localised	39	On explant (performed following diagnosis of cancer in the other kidney recipient)	Explant	Alive		26
Case 11	Donor 10 54 years female	Kidney recipient 1 39 years, male	Transmitted adenocarcinoma of lung, disseminated	849	Incidental (on biopsy performed to assess graft dysfunction)	Explant	Deceased	Yes	51
		Kidney recipient 2 53 years, male	Data not available			No	Alive		3
		Liver recipient 57 years, male	No cancer			No	Alive		47
Cases 12 and 13	Donor 11 50 years female	Kidney recipient 1 46 years, female	Transmitted lymphoma, localised	14	Biopsy performed following post-mortem examination of the donor	No	Alive		12
		Kidney recipient 2 58 years, male	Transmitted lymphoma, localised	14	Biopsy performed following donor post-mortem	No	Alive		12

	Donor age, gender	Recipient age, gender	Cancer extent: Localised to graft or disseminated	Time of diagnosis (days)	How the cancer was discovered	Explant / excision	Recipient outcome	Death due to DTC	Follow up (months)
Case 14	Donor 12 22 years male	Liver recipient 41 years, male	Transmitted neuroendocrine tumour, disseminated	265	Graft dysfunction	No	Deceased	Yes	11
		Kidney recipient 62 years, male	Sarcoma of kidney (not a proven DTC)	344		Explant	Deceased	No	60
Case 15	Donor 13 58 years male	Liver recipient 58 years, male	Transmitted adenocarcinoma of colon, localised	370	Incidental (focal abnormality on Ultrasound scan)	Explant – re-graft	Alive		68
		Kidney recipient 1 31 years, male	No cancer			No	Alive		93
		Kidney recipient 2 25 years, male	No cancer			No	Alive		91

3.4.4 Donor factors associated with cancer transmission

During the study period, 25697 organs were transplanted from 14986 donors. Organs from 13 donors resulted in cancer transmission giving a cancer transmission rate of 0·09% for donors (13 of 14986) and 0·06% for organs transplanted (15 of 25697). The cancer transmission rate was 0·14% for DBD donors (9 of 6559), 0·24% for DCD donors (4 of 1653). There was no case of cancer transmission from living donors. The donors resulting in cancer transmission were compared against the donors without cancer transmission. The results of univariate analysis are shown in Table 3.3. Multivariate analysis showed that the risk of cancer transmission was significantly associated with donor age ≥45 years (Odds ratio [OR] 9, 95% CI 1.2, 69.6). None of the other variables tested showed a significant association with transmission of cancer after adjusting for all other factors - donor gender (OR 2.2 for males, 95%CI 0.7, 7.3), smoking history (OR 1.6 for smokers, 95% CI 0.5, 4.8), donor obesity (OR 2.2, 95% CI 0.6, 7.3), donor type (OR 1.9 for DCD relative to DBD, 95% CI 0.6, 6.5).

While it would have been helpful to assess the transmission rates from donors with a past history of a specific cancer, since none of the donors whose donated organs resulted in transmission had a history of cancer at the time of transplantation, it was not possible to assess cancer-specific transmission rates.

Table 3.3 Donor characteristics and the association with cancer transmission: results of univariate analysis

		Donors who transmitted cancer	Donors who did not transmit cancer	Odds ratio (95% CI)	p-value
N		13	14973		
Mean age in years (95% CI)		50.7 (44.6, 56.7)	45.4 (45.2, 45.7)		0.08
Age group	<45 years	1 (7.7%)	6586 (44%)	1	0.004
	≥45 years	12 (92.3%)	8387 (56%)	9.4 (1.2, 72.5)	
Gender	Female	4 (30.8)	7489 (50%)	1	0.16
	Male	9 (69.2%)	7484 (50%)	2.3 (0.7, 7.3)	
Donor type	DBD	9 (69.2%)	6550 (43.8%)	1	0.36
	DCD	4 (30.8%)	1649 (11.0%)	1·8 (0.5, 5.7)	
Mean BMI, kg/m^2 (95% CI)		30.3 (22.9, 37.7)	26.1 (26.1, 26.2)		0.23
Obesity status	Non-obese	8 (61.5%)	11594 (77.4%)	1	0.4
	Obese	4 (30.8%)	2405 (16.1%)	2.4 (0.7, 8.0)	
	Unknown	1 (7.7%)	974 (6.5%)	1·5 (0.19, 11.9)	
Past smoking	No	6 (46.2%)	6276 (41.9%)	1	0·4
	Yes	7 (53.8%)	4583 (30.6%)	1.6 (0.5, 4.8)	

3.4.5 Time of diagnosis of DTC and its relation to outcome

In 11 recipients (of 15, 73%) the DTC were diagnosed within 6 weeks of transplantation. These were diagnosed at a median time from transplant of 7 days (range 0 to 39). Nine of these (6 renal cell cancers and 3 lung cancers) were detected incidentally on histology and/or ultrasound scan performed for other reasons or in the explanted graft. In the remaining two cases (of lymphoma from the same donor), DTC were diagnosed on biopsies of the grafted kidneys performed following identification of cancer during post-mortem examination of the donor. None of the cases of DTC diagnosed within 6 weeks of transplantation had evidence of spread of cancer outside the graft. Surgical treatment (explant/excision) was recommended to all the 11 recipients DTC (except one recipient who had <1mm renal cell cancer which could not be localised on cross sectional imaging) and was accepted by 8 recipients. The two recipients with donor transmitted lymphoma both refused surgery, and following chemotherapy, were well and cancer free 12 months post transplantation.

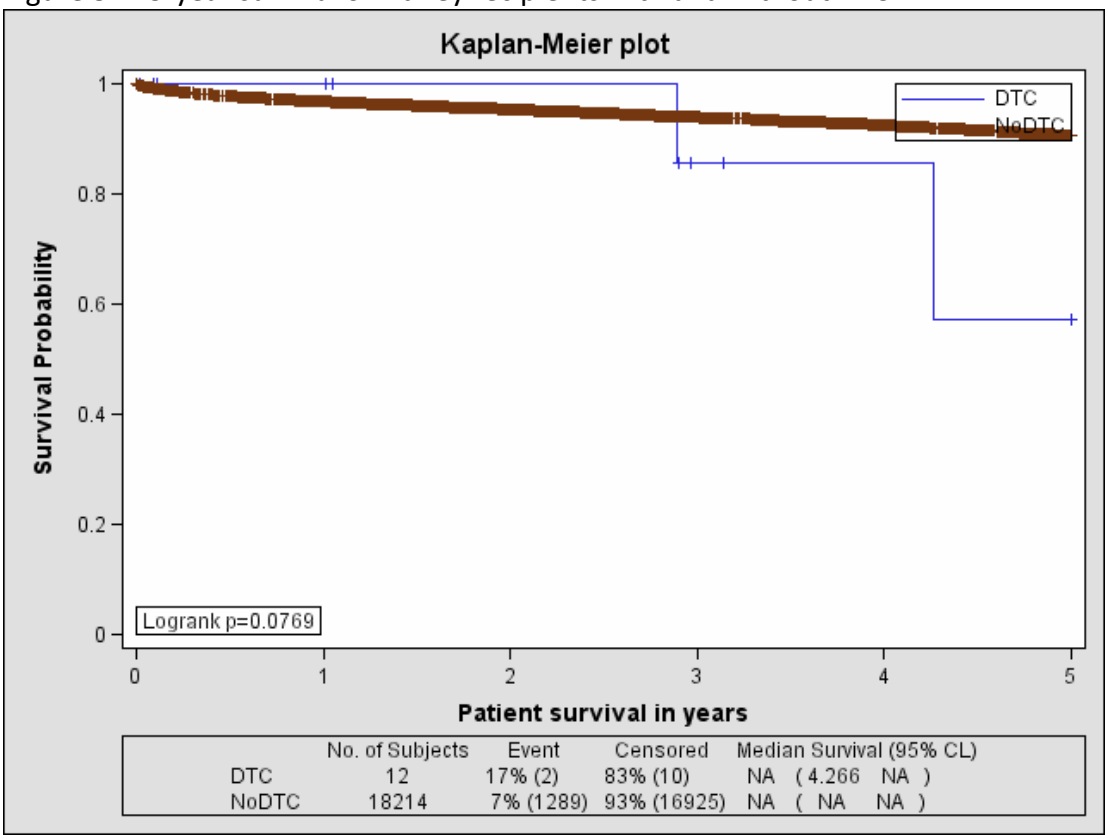
Four recipients had DTC diagnosed after 6 weeks of transplantation, including lung cancer (two), neuroendocrine tumour and colon cancer (one each). These were diagnosed after a median duration of 318 days (range 192 to 849). In three of these cases the cancer had metastasised outside the graft at the time of diagnosis.

3.4.6 Effect of DTC on recipient outcome

Three (of 15, 20%) recipients with DTC died as a direct consequence of cancer and all three had DTC diagnosed after 6 weeks of transplantation. Out of seven kidney

recipients undergoing explantation, six returned to long-term dialysis and the other one underwent re-transplantation. Five-year survival of kidney recipients is shown in Figure 3.1. The survival was lower in recipients with transmitted cancer (83%) as compared to recipients without transmitted cancer (93%) and this difference approached but did not reach statistical significance (p=0.077). The trend towards higher survival among kidney recipients without a transmitted cancer as compared to the recipients with transmitted cancer (some of whom underwent explantation and returned to dialysis) may be attributable to the higher survival in transplanted patients than patients on dialysis. Kidney recipients with DTC had an increased risk of death within five years of transplantation compared to recipients without DTC but this difference was not statistically significant (p=0.116) after adjusting for age and gender (hazard ratio [HR] = 3, 95% CI 0.8, 12.1).

Figure 3.1: 5-year survival of kidney recipients with and without DTC



3.5 Discussion

3.5.1 Clinical implications

The incidence of DTC in this study (0.05%) is higher than the rate of 0.01% reported by the OPTN/UNOS study (Myron Kauffman et al., 2002). The OPTN/UNOS study analysed 108062 recipients from 34933 donors over 51 months and reported 15 cases of DTC. There was only one case of transmitted renal cell cancer, which was diagnosed 37 months post transplantation. In contrast, I found six cases of transmitted renal cell cancer in the present study, diagnosed at a mean duration of 4 days post transplantation (7% of all DTC in the OPTN/UNOS study compared with 38% in my study). However a more recent report (Ison and Nalesnik, 2011) from OPTN/UNOS indicated that seven out of 20 (35%) DTC were renal cell cancers. In my study, all six cases of renal cell cancer were identified as incidental findings on biopsies performed routinely at the time of transplantation or to assess early graft dysfunction. There were two cases of transmitted lung cancer in the earlier OPTN/UNOS cohort compared to 5 cases in my cohort (13% of all DTC compared with 33% in my series). Two of the transmitted lung cancers in my cohort were identified on routine biopsies performed at the time of transplantation. Reasons for these differences may include different time periods, differing donor profiles, variations in reporting and in indications for biopsy.

Although many countries have efficient and large national transplant registries, the number of DTC cases remains small and this highlights the importance of global initiatives, such as the NOTIFY project, in helping understand the extent of problem (NOTIFY, 2010). NOTIFY project is a joint venture of WHO and CNT, which aims to

improve the donor and recipient safety and increase the transparency in the practice of transplantation. Started in 2010, this project aims to collect data from 36 countries on various complications of transplantation such as transmitted cancer, infection, clinical errors and reactions, with an intention provide evidence to facilitate risk reduction. Data collated from several countries are more likely to increase the robustness of the study and power of statistical analysis. However the limitations of such multi-national projects would include diverse demography of donors and recipients, varying inclusion/exclusion criteria for donors with known cancer and genetic differences which may result in heterogeneity in types of cancers and their biological behaviour.

3.5.2 Strengths and limitations of the study

The estimation of the risk of cancer transmission from a national cohort is useful in informing the transplant specialists and prospective recipients about the extent of the risk. This information enables better assessment of the risks involved with transplantation and a comparison with the risks of continuing without transplantation. This study identified the differences between early and late DTC in terms of the clinical presentation, extent of the disease, recipient management and outcome. These differences provide guidance for the management of the recipients with DTC. This study also provides evidence about the higher risk of DTC from older donors. Although the increased donor age was the only donor factor associated with an increased risk of cancer transmission, the effect of small numbers must be noted. There may be other donor factors associated with increased cancer transmission

risk, which did not reach statistical significance due to the small number of donors who transmitted cancer.

This study has some important limitations. The reported incidence of DTC must be an underestimate. DTC were identified retrospectively and only those cases were included where donor origin was confirmed (or suspected in one case). It is possible that in some cases of cancers in the recipient, donor origin was not suspected or investigated and some recipients may have died with transmitted cancer that was not identified. I worked exhaustively in searching databases at individual transplant centres to identify for all cases of DTC but it is possible that not all cases were identified. The history of cancer in the donors was obtained from the cancer registries. The UK is widely recognised to maintain one of the most comprehensive cancer registration system in the world (UKACR, 2013). The cancer registries make constant efforts to register all diagnosed cancers to ensure a comprehensive register including regular cross verification with hospital/primary care records (Kaye et al., 2000). However, it is possible that there may be some under-registration.

A detailed and critical discussion of the strengths and the limitations of these data is included in sections 8.2 and 8.3.

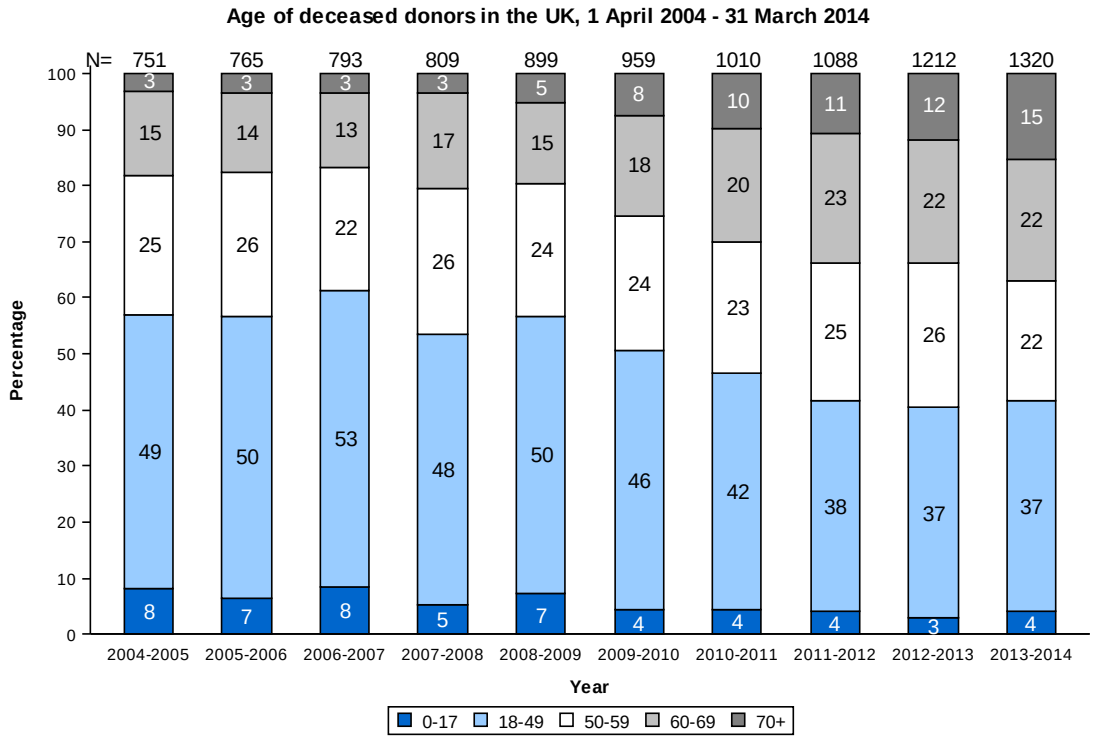
3.5.3 Reducing the risk of cancer transmission

All donors undergo assessment to detect transmissible diseases prior to organ donation. This includes history, examination, chest X-ray and blood tests. The details of previous cancer are obtained by enquiry with family, carers and primary care physician. In the UK, cross sectional imaging and tumour markers are not routinely

performed as a part of donor assessment but reports are reviewed, if available. As detailed in section 1.13 and Table 1.7, a history of several types of cancer in the donor is considered to pose a high-risk of transmission to the recipient. In my study, none of the donors whose organs resulted in cancer transmission was known to have a past history of cancer or active cancer at the time of donation. This highlights the difficulty in eliminating the risk of cancer transmission completely, despite a thorough assessment of the donor. A small but definite risk of transmission of occult donor cancer remains and should be considered an inherent risk of transplantation whilst assessing the overall benefit of transplantation to the recipient.

In the UK, the donors are getting older. As shown in Figure 3.2, 59% of the donors in 2013-14 were aged ≥ 50 years as compared to 43% in 2004-05 (NHSBT, 2014b). With increasing proportion of older donors, the likelihood of occult cancer in the donors is likely to increase, resulting in increased chance of cancer transmission to the recipients.

Figure 3.2. Increasing proportion of older organ donors in the UK



Source: Transplant activity in the UK, 2013-2014, NHS Blood and Transplant

3.5.4 Management of the recipients with transmitted cancers

Based on the observations in the present study and those in the literature, it is possible to make some tentative recommendations. However, more robust evidence and wider discussion is needed before these observations can be translated into formal guidelines.

3.5.4.1 Before transplantation

All potential transplant candidates should be counselled about the benefits and the risks of transplantation in line with current practice. Informed consent should include the information about the risk of cancer transmission. As shown in this study with incidence of 0.05% and cancer-related death in 20% recipients developing DTC, it is important to highlight the rarity of transmission and also the possible outcome when such transmission does occur. Informed consent provides significant advantages in clinical management in that the transplant team and the recipient can be alert to the risk factors in the donor which may increase the risk of an occult cancer and also look out for manifestations of a transmitted cancer in the recipient. Comprehensive provision of information to the prospective recipient at the time of consent, apart from providing advantages in the clinical management of the recipient, also has medico-legal implications.

3.5.4.2 After transplantation

Management of the recipient with transmitted cancer will be dependant on many factors, including the type and stage of cancer, organ transplanted, co-morbidities, time after implantation, immunosuppression and recipient's wishes. As the number of recipients who developed transmitted cancer in this cohort was small and treatment varied, it is not possible to provide evidence-based guidelines. However some trends can be identified which may enable improved management of patients with a DTC.

Excision of tumour or graft explantation is likely to benefit the kidney and pancreas recipients with transmitted cancer diagnosed in the early post–transplant period, and is likely to be most beneficial when there is no evidence of spread of cancer outside the graft. In presence of metastatic disease, explantation should be discussed: the outcome from cancer is likely to improve after stopping immunosuppression as the tumour is rejected (Wilson et al., 1968). However the ability of the transmitted cancer cells to be rejected by the host immunity may also be a reflection of the degree of tumour differentiation and expression of donor HLA. A higher degree of expression of HLA, its correlation with a higher degree of tumour differentiation and a higher degree of host immunological response has been demonstrated in several cancers including cancer of prostate (Levin et al., 1994), stomach (Ma et al., 1994), oesophagus (Hosch et al., 1997) and other cancers (Cordon-Cardo et al., 1991). In transplants other than kidney/pancreas transplants, the benefits of explantation should be weighed against the risks associated with re-transplantation and the likelihood that the tumour may already have spread beyond

the donor organ. In cases where explantation is not an option, lowest possible immunosuppression should be used. As discussed in Section 1.7.5, mTOR inhibitors have inhibitory action against some cancers, therefore these agents may have a role in selected recipients with DTC, although conclusive evidence for this is limited.

3.5.5 Management of the recipients of other organs

When a recipient develops a transmitted cancer, recipients of other organs from this donor should be informed and investigated for cancer transmission. The risk of cancer transmission to these recipients is difficult to assess. This risk depends on the type, stage and grade of cancer in the index recipient, tumour biology and the organ transplanted. It is notable in the UK transplant recipients I studied, that transmission of cancer to multiple recipients was seen when the donor cancer was a lymphoma or small cell lung cancer. The recipients with no evidence of cancer transmission should undergo cancer surveillance. The benefits of graft explantation in such situations should be assessed based on the details of the cancer in the index recipient. In absence of high quality evidence, it is difficult to develop guidelines for management of all the other organ recipients from a donor who resulted in cancer transmission, however, the knowledge of common sites of metastases of different types of cancers may be useful in assessing the risk of cancer transmission to the recipients of different organs: for example, when the transmitted cancer is a breast cancer, the risk to the cardiothoracic organ recipients is likely to be higher than the risk to the kidney or pancreas recipients. Similarly, the risk of transmission of donor colon cancer to the liver recipient is likely to be higher than the risk to the heart recipient.

In summary, these data demonstrate that the incidence of DTC among the transplant recipients in the UK is 0.05%. There is no significant difference in the incidence of DTC between the recipients of different organ transplantation. Transmission exclusively occurred from donors without a known cancer indicating that, with continued implementation of standard donor assessment further reduction of the risk of cancer transmission cannot be achieved. This highlights the importance of informed consent of all prospective organ transplant recipients. (Desai et al., 2012)

CHAPTER 4

DONORS WITH A HISTORY OF CANCER

(Data and text from this chapter have been published

(Desai et al., 2014))

Disclaimer

This is to confirm that some of the text and data included in this Chapter has been published in peer-reviewed journal (Desai et al., 2014). Inclusion of this work has been approved by the Editor of the journal.

The published manuscript is included in the Appendix 3.

I confirm that all the work reported in this manuscript has been done be myself except where stated. This includes designing the study, conducting literature search, data collection, data analysis, interpretation of results and writing the manuscript. Apart from the text referenced to other sources, I wrote all the text in the publication and prepared all the Tables and Figures.

Professor James Neuberger and Professor Philip Johnson supervised this work and helped with the design of the study. Professor Dave Collett supervised the statistical analysis which I performed independently. Professor Christopher Watson helped with facilitating the collection of data from the transplant centres. Dr Tim Evans helped with providing access to the data held by the cancer registries.

All the coauthors read and approved the final manuscript in line with current guidance and suggested minor changes.

4.1 Introduction

The guidelines from the Council of Europe (COE, 2010), described in Table 1.7, characterise some deceased organ donors with a previous history of cancer as having an unacceptable risk of cancer transmission. The guidelines recommend that organs from such donors should not be used unless in exceptional circumstances where a life-saving transplantation is needed. Whilst the terminology used to classify the donor risk itself can be misguiding (for example, an organ from a donor with "unacceptable risk" as per the classification may be lifesaving for a patient who is at a much higher risk of death due to organ failure), it is clear from the published literature, summarised in Table 1.6 that cancer transmission can occur from donors without a known history of cancer. As discussed in chapter 3, in all the 15 cases of DTC in the UK between 2001 and 2010, the donors whose organs transmitted cancer were standard risk donors.

While offering transplantation to patients, an important priority is the reduction of risks associated with transplantation. The CoE guidelines focus primarily on reduction of the risk of cancer transmission. An inevitable consequence of reducing this risk by excluding some donors is further aggravation of the donor shortage and an increase in transplant waiting-list morbidity and mortality. Every year, up to 16% of patients listed for heart transplantation, 13% of patients listed for liver transplantation, 15% of patients listed for lung transplantation and 6% of patients listed for kidney transplantation die or are withdrawn before a graft becomes available (NHSBT, 2014b). The number of patients dying whilst awaiting transplantation is considerably higher than the patients developing a DTC. In the UK,

in the same period between 2001 and 2010 in which there were 15 cases of DTC of whom three died, 4093 patients died whilst awaiting transplantation (NHSBT, 2013).

The actual risk of cancer transmission posed by the donors who are classified as unacceptable risk has not been assessed in a large cohort. Such an assessment has the potential to verify the accuracy of present risk classification and also to explore the possibility of increasing the number of organ donors. In this Chapter, I present the findings of a study of organ donors with a history of cancer and the outcome of the recipients from these donors.

4.2 Aims

The aims of this chapter are

1. To assess the proportion of actual and potential organ donors with a history of cancer
2. To investigate the risk of cancer transmission from organs donors classified as unacceptable risk
3. To identify a sub-group of donor cancers which are classed as unacceptable group by the CoE guidelines, who may actually have a lower risk of cancer transmission

4.3 Methods

Methods used for assessing cancer history in actual donors, their recipients and cancer history in potential donors are described separately. The definitions of actual and potential donors described in section 1.8.1 are used throughout this Chapter.

4.3.1 Actual donors and their recipients

Actual donors were defined as donors where at least one solid organ (kidney, liver, heart, lung or pancreas) was transplanted. Using the UK Transplant Registry, living and deceased actual organ donors who donated between 1st January 1990 and 31st December 2008 and their recipients were identified. The details of cancer in organ donors and the recipients were obtained by matching their details with the National Cancer Data Repository, as described in section 3.2.1. This duration was selected, as the data from the National Cancer Data Repository were limited to this period. The cancer registration data for the donors and the recipients who lived outside England were not available in the National Cancer Data Repository, so the data were restricted to the donors and the recipients resident in England. Donors with insufficient data for matching with the National Cancer Data Repository (n=15) were excluded. All donor cancers diagnosed up to the day of donation were included. Donors registered with cancer after donation or in-situ carcinoma only were considered not to have had a history of cancer at donation. All recipient cancers diagnosed after transplantation were included. Actual and potential/possible donors with unacceptable risk of cancer transmission were identified according to the guidelines described in Table 1.7.

4.3.2 Identifying cancer diagnosed at organ retrieval

With a few exceptions, all cancers diagnosed at the time of organ retrieval are considered to pose an unacceptable risk of transmission. The exceptions include low-grade CNS tumours, localised non-melanoma skin cancers and small low-grade renal

cell cancer. So, the risk of transmission of cancers diagnosed at the time of organ retrieval was studied separately to those donor cancers with a longer interval between diagnosis and organ donation. Using the data from the UK Transplant Registry it was not possible to identify donor cancers diagnosed at the time of organ retrieval. Therefore, donors diagnosed with an extra-cranial cancer within a day of donation were considered as diagnosed at the time of organ retrieval and these were studied separately.

4.3.3 Potential donors

In the UK Transplant Registry, the data for the potential/possible donors were not available for the entire duration between 1990 and 2008, as the potential donor audit did not exist prior to 2003 (NHSBT, 2014a). Furthermore, in October 2009, the data collection form for the potential donor audit was revised and definitions used were clarified to improve the data quality. For these reasons, the data for all potential/possible donors (defined below) in the UK, between 1st October 2009 and 30th September 2012 were selected and those with cancers were identified.

The following definitions (NHSBT, 2014a) were used:

Possible DBD: suspected neurological death meeting the following criteria: apnoea, coma from known aetiology, ventilated, fixed pupils.

Possible DCD: anticipated imminent death receiving ventilatory support and clinical decision to withdraw treatment.

Potential DBD/DCD donor: possible DBD/DCD donor with no absolute/relative contraindication to donation.

4.3.4 Statistical analysis

The mean donor age was compared between donors with and without a history of cancer using unpaired t-test, without assuming equal variances. Recipient survival was calculated using Kaplan-Meier estimate and compared using the log-rank test. Median survival times for the recipients were calculated, where possible. In some cases, less than 50% of the patients had died in the follow-up period. In these cases, the 25th percentile of distribution of survival time was used. Cox regression modelling was used to compare the hazard of death in single-organ recipients from donors in the two groups, using the following factors for risk adjustment: donor age, recipient age, donor sex, recipient sex, donor type, donor cause of death, primary disease (kidney, liver and heart recipients), HLA mismatch (kidney recipients) and ischemia time (cold ischemia for liver, total for heart/lung). An 'unknown' category was used to include the missing values. Recipients with missing ischemia time (liver: 18%, heart: 40%, lung: 27%) were excluded from Cox regression. Additional life-years gained by using organs from donors with unacceptable/high risk were obtained as the average survival time up to 10 years, calculated from the area under survivor function curve up to 10 years after transplantation.

All calculations were performed using SAS version 9.3 (SAS Institute, Cary).

4.4 Results

4.4.1 Cancers diagnosed at organ retrieval

Of the 17639 donors, 13 (0.07%) were diagnosed with cancer at organ retrieval. These donors donated 17 kidneys, two hearts, one liver, one lung and one pancreas to 22 recipients. The details of these donors and their recipients are shown in Table 4.1.

One of these donors resulted in transmission of cancer to the recipient. A 62-year-old DBD donor was identified to have adenocarcinoma of the pancreas at the time of organ retrieval. Two kidneys and liver were transplanted from this donor into three recipients. One of the kidney recipients was diagnosed with transmitted cancer, two days after transplantation. The transmitted cancer was surgically excised. This recipient was followed up for 1.1 years without a recurrence of cancer, when he died following myocardial infarction. At the time of death he had a functioning graft. The liver recipient did not develop cancer transmission until his death, 2.6 years after transplantation. The cause of death was multi-organ failure. The recipient of the other kidney from this donor developed a graft failure on the day of transplantation due to post-operative vascular and ureteric complications. The long-term follow-up data for this recipient were not available.

Table 4.1 Donor cancers identified at organ retrieval and recipient outcome

Donors Age in years, gender	Cancer in the donor	Recipients Age at transplant, gender	Organ transplanted	Transmission to recipient	Outcome
Donor 1 44, male	Non-Hodgkin's lymphoma	Recipient 1 51, male	Heart	No	Died on day 3 due to allograft dysfunction
		Recipient 2 22, male	Lung	No	Alive at 13 years
Donor 2 53, female	Unspecified cancer	Recipient 1 30, male	Kidney	No	Alive at 13.9 years
		Recipient 2 30, male	Kidney	No	Died after 6.4 years due to myocardial infarction
Donor 3 38, female	Unspecified cancer	Recipient 1 69, female	Kidney	No	Died after 17.2 years due to pneumonia
		Recipient 2 48, male	Kidney	No	Alive at 13.8 years
		Recipient 3 48, male	Heart	No	Died after 4 days due to pulmonary hypertension
Donor 4 51, female	Adenocarcinoma-brain metastases	Recipient 1 58, male	Kidney	No	Alive at 12.8 years
Donor 5 62, female	Pancreas adenocarcinoma	Recipient 1 47, female	Kidney	No	Graft failure on the day of transplant, no follow-up data
		Recipient 2 56, male	Kidney	Yes	Died 1.1 year post-transplantation due to myocardial infarction
		Recipient 3 21, female	Liver	No	Died after 2.6 years due to multi-organ failure

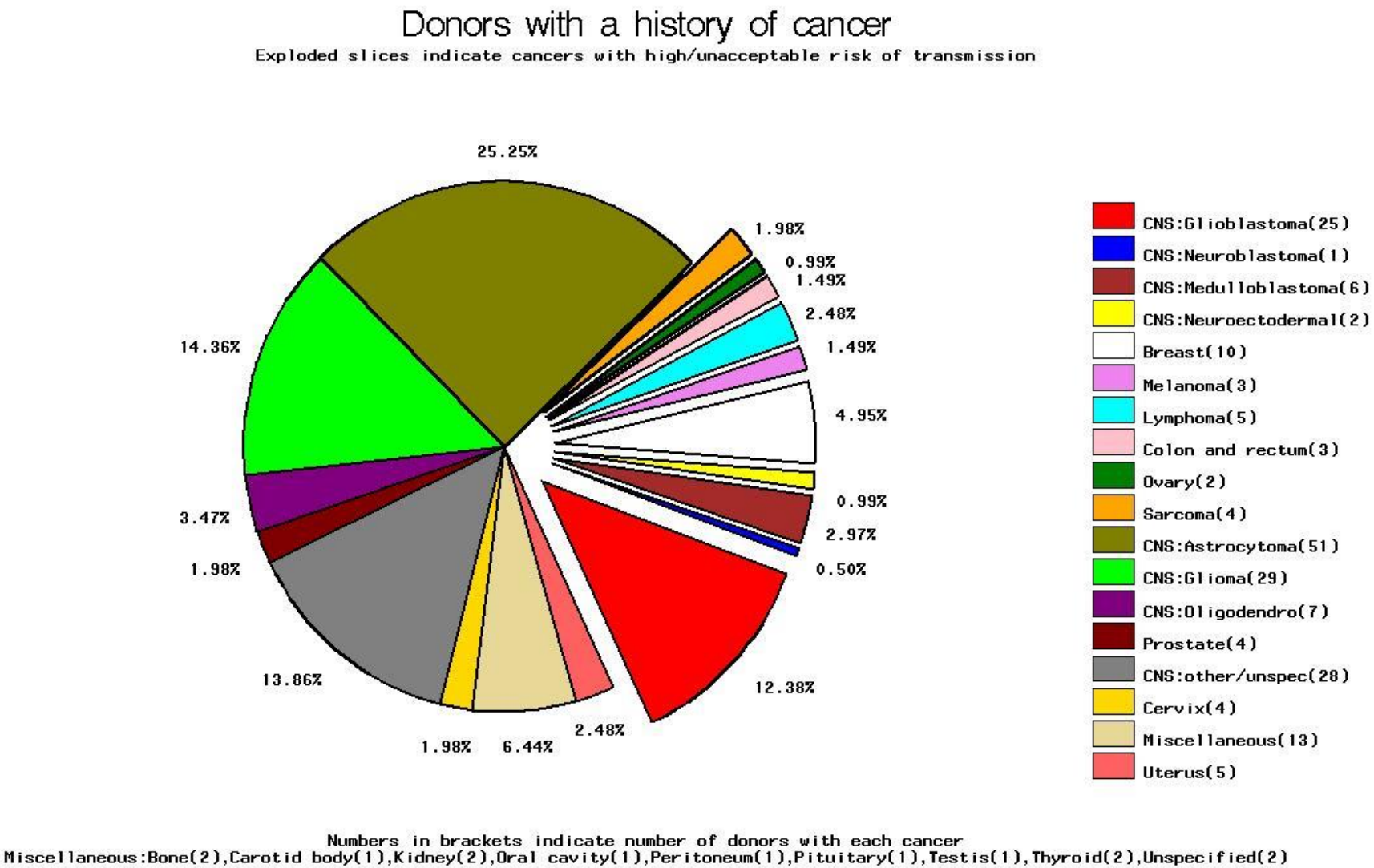
Donors Age in years, gender	Cancer in the donor	Recipients Age at transplant, gender	Organ transplanted	Transmission to recipient	Outcome
Donor 6 57, male	Renal cell carcinoma	Recipient 1 48, female	Kidney	No	Died after 3.4 years due to pancreatitis
Donor 7 58, female	Non-Hodgkin's lymphoma	Recipient 1 34, female	Kidney	No	Alive at 9.8 years
Donor 8 63, male	Retroperitoneal liposarcoma	Recipient 1 49, female	Kidney	No	Alive at 4.9 years
Donor 9 33, male	Renal cell carcinoma	Recipient 1 58, female	Kidney	No	Alive at 5.0 years
		Recipient 2 60, male	Kidney	No	Alive at 5.0 years
		Recipient 3 30, female	Pancreas	No	Alive at 4.7 years
Donor 10 42, female	Renal cell carcinoma	Recipient 1 46, male	Kidney	No	Alive at 3.8 years
Donor 11 63, female	Renal cell carcinoma	Recipient 1 65, female	Kidney	No	Alive at 0.8 years
Donor 12 69, female	Lung adenocarcinoma	Recipient 1 54, male	Kidney	No	Alive at 3.0 years
		Recipient 2 47, male	Kidney	No	Alive at 3.0 years
Donor 13 53, male	Renal cell carcinoma	Recipient 1 55, male	Kidney	No	Alive at 2.9 years

4.4.2 Donors with a history of cancer

Of the 17639 donors, 202 (1.14%) had a history of cancer. Figure 4.1 shows the number of donors with different types of cancer. The exploded slices of the pie chart indicate cancers which are currently classified as unacceptable risk of transmission according to the CoE guidelines (COE, 2010).

Comparison of donors with and without history of cancer showed no significant difference in age (mean age 40.7 years [95%CI 38.5, 43.0] and 42.4 years [95%CI 42.2, 42.6] respectively, p=0.15) or gender (males 45.5% and 51.4% respectively, p=0.37). Significantly more DCD donors (24 of 1047, 2.3%) had a cancer history compared with DBD donors (164 of 11047, 1.5%, p=0.04). Among the living donors 0.25% (14 of 5545) had a cancer history.

Figure 4.1 Donors with a history of cancer: exploded slices show cancers with unacceptable risk



4.4.3 Actual donors with unacceptable risk of cancer transmission and their recipients

Of the 202 donors with cancer, 61 had cancers classed as unacceptable risk of transmission. These 61 donors donated 140 organs to 133 recipients (86 kidney, 22 liver, 10 heart, eight lung and seven multi-organ [four kidney-pancreas, two heart-lung and one kidney-heart]). Comparison of the survival of recipients of single organs from donors with unacceptable risk and standard/non-standard risk revealed no significant difference in unadjusted survival or risk-adjusted hazard of death. These results are shown in Table 4.2. There were insufficient data to assess the circumstances of acceptance of organs classed as unacceptable risk: I could not assess whether the data regarding the cancer in the donor were available to the transplanting team, whether there were discussions with the prospective recipients and their families regarding the risk of cancer transmission and if such organs were used because of the urgent need of transplantation.

Table 4.2 Recipient survival and risk-adjusted hazard of death in single-organ recipients from donors with unacceptable risk and standard/non-standard risk of cancer transmission

Recipient group	Transplants from donors with an unacceptable risk of cancer transmission			Transplants from donors with standard/non-standard risk of cancer transmission				Risk-adjusted hazard of death for recipients from donors with unacceptable risk†	
	N	Mean age in years	Recipient survival in years	N	Mean age in years	Recipient survival in years	p-value#	Hazard ratio	p-value
Kidney	86	47.4 (43.7, 51.0)	8.79 (3.80, -)*	23994	42.6 (42.4, 42.8)	10.96 (10.69, 11.27)	0.522	0.87 (0.55, 1.39)	0.566
Liver	22	41.2 (32.6, 49.9)	5.37 (0.11, -)*	6560	39.4 (39.0, 39.8)	4.86 (4.43, 5.42)	0.807	1.07 (0.43, 2.64)	0.884
Heart	10	34.3 (22.8, 45.8)	3.75 (0.01, -)*	2720	32.2 (31.7, 32.7)	3.56 (2.72, 4.17)	0.686	0.73 (0.16, 3.18)	0.670
Lung	8	39.0 (28.1, 49.9)	0.43 (0.04, 5.94)	1245	36.6 (35.8, 37.3)	0.94 (0.70, 1.29)	0.400	2.85 (0.94, 8.62)	0.063
Pancreas	0	-	-	149	32.7 (30.7, 34.6)	6.20 (5.84, 10.32)	-	-	-

Values in parentheses indicate 95% confidence intervals. *Upper confidence limit for survival of recipients was not under 75%, therefore not estimable. # Comparison of recipient survival (logrank test), † Cox regression modeling

At ten years after transplantation, the additional survival benefit of transplanting the organs from donors with unacceptable risk was 944 life-years (95%CI 851, 1037) with mean survival of 7.1 years (95%CI 6.4, 7.8) per recipient. Eight of these recipients developed post-transplant cancers but none had the same type of cancer as their donor indicating these were de novo cancers. These results are shown in Table 4.3.

Table 4.3 Post transplant cancers* in the recipients from donors with unacceptable risk cancers

Donor cancer	Time of donor cancer diagnosis prior to donation	Organ transplanted	Recipient cancer	Time from transplant to diagnosis of recipient cancer
Haemangiosarcoma	3 days	Kidney	Glioma	307 days
Medulloblastoma	0 days	Kidney	Small cell cancer liver secondaries	339 days
Hodgkin's lymphoma	4715 days	Kidney	Colon adenocarcinoma	828 days
Glioblastoma	2 days	Kidney	Thyroid adenocarcinoma	933 days
Medulloblastoma	0 days	Heart	Acute myeloid leukaemia	1371 days
Glioblastoma	2 days	Kidney	Melanoma	3751 days
Neuroectodermal tumour	2 days	Heart	Prostate adenocarcinoma	3930 days
Glioblastoma	1 day	Liver	Non-Hodgkin's lymphoma	3994 days

*excluding primary liver tumours found in the explant, non-melanoma skin cancer and in-situ carcinoma

4.4.4 Factors associated with non-transmission of donor cancer

In spite of being classed as having unacceptable risk of cancer transmission, some donor cancers did not transmit to the recipients. These donor cancers were assessed for identification of factors, which may be associated with non-transmission of cancer. Table 4.4 shows factors associated with non-transmission of donor cancers.

Table 4.4 Donors with unacceptable risk cancer (excluding CNS cancers): features associated with non-transmission of cancer

Donor cancer type	No of donors	No of recipients (organs)	Duration from cancer to organ donation (completed months)	Treatment of donor cancer (where known)	Other features
Melanoma	3	3 (kidney)	106, 107 and 15	Surgery in one case	Superficial spreading subtype in 2 cases
Breast	10	20 (14 kidney, 4 liver, 1 lung, 1 kidney+pancreas)	97, 115, 118, 73, 196, 161, 65, 115, 102 and 190	Surgery +/- radiotherapy in 8 cases (surgery details unknown in the remaining 2 cases) Hormone therapy in 6 cases	Adenocarcinoma in 9 cases Medullary carcinoma in 1 case
Ovary	2	3 (1 kidney, 1 liver, 1 kidney+pancreas)	142 and 156	Surgery in one case	Mucinous cystadenocarcinoma in both cases
Colon/rectum	3	5 (kidney)	20, 78 and 101	Surgery in all cases Chemotherapy in 1 case	Adenocarcinoma in all cases Rectum in one case Ascending colon in 2 cases
Lymphoma	5	8 (5 kidney, 1 liver, 1 lung, 1 heart)	70, 154, 49, 12 months 1 day*	Surgery 1 case Radiotherapy 1 case Radiotherapy + chemotherapy in 1 case	2 Hodgkin's 2 Non-Hodgkin's 1 Unspecified
Sarcoma	4	10 (6 kidney, 1 liver, 1 heart, 1 lung, 1 kidney+pancreas)	0, 1 and 3 days in 3 cases* 172 months in one case	Surgery 1 case	1 haemangiosarcoma 1 liposarcoma 1 embryonal rhabdomyosarcoma 1 Ewing's sarcoma

*Information regarding recently diagnosed lymphoma/sarcoma in the donor was not available to the team transplanting the organs

4.4.5 Possible/potential donors excluded based on their history of cancer

Data from 23376 possible donors were examined including 3996 DBD and 19380 DCD donors. Six cases were identified with a history of cancer classed as unacceptable risk and no other contraindication to donation: 3 cases with treated breast cancer without recurrence at 5, 10 and 15 years, 2 cases with treated colorectal cancer without recurrence for 12 and 18 years and one case of melanoma treated 15 years prior, without evidence of recurrence. All 6 were possible DCD donors. At present in the UK, the average number of organs retrieved are 2.6 per DCD donor and 4.0 per DBD donor (NHSBT, 2014b). Thus, these 6 donors would be anticipated to have donated 15 additional organs for transplantation (5 additional organs per year).

4.5 Discussion

This study points to a potential overall benefit in recipient survival if organs from selected donors with a history of cancer are used for transplantation. A small, yet real risk of cancer transmission is present, of which the recipient should be advised. Notably, although the risk can be reduced by careful assessment, it cannot be abolished.

4.5.1 Balancing the cancer transmission risk against the risk of waiting-list mortality

In the UK, the proportion of patients annually removed from or dying on the waiting list for transplantation ranges from 6% for kidney, 13% for liver, 16% for heart and 15% for lung candidates (NHSBT, 2014b). When organs from a donor with past history of cancer are offered for transplantation, the risk of cancer transmission has to be balanced against the consequence of declining such organs. The present study found that the recipients of organs from donors with unacceptable risk cancer had no different survival and risk of death as

recipients of organs from standard/non-standard risk donors. In addition, there was no cancer transmission from 61 donors with unacceptable risk cancers. It must be noted that the cohort of such donors was small and these organs were transplanted after careful risk assessment. Nonetheless, this evidence indicates that there is a proportion of donors with a cancer history currently classified as unacceptable risk, whose organs can be transplanted without a negative impact on the recipient survival and with very low rates of cancer transmission. Therefore, it is likely that strict adherence to present guidelines may have resulted in inappropriate exclusion of some donors whose organs could have been transplanted with very low risk of cancer transmission.

4.5.2 Strengths and limitations of this study

Most donors with an unacceptable cancer transmission risk would be excluded from organ donation. Non-transmission of cancer from such donors must be demonstrated in a substantial cohort of recipients in order for the results to be reliable. In the present study, 0.35% donors (61 of 17639) had a history of unacceptable risk cancer. Evidence for non-transmission of cancer was demonstrated in 133 recipients. The data from the Cancer Registry included useful data such as date of diagnosis of cancer, details of treatment of primary cancer and date and cause of death. These details were useful in showing the association between non-transmission and factors such as curative surgery and cancer-free period prior to donation. Therefore, the size of the cohort and the degree of detail of data of individual cases were strengths of this study.

The quality of the data held by the cancer registries is rigorously verified to maintain the accuracy. Cancer registries make every effort to record all malignancies by use of a range of

data sources, in order to ensure that the most accurate information is captured. The number of cancer registrations that each registry records is closely monitored for discrepancies between the actual number of registrations and the expected number of registrations. The national cancer registration data have also been compared to independently collected data held within the General Practice Research Database, and it was shown that no significant difference was noted in registration of breast cancer (Kaye et al., 2000). In spite of these measures, it is possible that there has been some under-registration of cancer, which in turn may result in under-estimation of cancer transmission for organ donors to their recipients.

Among the recipients from high risk donors, 133 (86%) recipients (residents of England) were included in our study; from the same donors, there were 22 (14%) other recipients who lived outside England and cancer transmission to these recipients was not assessed. An occult transmitted cancer may have gone undiagnosed in cases where the recipient died soon after transplantation. Extending recurrence rates of dormant cancers from the immunocompetent population to recipients of non-renal transplants (where stopping immunosuppression is not an option) is also likely to result in imprecise risk estimation. For these reasons, this study may underestimate the cancer transmission risk. The donors in this study represent a carefully selected cohort and caution must be used while extrapolating our conclusions to all potential donors with history of cancer.

A more detailed discussion of the strengths and the limitations of this research is included in sections 8.2 and 8.3.

4.5.3 Existing evidence and the need to consider modifications to present guidelines

Evidence supporting the present classification of cancer transmission risk was from non-consecutive case series, transplant registry reports, survival data in non-transplant patients and expert opinion (COE, 2010, Nalesnik et al., 2011). The published reports preferentially highlight the cases of cancer transmission as opposed to the cases of non-transmission: an OPTN/UNOS report (Kauffman et al., 2007) included 440 transplants from high risk donors and apart from one case of transmitted melanoma, none of the other recipients developed transmitted cancer. In the present study there were 133 recipients from 61 donors with unacceptable risk cancer and none of the cancers were transmitted. Therefore, this evidence offers an opportunity for exploring methods of safe expansion of the donor pool by modifying the present guidelines.

4.5.4 Donors with cancer of CNS

A study by Watson and colleagues (Watson et al., 2010) assessed donors with CNS cancers in England, Wales and Northern Ireland between 1985 and 2001. This cohort was partly overlapping with and larger than the cohort I studied. Watson reported no case of transmission of CNS cancer from 177 donors to any of their 448 recipients. These included 24 donors with glioblastomas and 9 with medulloblastomas. Several of these patients had undergone cerebrospinal fluid shunt. This study concluded that organs from donors with CNS cancers should be considered for transplantation. A further analysis of the same data (Warrens et al., 2012) demonstrated that using organs from the donors with CNS cancer provided additional survival benefit of 8 years for a kidney recipient, 3 years for a liver recipient, 2 years for a heart recipient and 1 year for the lung recipient.

4.5.5 Donors with non-CNS cancers – features associated with non-transmission

In the present study 6 types of non-CNS cancers that were classed as unacceptable risk, did not result in transmission to the recipients: melanoma, lymphoma, sarcoma and cancers of the breast, colon and ovary. There are similar reports in the published literature where donors with these cancers have not resulted in cancer transmission. These reports were studied to identify features associated with non-transmission.

4.5.5.1 Donors with past melanoma:

Prolonged dormancy followed by late recurrence of melanoma is well recognised in non-transplant patients (Crowley and Seigler, 1990) with recurrence rates up to 2% after 15 years (Tsao et al., 1997). Recurrence rates depend on Breslow tumour thickness – recurrence rates between five and ten years after diagnosis are 0.3% for tumours thinner than 1mm, 1.5% for tumours between 1mm and 3.55mm and 3.5% for tumours more than 3.55mm thick (Dicker et al., 1999). A higher degree of suspicion should be adopted when a potential donor with past melanoma has an unclear cause of death. In particular, when the cause of brain death is cerebral haemorrhage or an apparently primary brain tumour diagnosed without histology, the possibility of cerebral metastasis from melanoma should be considered (Penn, 1996b). Cerebral metastasis of amelanotic melanoma can be misdiagnosed as primary oligodendroglioma resulting in underestimation of transmission risk. In early stages, superficial spreading subtype of melanoma is known to spread laterally and outwards (rather than deeper) resulting in early identification. Superficial spreading melanoma subtype is reported to contain smaller proportion of 'thick' (>2mm) melanoma compared to other subtypes (Carli et al., 2004). In the present study, organs from two donors with superficial spreading subtype of melanoma diagnosed 8·9 years before

donation (in both cases), did not transmit the cancer. So organs from donors with past melanoma but no features of recurrence for five or more years can be considered for transplantation. Superficial spreading subtype and tumour thickness less than 1mm are likely to have low transmission risk.

4.5.5.2 Donors with past breast cancer:

Breast cancer is also noted for late recurrence in non-transplant population with recurrence rates of 5 to 7% after five years (Bosco et al., 2009, Brewster et al., 2008) and annual recurrence rate of 0·5% after ten years (Lousberg et al., 2011). Late recurrence of breast cancer depends on stage/grade, hormone receptor status and the treatment of the primary tumour. Stage I tumours (<2cm diameter without nodal spread) have a lower recurrence rates after five years (7%) compared with stage III (>5cm or infiltrating locally or with ipsilateral nodal spread) tumours (13%) and the risk is lower for hormone receptor negative tumours, localised tumours and those receiving curative surgery (Lousberg et al., 2011, Cheng et al., 2012).

In the UNOS/OPTN cohort (Kauffman et al., 2007), there were 126 transplants using organs from donors with past breast cancer (of whom 73% had the cancer more than five years before donation) and no cases of transmission. In the series I studied, there were ten donors with past breast cancer (minimum 5·5 years before donation, eight undergoing surgical resection) and there was no transmission of cancer to recipients of their 21 donated organs. Therefore, it can be recommended that organs from donors with stage I breast cancer treated with curative surgery at least five years before donation can be considered for transplantation. Recipient selection should include careful assessment of risks-benefits and

informed consent. Hormone receptor negative status is likely to be associated with low recurrence risk.

4.5.5.3 Donors with past ovarian cancer:

Ovarian cancer often presents late with 60% women in stage III/IV at diagnosis and 29% cases present as an emergency (CancerResearchUK, 2013). Both advanced stage and emergency presentation are associated with poor outcome. Therefore, there are limited data about late recurrence of ovarian cancer. In the non-transplant population recurrence of ovarian cancer after 46 months of diagnosis is reported (Gadducci et al., 2007). Transmission of ovarian cancer to a kidney recipient is reported (Bellati et al., 2009) but the donor had no history of cancer. In the cohort I studied, two donors with mean cancer-free period of 12.4 years donated four organs to three recipients without transmission of cancer. In the OPTN/UNOS cohort (Kauffman et al., 2007), there were 75 transplants (and no transmission) from donors with ovarian cancer of which 85% donors had been cancer-free for 10 or more years. Based on this evidence it can be recommended that organs from donors with past ovarian cancer, cancer-free for more than ten years can be considered for transplantation following informed consent.

4.5.5.4 Donors with past colon cancer

Recurrence of colon cancer following curative surgery is uncommon after five years although long-term follow-up data are sparse as most surveillance programmes stop after five years. Late recurrence in 1.6% of all surgically treated colorectal cancers is reported (Cho et al., 2007). Cancer of the left colon/rectum accounted for 95% of recurrences. Two cases of transmission of colon cancer from donors with brain death due to cerebral

metastases are reported (Buell et al., 2004). In addition to the data from the UK Transplant Registry presented in this chapter, at least two other registry reports (Kauffman et al., 2007, Birkeland and Storm, 2002) have reported no transmission of colon cancer from donors after a minimum cancer-free period of five years. Based on this evidence, it can be recommended that organs from a donor with non-metastatic colon cancer surgically resected at least five years prior to donation can be considered for transplantation after risk assessment and informed consent.

4.5.5.5 Donors with past sarcoma/lymphoma

Three of the four donors with sarcoma and one donor with lymphoma in my study were diagnosed within the week before donation and this information was not available to the transplanting team. Therefore, it is not possible to suggest changes to the current recommendations about the transmission risk of lymphoma/sarcoma.

Table 4.5 Suggested changes to present guidelines: donor cancers proposed to have a low risk (NHSBT, 2014c)

Cancer type	Characteristics
Melanoma	Superficial spreading subtype Tumour (Breslow) thickness < 1mm Curative Surgery Minimum cancer-free period of 5 years
Breast cancer	Stage I Hormone receptor negative Curative surgery Minimum cancer-free period of 5 years
Ovarian cancer	Curative surgery Minimum cancer-free period of 10 years
Colon cancer	Curative surgery Minimum cancer-free period of 5 years

4.5.6 Impact on the number of organs available for transplantation

The information obtained from the potential/possible donors demonstrates that an increase in the number of donor organs can be achieved by including selected donors with past cancer. The details of the cancers among potential/possible donors recorded on the UK Transplant registry was significantly less than the data recorded by the Cancer registries. There were also many potential/possible donors who were recorded as having 'medical contraindication to donation' in some of whom the medical contraindication may have been a past history of cancer. Therefore, the estimated number of additional organs of 5 per year is likely to be an underestimate. Considering the high mortality of patients on the transplant waiting list, these additional organs are likely to make a real difference to the outcomes especially in cases where an urgent life-saving transplantation is needed.

4.5.7 Role of informed consent

In the UK, the guidelines for consenting potential adult recipients for transplantation are published by NHSBT and the British Transplantation Society (NHSBT, 2011). These specify that the risks of transplantation should be explained to the recipient at two stages: at the time of listing for transplantation and at the time of the offer of an organ. The risk of cancer transmission (0.05% in the UK, as discussed in Chapter 3) should be explained at the time of listing. A list of donor details, which the recipient is entitled to know, is specified including whether the donor has high risk of cancer transmission. Although the risk of cancer transmission is small, the outcome for the recipient when a transmission occurs is poor in terms of graft loss and/or recipient survival, hence informed consent is vital.

In conclusion, it is clear that there is an overall benefit in survival if organs from selected donors with a history of cancer are used for transplantation. Surgeons are faced with difficult decisions when offered an organ from a higher risk donor. Guidelines, designed to facilitate making these decisions, may have the unintended consequence of reducing the survival of those listed for transplantation. The data presented in this chapter confirm that surgeons make balanced and appropriate judgement although it is not possible to accurately estimate how many donor organs with similar risk are declined. There is a real but small risk of cancer transmission so the potential recipients need to be advised of these risks and understand that, while risks can be reduced by careful assessment, they cannot be abolished. (Desai et al., 2014)

CHAPTER 5

RECURRENCE OF CANCER IN ORGAN TRANSPLANT RECIPIENTS

5.1 Introduction

Although organ transplantation is highly effective in improving both the quality and the length of life in patients with end-stage organ failure, because of the relative shortage of organs, the offer of transplantation is limited to patients who would benefit the most: for example in the UK, a predicted survival of less than 50% at 5 years is generally a contraindication for liver transplantation (NHSBT, 2012). Co-morbid conditions in the recipient are among the important factors influencing the overall benefit from transplantation. An increased risk of cancer in patients with liver and kidney disease compared with a matched general population is recognised: 18% increase in standardised risk of all cancers among patients with renal failure and 100% increase in patients with cirrhosis (Sorensen et al., 1998, Maisonneuve et al., 1999). Five to 10% of patients on the transplant waiting list are known to have a history of cancer (Mosconi et al., 2011, Fischereder and Jauch, 2005). Furthermore, as the age of transplant candidates is increasing, the probability of a history of cancer will be greater.

All recipients of organ transplantation are at an increased risk of de novo cancer compared with the matched general population. In addition, those recipients with a history of cancer treated prior to transplantation are at an added risk of recurrence of such cancers after transplantation. The clinical course of cancer is shown to be more aggressive in the immunosuppressed transplant recipient (Barrett et al., 1993, Veness et al., 1999, Martinez et al., 2003). Therefore, a thorough understanding is essential, of the risk of recurrent cancer in determining access to transplantation, follow-up and surveillance after transplantation and, potentially, the choice of immunosuppression.

However, there are limited data regarding rates of recurrence following transplantation of cancers treated prior to transplantation. The IPITTR (Penn, 1993, Penn) remains the most widely used database on which the present recommendations for listing are based, but these data are not comprehensive and may be subject to important bias. The IPITTR is a registry of cases reported voluntarily, so it does not include all cases of transplantation performed. So the denominator to calculate the rates of cancer is incomplete. Additional information regarding the cancer recurrence following transplantation and the outcome following recurrence in recipients of different organs will be useful in ensuring just selection of prospective recipients for transplantation and equitable use of scarce donor organs. In this chapter, the outcomes of solid organ allograft recipients with a history of cancer with respect to recurrence of cancer are discussed.

5.2 Aims

The aims of this chapter are:

1. To identify the proportion of transplant recipients with a history of cancer prior to transplantation
2. To study which of these recipients developed a recurrence of cancer following transplantation
3. To study the outcome of transplant recipients with a recurrence of cancer

5.3 Methods

5.3.1 Data

The recipients of first solid organ transplantation from deceased and living donors who were transplanted between 1st January 1985 and 31st December 2010 were identified from the UK Transplant Registry. Although the data for primary diagnosis of cancer are recorded by all the cancer registries in the UK, the practice of recording the data regarding the recurrence of cancers is not uniform across different cancer registries. The data were restricted to recipients residing in the West Midlands region of the UK (which had a population 5.6 million in 2011) as the data regarding recurrence of cancer were recorded by the West Midlands Cancer Intelligence Unit for the duration of this study. The cases of recurrence of cancer were recorded following confirmation by histology, imaging and/or clinical evidence. The details of the recipients undergoing transplantation during the study period were obtained from the UK Transplant Registry (name, dates of birth and death, gender, address, NHS number) and matched with the data held by the West Midlands Cancer Intelligence Unit. Those recipients who were diagnosed to have new or recurrent cancer (excluding non-melanoma skin cancer, as these data were unavailable) were identified. The cancers diagnosed before the date of transplantation and recurrences after transplantation were included. The 51 liver recipients transplanted with cancer of the liver (including hepatocellular cancer, hepatoblastoma, cholangiocarcinoma or embryonal sarcoma) were excluded.

For recipients with multi-organ transplantation, recipients of kidney-pancreas (n=75), kidney-liver (n=13) and kidney-heart (n=2) were included with kidney recipients. The recipients of liver-pancreas, liver-heart and liver-lung (n=1 each) were included with liver

recipients. The recipients of heart-lung (n=74) were included with heart recipients. The recipients of pancreas only (n=7) were excluded.

5.3.2 Statistical Analysis

The survival of recipients with and without a pre-transplant cancer was analysed using Kaplan-Meier estimates and compared using the log rank test. All calculations were performed using Statistical Analysis Software, version 9.3 (SAS Institute, Cary).

5.4 Results

5.4.1 Study cohort

The study cohort of 4835 recipients included 3321 (69%) kidney, 821 (17%) liver, 495 (10%) heart and 198 (4%) lung recipients. A history of cancer was noted in 64 (of 4835, 1.32%) recipients including one recipient with two cancers. Table 5.1 shows the age, gender and survival of these recipients.

Table 5.1 Recipients with and without a pre-transplant cancer: comparison of age, gender and survival of recipients of different organs

	Recipients with pre-transplant cancer				Recipients without pre-transplant cancer			
	Number (%)	Mean age in years (95% CI)	Gender M (%)	Median survival in years (95% CI)	Number (%)	Mean age in years (95% CI)	Gender M (%)	Median survival in years (95% CI)
Kidney	35 (1)	57.0 (54, 63)	19 (54)	11.76 (9.23,-)	3286 (99)	43.0 (42, 44)	2041 (62)	20.28 (18.67, 22.97)
Liver	16 (2)	53.5 (50, 62)	7 (44)	7.53 (0.05, -)	805 (98)	47.0 (44, 48)	395 (49)	17.50 (15.27, 20.76)
Heart	8 (2)	34.5 (14, 61)	5 (63)	5.75 (0.01, 5.75)	487 (98)	46.0 (44, 47)	380 (78)	8.62 (7.16, 10.59)
Lung	5 (3)	56.0 (33, 58)	4 (80)	-	193 (97)	53.0 (50, 54)	111 (58)	3.35 (1.51, 6.40)

5.4.2 Recipients with recurrence of cancer after transplantation

Of the 64 recipients with a history of cancer, 5 developed recurrence with a rate of recurrence within 10 years of transplantation of 11.9% (95%CI 0.4, 23.5). For each of these five recipients, the time from diagnosis of primary cancer to transplantation and the time from transplantation to recurrence of cancer are shown in Table 5.2. Melanoma was the most common cancer to recur (3 cases) followed by leiomyosarcoma and testicular germ cell cancer (1 each). In all five cases, the recipients died as a direct consequence of recurrent cancer.

Table 5.2 Recipients with recurrence of cancer after transplantation

Recipient No	Type of cancer	Time from diagnosis of primary cancer to transplantation (days)	Time from transplantation to recurrence (days)	Outcome
1	Melanoma	5	4294	Death due to cancer
2	Melanoma	745	421	Death due to cancer
3	Melanoma	559	573	Death due to cancer
4	Leiomyosarcoma	190	1199	Death due to cancer
5	Germ cell tumour of testis	1627	2100	Death due to cancer

5.4.3 Recipients without recurrence of cancer after transplantation

There were no cases of cancer recurrence among 59 recipients with a history of cancer at a median follow-up of 4.0 years (95%CI 2.9, 5.8). Of these, 38 (65%) had been cancer-free for more than 5 years at the time of transplantation, 9 (15%) had been cancer-free for less than 2 years and in the remaining 12 recipients (20%) the cancer-free period was between 2 and 5 years (Table 5.3). Of the 9 recipients undergoing transplant within 2 years of cancer diagnosis, 4 received liver transplants (1 urgent), 2 received heart transplants (both urgent) and the remaining 3 received kidney transplants.

Table 5.3 Recipients without cancer recurrence (numbers is brackets indicate the number of recipients with cancer)

Cancer-to-transplant duration > 5 years	Cancer-to-transplant duration 2 - 5 years	Cancer-to-transplant duration < 2 years
Bladder - transitional cell cancer (3)	Bladder cancer (1)	Acute myeloid leukaemia (3)
Osteosarcoma (1)	Osteosarcoma (1)	Chronic myeloid leukaemia (1)
Breast – adenocarcinoma (6)	Breast adenocarcinoma (1)	Parathyroid carcinoma (1)
Cervix – adenosquamous carcinoma (1)	Colorectal adenocarcinoma (2)	Breast adenocarcinoma (1)
Colorectal cancer (4)	Prostate adenocarcinoma (2)	Colorectal adenocarcinoma (1)
Acute leukaemia (myeloid 1, lymphoid 1)	Thyroid adenocarcinoma (1)	Renal cell carcinoma (2)
Lymphoma (Hodgkin's 3, Non-Hodgkin's 3)	Renal cell carcinoma (1)	
Kidney: Renal cell carcinoma (2), Nephroblastoma (2)	Nephroblastoma (1)	
Nasopharyngeal carcinoma (1)	Hepatoblastoma (1)	
Oral cavity: adenocarcinoma (1)	Lung (1)	
Penis: squamous cell carcinoma (1)		
Prostate: adenocarcinoma (2)		
Melanoma (1)		
Testis: endodermal sinus tumour (1)		
Thyroid: adenocarcinoma (2)		
Uterus: adenocarcinoma (3)		

5.4.4 Impact of immunosuppression on the risk of recurrence

The available immunosuppression data were limited to the agent the recipients were receiving at the time of transplantation, at 3 months and 12 months post-transplantation. The data were available for azathioprine (77% recipients), ciclosporin (70%), tacrolimus (14%) and MMF (42%). Cox regression analysis was performed to assess the use and non-use of these agents individually, with correction for age and gender. This analysis showed no association between immunosuppressive agent and the risk of cancer recurrence. These results are shown in Table 5.4.

Table 5.4 Impact of individual immunosuppressive agents on the risk of recurrence of cancer after transplantation

		Number of recipients		Hazard ratio (95% CI)	p-value
		With cancer recurrence	Without cancer recurrence		
Azathioprine	Not used	1	16	1	
	Used	3	29	1.00 (0.08, 12.55)	0.998
	No data	1	14	0.35 (0.01, 11.60)	0.55
Ciclosporin	Not used	2	17	1	
	Used	2	23	0.24 (0.02, 3.41)	0.29
	No data	1	19	0.15 (0.01, 3.70)	0.25
Tacrolimus	Not used	1	7	1	
	Used	0	1	-	
	No data	4	51	0.22 (0.02, 2.50)	0.22
MMF	Not used	1	11	1	
	Used	0	15	-	
	No data	4	33	3.30 (0.19, 57.08)	0.41

5.5 Discussion

5.5.1 Summary of findings and comparison with literature

In this study, a majority of the recipients with a pre-transplant cancer (59 of 64, 92%) did not develop a recurrence after transplantation, including 50 recipients (78%) with at least 2-year wait between the diagnosis of cancer and transplantation.

In the IPITTR report (Penn, 1993), of the 185 recipients with recurrence of cancer, 53% had waited for transplant for less than 2 years after cancer, 34% had waited for transplant between 2 and 5 years after cancer. There were 13% cases of recurrence in recipients who had waited for transplantation for more than five years after cancer whereas in the cohort I studied, there were no cases of recurrence among 38 recipients. The reasons for the differences between the two studies are likely to include the differences in the recipient cohort, time of the study, method of reporting and the definition of a recurrence. The IPITTR report was based on voluntary reporting from transplant centres around the world, over a period of 24 years. Whilst the number of patients is a clear strength, interpretation of the findings is limited by the nature of the registry in that the denominator (the number of all the transplantations performed during the study period) is not known, hence the study was not comprehensive and it is not possible to calculate the rate of recurrence accurately. Furthermore, as the authors acknowledged (Penn, 1993), they could not distinguish true recurrences from de novo post-transplant cancers. The other limitation in interpreting the recurrence rates reported in the IPITTR study is that it included post-transplant recurrences of both post-transplant cancers as well as cancers diagnosed before transplantation.

In the literature, there are other reports describing recurrence of cancer among transplant recipients: these are summarised in Table 5.5.

Table 5.5 Published cases of transplant recipients with a history of cancer

Author, year	Transplant	Recipients with pre-transplant cancer	Cancer-free period at transplantation (mean, range)	Post-transplant recurrence		
				Cancer type	Cancer-free period at transplantation	Outcome
Dillon, 1991 (Dillon et al., 1991)	Heart	7 (breast [2], endometrium, bladder, testis, leukaemia and skin:basal cell cancer)	6.4 years (20 days to 14 years)	Basal cell cancer*		No death related to cancer recurrence
Ladowski, 2006 (Ladowski et al., 2006)	Heart	13 (breast[4], uterus, bladder [2], testis, sarcoma, lymphoma [2], leukaemia and skin:basal cell cancer)	6.2 years (0 to 26 years)	None		
Metcalfe, 2010 (Metcalfe et al., 2010)	Lung / Heart-lung	23 (skin:basal cell [3], skin:squamous cell [2], lung[5], cervix [3], breast [2], melanoma [2], prostate, myxosarcoma, uterus, leukaemia, renal, bladder	7.4 years (0 to 27 years)	Myxosarcoma, breast	Myxosarcoma: 1.7 years Breast: 7.2 years	Death due to cancer in both cases
Saigal, 2001 (Saigal et al., 2001)	Liver	18 (myeloproliferative disorder[6], colon [4], lymphoma, breast, bladder, melanoma, skin:basal cell, renal, thyroid, uterus)	2.6 years (0 to20 years)	NHL	NHL: 23 months	Alive at 31 months

Author, year	Transplant	Recipients with pre-transplant cancer	Cancer-free period at transplantation (mean, range)	Post-transplant recurrence		
				Cancer type	Cancer-free period at transplantation	Outcome
Benten, 2008 (Benten et al., 2008)	Liver	37 (myeloproliferative disorder[7], NHL[3], leukaemia, leiomyosarcoma, ovary, cervix[2], vulva, uterus, breast[2], oral, melanoma[3], skin:basal cell[2], tests[2],prostate, renal, colon [3], rectum, osteoclastoma, oligodendroglioma, desmoid tumour, neurofibroma),	3.7 years (0 to 26 years)	Colon	Colon cancer: found incidentally at transplantation	Death due to cancer
Kelly, 1998 (Kelly et al., 1998)	Liver	29 (skin:squamous cell, skin: basal cell[5], Hodgkin's lymphoma [5], palate [4], colon [3], thyroid [3], breast [2], larynx [2], melanoma [2], uterus, gall bladder, lung, gastric carcinoid)	8.7 years (0.5 to 35 years)	Breast (2), palate, thyroid (papillary)	Breast: 5 and 7 years (stage III), palate: 8 months, thyroid: 4 years	Breast cancer: death due to cancer
Dousset,1995 (Dousset et al., 1995)	Liver	5	2.5 years (0 to 4 years)	None		
Chapman, 2001 (Chapman et al., 2001)	Kidney	210	NS	Kidney, melanoma, cervix(2 each), bladder, prostate	NS	NS

*Authors acknowledged that this could be a de novo caner related to Sun exposure

In contrast to the IPITTR report (Penn, 1993), other published reports shown in Table 5.5 and the results of the cohort I studied demonstrate a lower rate of recurrence. The factors contributing to these differences are likely to include the criteria used for selection of recipients, choice of immunosuppressive agent and post-transplant cancer surveillance and reporting bias. Among the cases listed in Table 5.5, with the exception of three cases of breast cancer (that recurred in spite of a pre-transplant cancer free period of 5, 7 and 7.2 years) all the other cases which recurred post-transplantation had been treated within 5 years before transplantation.

Present guidelines for selection of transplant candidates include the guidelines from American Society of Transplantation (Kasiske et al., 2001) European best practice guidelines for renal transplantation (Europeanguidelines, 2000) and the UK Renal Association guidelines (Renalassociation, 2011). These guidelines recommend that most patients with a previous cancer would benefit from a two-year wait before transplantation. Some cancers such as non-melanoma skin cancers, in-situ cancers and small renal cell cancers (under 5cm) discovered incidentally do not require a waiting period before transplantation and some cancers with a high risk of recurrence such as large (over 5cm) or invasive renal cell cancers, breast cancer, colon cancer (other than Dukes A or B1) or melanoma require a minimum waiting period of 5 years before transplantation. However, it is evident from the data presented in Table 5.2 that selected recipients can benefit with recurrence-free post-transplant survival even when the wait between cancer and transplant is shorter, although emphasis should be placed on the need for rigorous pre-transplant assessment, careful selection and close post-transplant monitoring.

5.5.2 Impact of immunosuppression

The mechanism of action of different immunosuppressive agents, their side effects and the impact of immunosuppression on post-transplant cancer has been discussed in Sections 1.6 and 1.7. There is limited evidence assessing the impact of immunosuppression on the risk of cancer recurrence following transplantation. The impact of different immunosuppressive agents varies. This is discussed here.

5.5.2.1 Calcineurin inhibitors – ciclosporin and tacrolimus

These are used in nearly all regimens (Kapturczak et al., 2004). Both ciclosporin (Hojo et al., 1999) and tacrolimus (Maluccio et al., 2003) amplify the growth and metastatic potential of cancer cells in mouse models, primarily by increasing TGF-β1 expression. The risk of cancer in patients using ciclosporin is higher than the risk of cancer in patients using azathioprine in several epidemiological studies (Shuttleworth et al., 1989, Kyllonen et al., 2000, Hiesse et al., 1997, Marcen et al., 2003, Tremblay et al., 2002) but studies comparing ciclosporin against tacrolimus have been inconclusive. While animal models suggest that ciclosporin is associated with more aggressive tumour growth, this has been seen less clearly in humans (Webster et al., 2005, Bustami et al., 2004, Caillard et al., 2005).

5.5.2.2 mTOR inhibitors – Sirolimus and everolimus

Sirolimus and everolimus exert their immunosuppressive effect by blocking the mTOR pathway and subsequent blockage of IL-2 mediated T cell activation. Several clinical studies have shown a lower risk of de novo cancer after transplantation when sirolimus is used as primary immunosuppression (Alberu et al., 2011, Mathew et al., 2004, Campistol et al.,

2006). However, there is limited evidence supporting use of sirolimus to reduce the risk of recurrence of previously treated cancer.

The data presented here must be treated with some caution. Although the results of my study compare favourably with other series, the number recipients is relatively small so misleading conclusions may be drawn by generalisation of conclusions. The conclusions from this cohort in the West Midlands of the UK may not be directly applicable to transplant candidates in other countries. The patients who underwent organ transplantation were carefully evaluated prior to transplant and so are likely to represent a selected cohort and any conclusions drawn from this analysis may not be directly applicable to all candidates. The data regarding immunosuppression were limited to the name of immunosuppressive agents at three time points within the first year of transplantation. Most transplant recipients receive varying immunosuppressive agents in varying doses during their post-transplant period and such limited data would not capture the degree of immunosuppression accurately. It is therefore difficult to develop robust evidence-based guidelines to help identify patients with pre-existing cancer who may not benefit with transplantation because of lack of data, with small number of patients reported, inconsistency of reporting, the diversity in the type, stage and treatment of cancer and the immunosuppressive regimen. Prospectively and rigorously collected data by national transplant registries including data on type, stage, treatment of pre-transplant cancer, immunosuppression, surveillance, details of recurrence and outcome after recurrence would be useful.

CHAPTER 6

CYTOMEGALOVIRUS AND CANCER RISK AFTER TRANSPLANTATION

(Data and text from this chapter have been published (Desai et al., 2015))

Disclaimer

This is to confirm that some of the text and data included in this Chapter has been published in peer-reviewed journal (Desai et al., 2015). Inclusion of this work has been approved by the Editor of the journal.

The published manuscript is included in the Appendix 3.

I confirm that all the work reported in this manuscript has been done be myself except where stated. This includes designing the study, conducting literature search, data collection, data analysis, interpretation of results and writing the manuscript. Apart from the text referenced to other sources, I wrote all the text in the publication and prepared all the Tables and Figures.

Professor James Neuberger and Professor Philip Johnson supervised this work and helped with the design of the study. Professor Dave Collett supervised the statistical analysis which I performed independently. Professor Christopher Watson helped with facilitating the collection of data from the transplant centres. Professor Paul Moss helped with data interpretation and made minor suggestions to the manuscript.

All the coauthors read and approved the final manuscript in line with current guidance and suggested minor changes.

6.1 Introduction

CMV infection is common affecting 50 to 80% of adult population (CDC, 2010). The initial infection, which usually occurs in childhood, is either subclinical or characterised by mild non-specific self-limiting symptoms. This is followed by a state of life-long chronic viral carriage. In an immunocompetent host, the CMV infection is generally well controlled but in the immunosuppressed, it is often associated with significant morbidity. Some viruses, such as HPV, HBV, HCV, EBV and HHV-8 have an established role in the development of cancer both in the immunocompetent and the immunosuppressed organ transplant recipient populations. There is limited evidence assessing the association of CMV and cancer. While CMV antigens have been identified in cells of certain tumours such as cancers of the colon, prostate, lymphoma and glioblastoma (Soderberg-Naucler, 2006), it is not known if the presence of CMV is an epiphenomenon or whether there is a causative association. Epidemiological studies investigating the association between CMV and post-transplant cancer have shown conflicting evidence: some have shown a protective effect (Couzi et al., 2010) whereas others, an increased risk (Courivaud et al., 2012). These studies have important limitations including relatively small cohort size and lack of long-term follow-up data.

Although survival after transplantation is increasing, recipients of solid organ transplantation remain at increased risk of premature death (Lindholm et al., 1995, Morales et al., 2012, Pruthi et al., 2001, Blankenberg et al., 2001, Muhlestein et al., 2000). Important causes of this increased mortality are cardiovascular disease, cancer, infection and recurrent disease. While some studies, both in the normal and the transplant population, have found

an increased risk of cardiovascular disease and death in CMV infected individuals (Blankenberg et al., 2001, Thomas et al., 2009, Zhou et al., 1996, Li et al., 2007), this has not been confirmed by all (Zhu et al., 1999, Johnson et al., 2009, Kaufman et al., 2001, Arthurs et al., 2007). However, all the studies in the transplant population have been relatively short term (less than five years).

In this chapter, the risk of development of post-transplant cancer and its association with the CMV status of the organ donor and the recipient are discussed.

6.2 Aims

The aims of this chapter are:

1. To assess the CMV status of organ donor (D) and recipient (R) and association of the CMV status with the risk of post-transplant cancer
2. To study the impact of D/R CMV status on the post-transplant recipient survival
3. To study the association of D/R CMV status with the cause of death among transplant recipients

6.3 Methods

6.3.1 Study cohort

Using the data held by the UK Transplant Registry, the recipients of first solid organ (kidney, liver, heart, lung) transplantation between 1st January 1987 and 31st December 2007 who

were resident in England, Wales or Scotland were identified. This duration was selected, as the available registry CMV data were limited to this period. The transplants where the CMV IgG status was not recorded for the donor or the recipient were excluded (n=12228, 35% of all the transplant recipients). Recipients of combined kidney-pancreas (n=764) were grouped with the kidney recipients and recipients of double-lung or heart-lung transplants (n=553) were grouped with the lung recipients. The recipients were divided into four groups based on the combination of donor and recipient CMV IgG status at the time of transplantation: both donor and recipient CMV positive (D+R+) or negative (D-R-), CMV positive donor with CMV negative recipient (D+R-) and CMV negative donor with CMV positive recipient (D-R+).

6.3.2 Data

Transplant and CMV data were obtained from the UK Transplant Registry. Cancer registration data were obtained from the Office for National Statistics by matching the details of the recipients (name, gender, date of birth/death, address and NHS number). All types of cancers other than non-melanoma skin cancer (for which data were unavailable) were included. The data for the first diagnosed cancer following transplantation were included. To exclude the cancers which may have been present at the time of transplantation, all cancers other than Hodgkin's lymphoma or Non-Hodgkin's lymphoma diagnosed within a month of transplantation were excluded.

6.3.3 Statistical analysis

Kaplan-Meier analysis and logrank test were used to assess the long-term post-transplantation patient survival. The risk-adjusted hazard of death was calculated using Cox proportional hazards model, correcting for the those risk factors that have been identified by NHSBT as having a significant impact on survival (NHSBT, 2010). Risk adjusted hazard of death for different solid organ recipients are shown separately because the risk adjustment varies. The risk factors included were: donor age, recipient age, donor sex, recipient sex, donor type (kidney and lung recipients), donor cause of death (kidney and heart recipients), transplant year, primary disease (kidney, liver and heart recipients), HLA mismatch (kidney recipients) and ischemia time (cold ischemia for liver, total for heart/lung). For this assessment, death of the recipient within ten years (or one year, when 1-year survival was assessed) was considered as an event and the recipients who were alive at ten years (or one year, when 1-year survival was assessed) from transplantation and those who were lost for follow-up were censored.

During Cox regression, missing data for a categorical covariate were grouped together as 'unknown' category. The recipients with missing ischemia time (12% of liver recipients, 35% of cardiothoracic recipients) were excluded from multivariate analysis using Cox regression only. The times to diagnosis of cancer in the four CMV groups were compared using the logrank test. Cox proportional hazards modelling was also used to assess the time to a diagnosis of cancer in various CMV groups with censoring at 10 years for those who survived to that time without the diagnosis of cancer. The factors used for risk-adjustment in this analysis were recipient age and gender. For this assessment, a diagnosis of cancer within ten years of transplantation was considered as an event and times to any other end-point in

absence of a diagnosis of cancer, such as death or end of follow-up were considered as censored survival times.

While comparing the hazard of multiple types of cancers in different CMV groups the Bonferroni correction was used to assess statistical significance in order to avoid inflating the overall type I error above its nominal level for each test. This involved using a significance level of 0.05/n, where n is the number of comparisons, to give an overall 5% significance level. The causes of death between the D-R- groups and other recipient group were compared using the chi square test. All data were analysed using SAS version 9.3 (SAS Institute, Cary).

6.4 Results

A total of 22461 recipients were studied, including 13215 (59%) kidney recipients, 4814 (21%) liver recipients, 2686 (12%) heart recipients and 1746 (8%) lung recipients. The baseline characteristics of the recipients in different CMV groups are shown in Table 6.1.

Table 6.1 Characteristics of recipients in different CMV groups

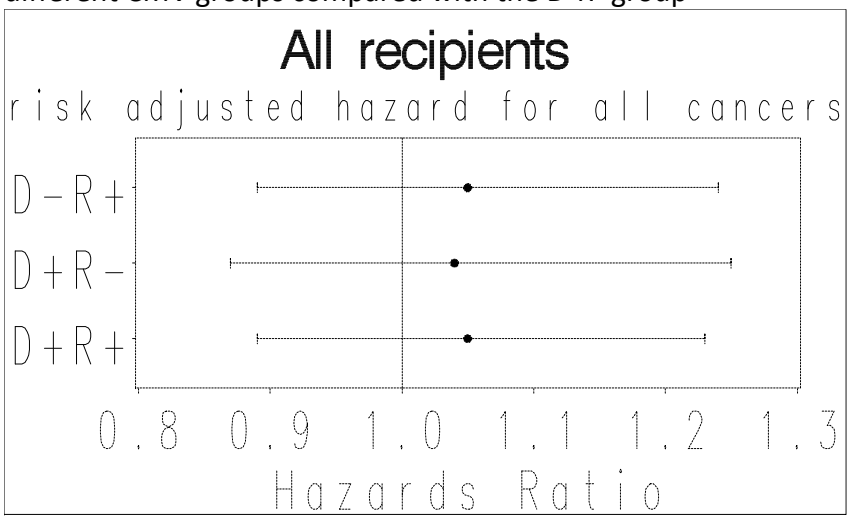
CMV status	Recipient details			
	N	Mean age In years (95% CI)	Male	Median follow-up in years (95% CI)
D+R+	6666 (30%)	47.6 (47.3, 47.9)	3985 (60%)	8.0 (7.9, 8.1)
D+R-	4520 (20%)	41.3 (40.8, 41.8)	2926 (65%)	7.6 (7.2, 7.8)
D-R+	5754 (26%)	46.7 (46.3, 47.1)	3415 (59%)	7.8 (7.6, 7.9)
D-R-	5521 (25%)	37.6 (37.1, 38.0)	3528 (64%)	8.0 (7.9, 8.3)
Total	22461 (100%)	43.6 (43.4, 43.9)	13854 (62%)	7.9 (7.8, 7.9)

6.4.1 Risk of cancer among recipients in different CMV groups

The unadjusted incidence of all cancers was 8.8% (95% CI 7.9, 9.6) among D+R+ group, 7.0% (6.0, 7.9) among D+R- group, 9.1% (8.1, 10.1) among D-R+ group and 6.4% (5.5, 7.3) among D-R- group and this difference was statistically significant ($p<0{\cdot}0001$). However, there was no statistically significant difference in the risk-adjusted hazard of all cancers between these groups following correction for age and gender. In this assessment, along with adjustment of risk for age (which is a recognised risk factor for cancer), I also adjusted for gender because male gender was found to be an independent risk factor for cancer even after excluding those cancers which are gender specific such as cancer of cervix, ovary uterus and prostate (HR for male 1.36, $p<0.0001$).

The risk-adjusted hazard ratios and 95% confidence intervals are shown in Figure 6.1.

Figure 6.1 Risk-adjusted hazard of cancer within 10 years of transplantation, among different CMV groups compared with the D-R- group



6.4.2 Risk of individual types of cancer among recipients in different CMV groups

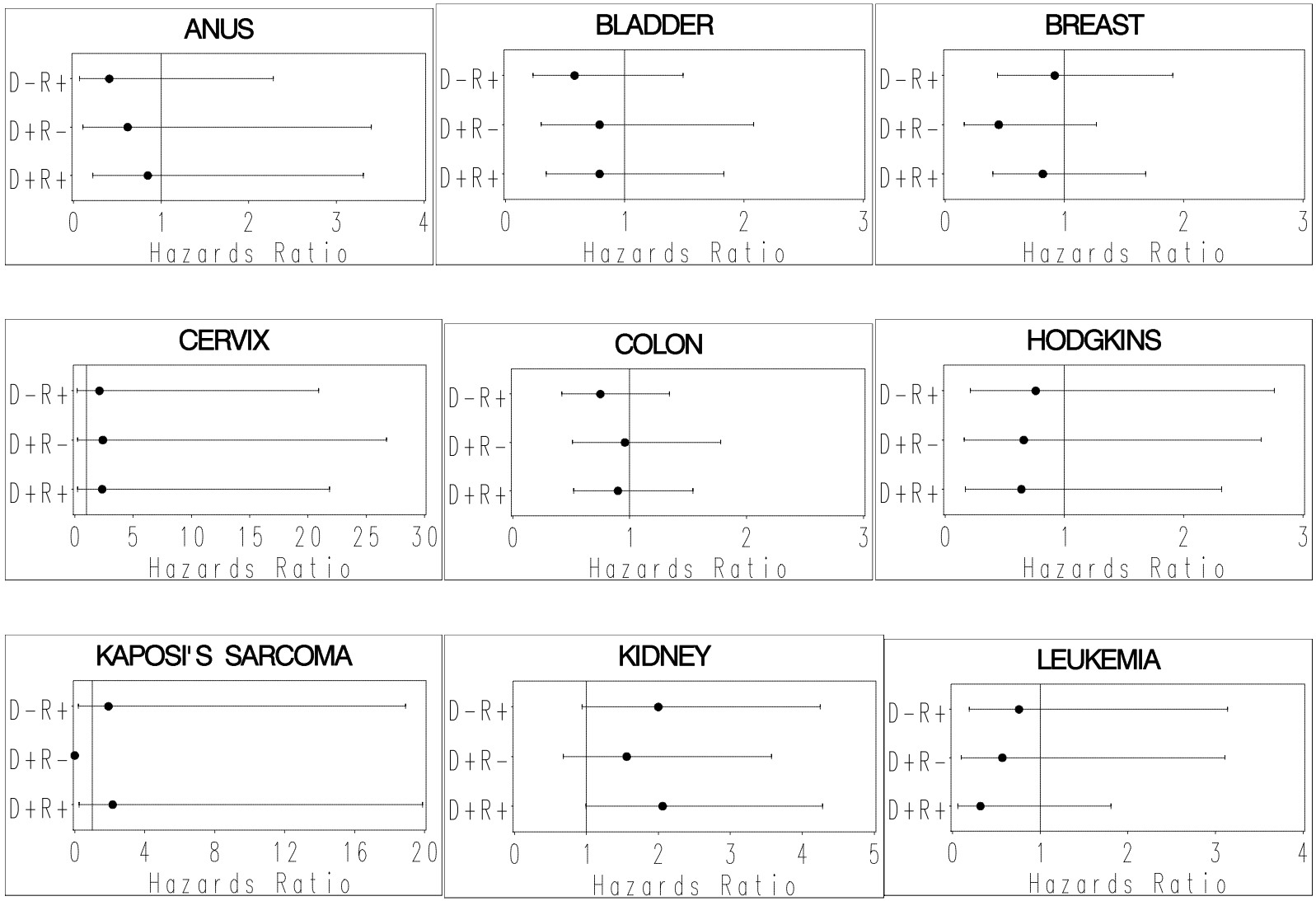
The risk of 23 different types of cancer was compared between the recipients in different CMV groups. Table 6.2 shows the frequency and unadjusted incidence of 23 types of cancers among the recipients in different CMV groups. The risk-adjusted hazard of different types of cancers is shown as forest plots in Figure 6.2.

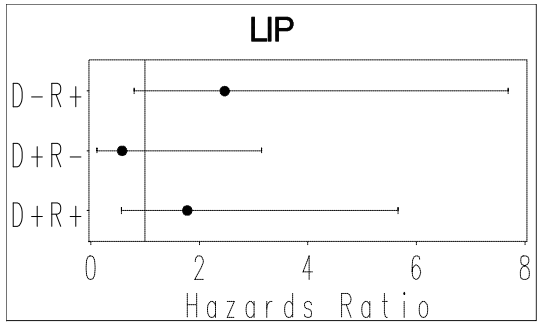
Table 6.2 Frequency and unadjusted incidence of different types of cancers in the recipient groups based on CMV status

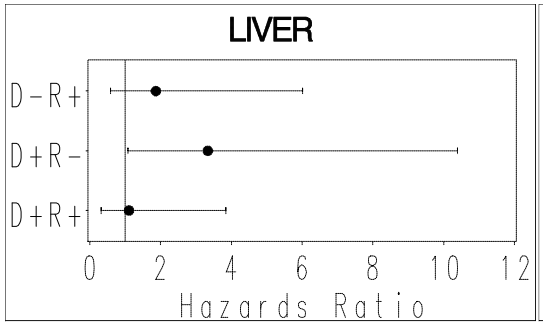
	Number of recipients (% incidence ± 95%CL)					
Cancer type	D+R+	D+R-	D-R+	D-R-	p-value	Total
Anus	7 (0.13 ±0.12)	2 (0.06 ±0.087)	4 (0.07 ±0.095)	5 (0.12 ±0.12)	0.78	18 (0.10 ±0.06)
Bladder	13 (0.29 ±0.16)	7 (0.24 ±0.18)	8 (0.22 ±0.16)	10 (0.28 ±0.18)	0.91	38 (0.26 ±0.09)
Breast	21 (0.45 ±0.20)	5 (0.17 ±0.16)	19 (0.52 ±0.25)	12 (0.31 ±0.18)	0.097	57 (0.38 ±0.10)
Cervix	4 (0.18 ±0.18)	2 (0.21 ±0.28)	3 (0.18 ±0.20)	1 (0.12 ±0.24)	0.77	10 (0.17 ±0.11)
Colon	37 (0.92 ±0.31)	19 (0.60 ±0.28)	26 (0.69 ±0.27)	21 (0.58 ±0.25)	0.50	103 (0.71 ±0.14)
Hodgkin's lymphoma	4 (0.10 ±0.10)	3 (0.12 ±0.14)	4 (0.14 ±0.14)	6 (0.17 ±0.14)	0.81	17 (0.13 ±0.06)
Kaposi's sarcoma	4 (0.08 +0.08)	0	3 (0.06 ±0.0.07)	1 (0.02 ±0.02)	0.30	8 (0.04 ±0.03)
Kidney	28 (0.64 ±0.25)	13 (0.49 ±0.27)	23 (0.72 ±0.31)	10 (0.30 ±0.50)	0.076	74 (0.54 ±0.13)
Leukaemia	2 (0.05 ±0.07)	2 (0.05 ±0.07)	4 (0.08 ±0.08)	4 (0.10 ±0.10)	0.72	12 (0.07 ±0.04)
Lip	11 (0.28 ±0.17)	2 (0.07 ±0.10)	13 (0.41 ±0.23)	4 (0.11 ±0.11)	0.035	30 (0.23 ±0.08)
Liver	7 (0.13 ±0.10)	12 (0.35 ±0.21)	10 (0.23 ±0.15)	4 (0.11 ±0.11)	0.048	33 (0.19 ±0.07)
Lung	54 (0.12 ±0.34)	23 (0.80 ±0.33)	39 (0.11 ±0.34)	24 (0.71 ±0.29)	0.037	140 (0.97 ±0.17)
Myeloma	4 (0.08 ±0.08)	5 (0.17 ±0.15)	9 (0.26 ±0.17)	4 (0.10 ±0.09)	0.30	22 (0.14 ±0.06)

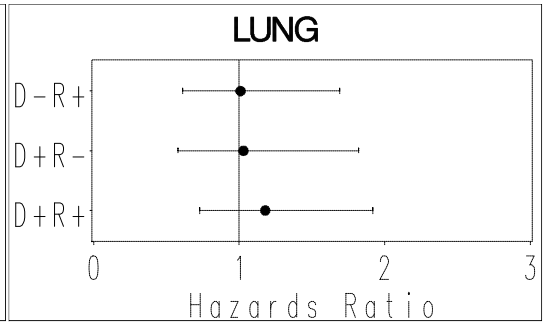
	Number of recipients (% incidence ± 95%CL)					
Cancer type	D+R+	D+R-	D-R+	D-R-	p-value	Total
Non-Hodgkin's lymphoma	77 (1.8 ±0.41)	46 (1.4 ±0.43)	78 (2.0 ±0.45)	60 (1.6 ±0.41)	0.35	261 (1.7 ±0.21)
Oesophagus	6 (0.13 ±0.26)	1 (0.03 ±0.05)	5 (0.13 ±0.12)	6 (0.16 ±0.13)	0.49	18 (0.12 ±0.06)
Oral cavity	3 (0.06 ±0.07)	8 (0.26 ±0.18)	6 (0.15 ±0.12)	7 (0.20 ±0.16)	0.19	24 (0.16 ±0.07)
Ovary	3 (0.15 ±0.17)	1 (0.08 ±0.15)	5 (0.37 ±0.34)	4 (0.27 ±0.26)	0.59	13 (0.22 ±0.13)
Pancreas	4 (0.09 ±0.10)	4 (0.17 ±0.17)	6 (0.17 ±0.14)	4 (0.08 ±0.08)	0.82	18 (0.12 ±0.06)
Prostate	22 (0.79 ±0.34)	13 (0.71 ±0.40)	17 (0.84 ±0.41)	18 (0.80 ±0.39)	0.95	70 (0.79 ±0.19)
Skin: melanoma	12 (0.25 ±0.15)	9 (0.30 ±0.20)	6 (0.16 ±0.13)	6 (0.17 ±0.15)	0.43	33 (0.22 ±0.08)
Stomach	11 (0.25 ±0.15)	1 (0.04 ±0.07)	6 (0.17 ±0.14)	4 (0.10 ±0.09)	0.11	22 (0.15 ±0.06)
Thyroid	4 (0.09 ±0.09)	1 (0.03 ±0.05)	6 (0.17 ±0.14)	2 (0.06 ±0.09)	0.29	13 (0.09 ±0.05)
Uterus	2 (0.09 ±0.12)	2 (0.15 ±0.21)	7 (0.49 ±0.37)	1 (0.06 ±0.12)	0.09	12 (0.20 ±0.12)

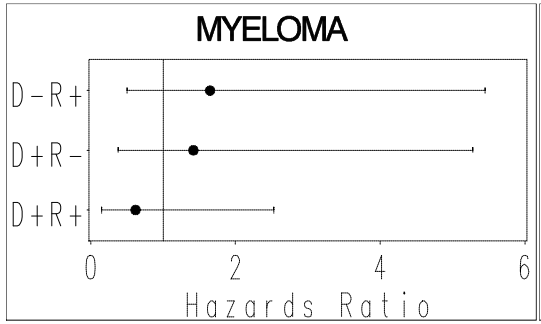
Figure 6.2 Comparison of risk-adjusted hazard (with 95% CI) of developing different types of cancers within 10 years of transplantation in different CMV groups, compared against the D-R- group

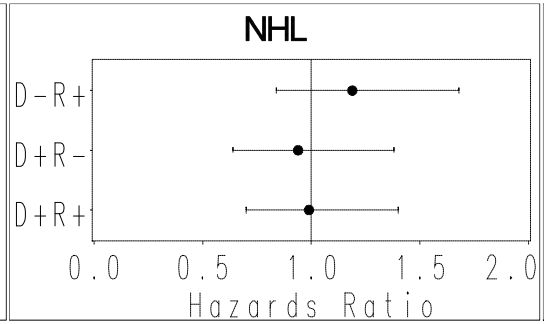


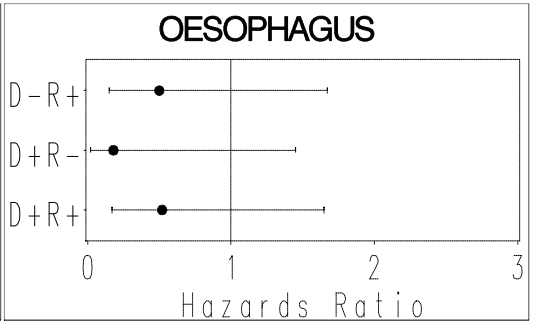

LIP
D-R+
D+R-
D+R+
0
2
4
6
8
Hazards Ratio

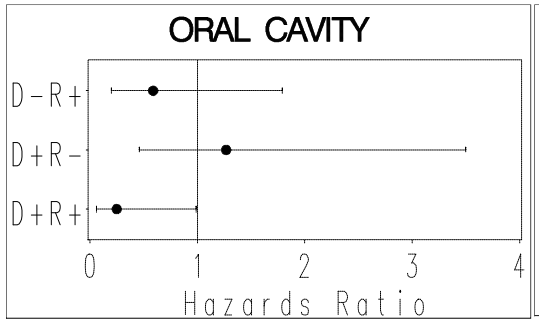

LIVER
D-R+
D+R-
D+R+
0
2
4
6
8
10
12
Hazards Ratio

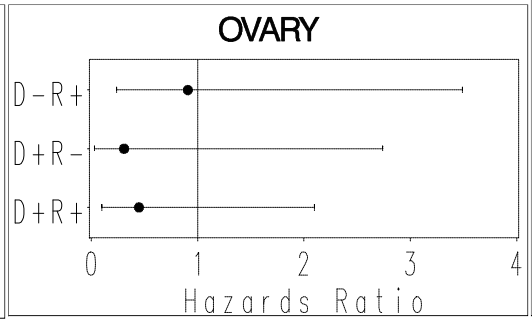

LUNG
D-R+
D+R-
D+R+
0
1
2
3
Hazards Ratio

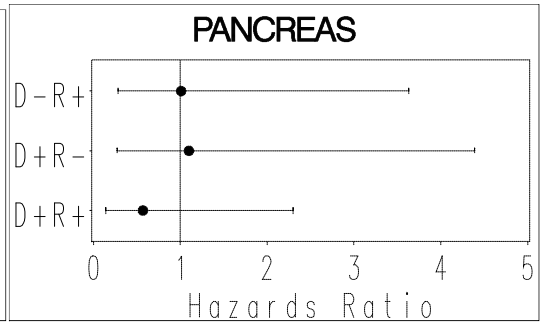

MYELOMA
D-R+
D+R-
D+R+
0
2
4
6
Hazards Ratio

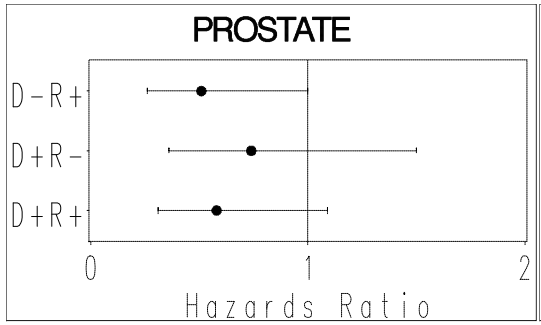

NHL
D-R+
D+R-
D+R+
0.0
0.5
1.0
1.5
2.0
Hazards Ratio

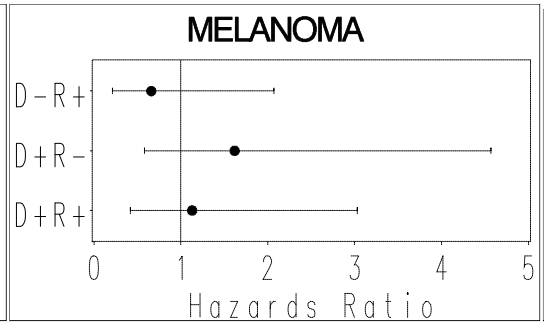

OESOPHAGUS
D-R+
D+R-
D+R+
0
1
2
3
Hazards Ratio

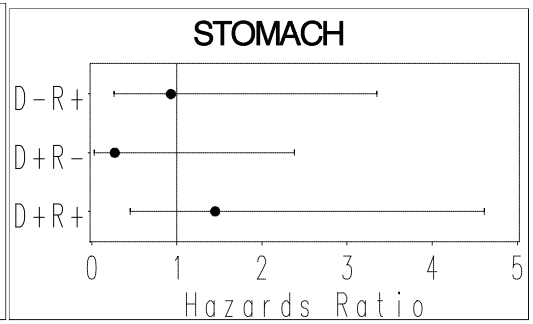

ORAL CAVITY
D-R+
D+R-
D+R+
0
1
2
3
4
Hazards Ratio

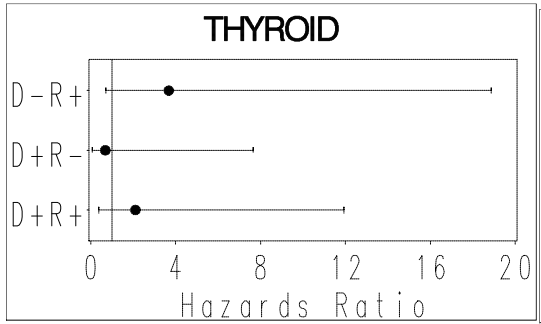

OVARY
D-R+
D+R-
D+R+
0
1
2
3
4
Hazards Ratio

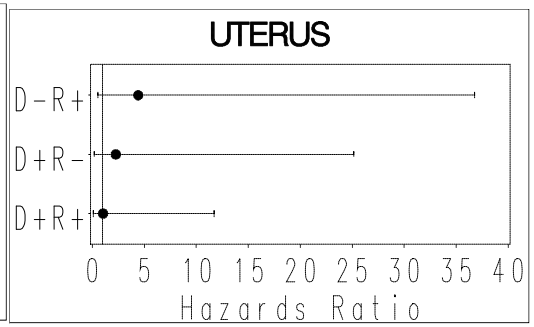

PANCREAS
D-R+
D+R-
D+R+
0
1
2
3
4
5
Hazards Ratio


PROSTATE
D-R+
D+R-
D+R+
0
1
2
Hazards Ratio


MELANOMA
D-R+
D+R-
D+R+
0
1
2
3
4
5
Hazards Ratio


STOMACH
D-R+
D+R-
D+R+
0
1
2
3
4
5
Hazards Ratio


THYROID
D-R+
D+R-
D+R+
0
4
8
12
16
20
Hazards Ratio


UTERUS
D-R+
D+R-
D+R+
0
5
10
15
20
25
30
35
40
Hazards Ratio

These graphs show that, there was no significant difference in the hazard of developing any of the 23 different types of cancer between the recipients in different CMV groups.

6.4.3 CMV and post-transplant recipient survival

Survival curves for the recipients of organ transplantation are shown in Figure 6.3. At ten years from transplantation, recipient survival of D-R- group (73·6% [95%CI 72·3, 74·9]) was significantly higher ($p<0·0001$) compared with the combined survival of all the other recipients (66·1% [65·3, 66·9]). The donor-recipient CMV matching was associated with significant survival advantage for CMV negative recipients (ten year survival: 73·6% [72·3, 74·9] for D-R- group and 68·4% [66·9, 69·9] for D+R- group) but not for CMV positive recipients (ten year survival: 64·6% [63·3, 65·8] for D+R+ group and 66·1% [64·7, 67·5] for D-R+ group).

Figure 6.3 Comparison of 10-year recipient survival between four groups based on CMV status

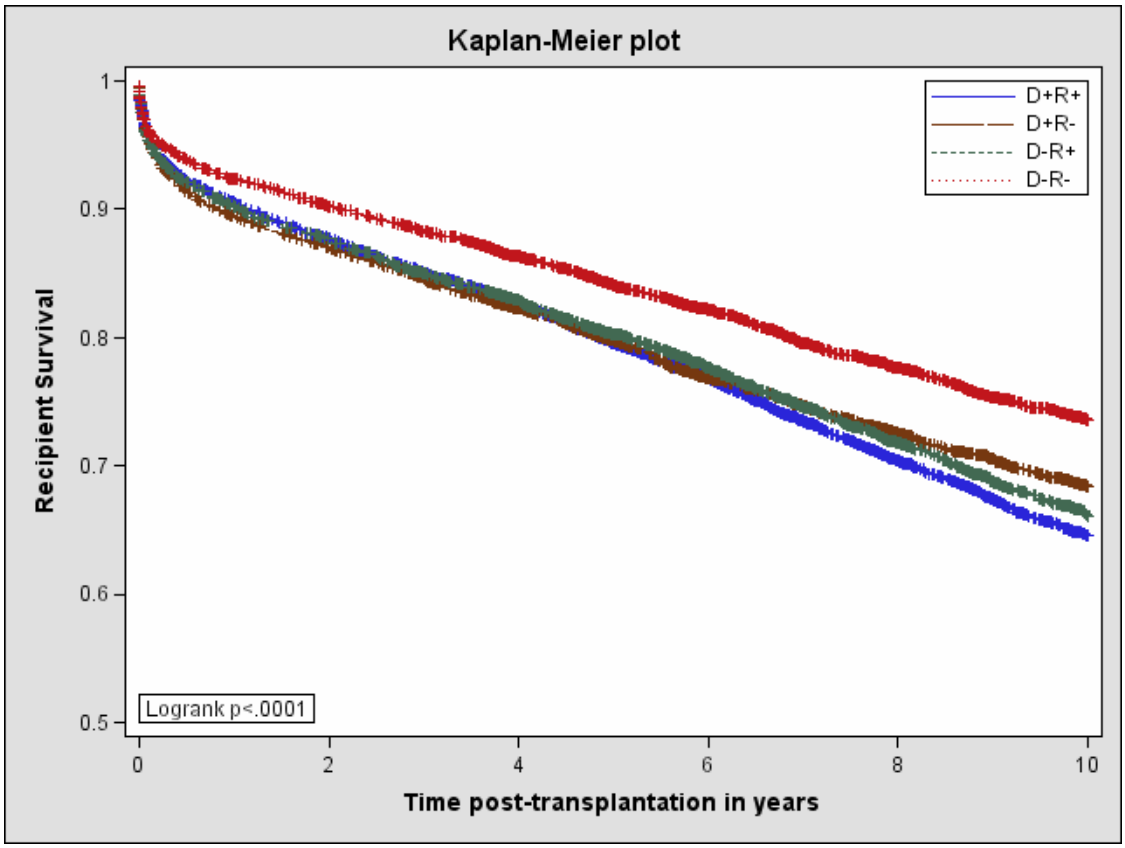


Table 6.3 shows the risk-adjusted hazard of death within one-year and ten-years from transplantation, assessed separately for the recipients of kidney, liver, heart and lung transplantation.

Table 6.3 1-year and 10-year patient survival and risk-adjusted hazard of death

Organ			CMV status				p-value for patient survival
			D+R+	D+R-	D-R+	D-R-	
Kidney	N		4072	2797	3120	3226	
	1-year survival% ± 95%CL		95.2±0.7	95.0±0.8	95.6±0.7	97.6±0.5	<0.0001
	Risk adjusted hazard of death within 1 year	HR	1.27 (0.96, 1.67)	1.74 (1.30, 2.31)	1.26 (0.95, 1.68)	1	
		p-value	0.10	0.0002	0.11		
	10-year survival% ± 95%CL		70.9±1.6	76.8±1.8	73.4±1.8	82.5±1.5	<0.0001
	Risk adjusted hazard of death within 10 years	HR	1.11 (0.99, 1.25)	1.14 (1.00, 1.30)	1.05 (0.93, 1.19)	1	
		p-value	0.08	0.044	0.44		
Liver	N		1445	896	1375	1098	
	1-year survival% ± 95%CL		87.7±1.7	85.3±2.3	86.2±1.8	89.3±1.8	0.036
	Risk adjusted hazard of death within 1 year	HR	0.99 (0.77, 1.28)	1.20 (0.92, 1.57)	1.15 (0.89, 1.47)	1	
		p-value	0.94	0.18	0.29		
	10-year survival% ± 95% CL		63.2±2.8	63.4±3.5	66.1±2.8	71.3±3.0	0.002
	Risk adjusted hazard of death within 10 years	HR	1.03 (0.88, 1.22)	1.13 (0.94, 1.34)	0.99 (0.84, 1.17)	1	
		p-value	0.71	0.19	0.87		

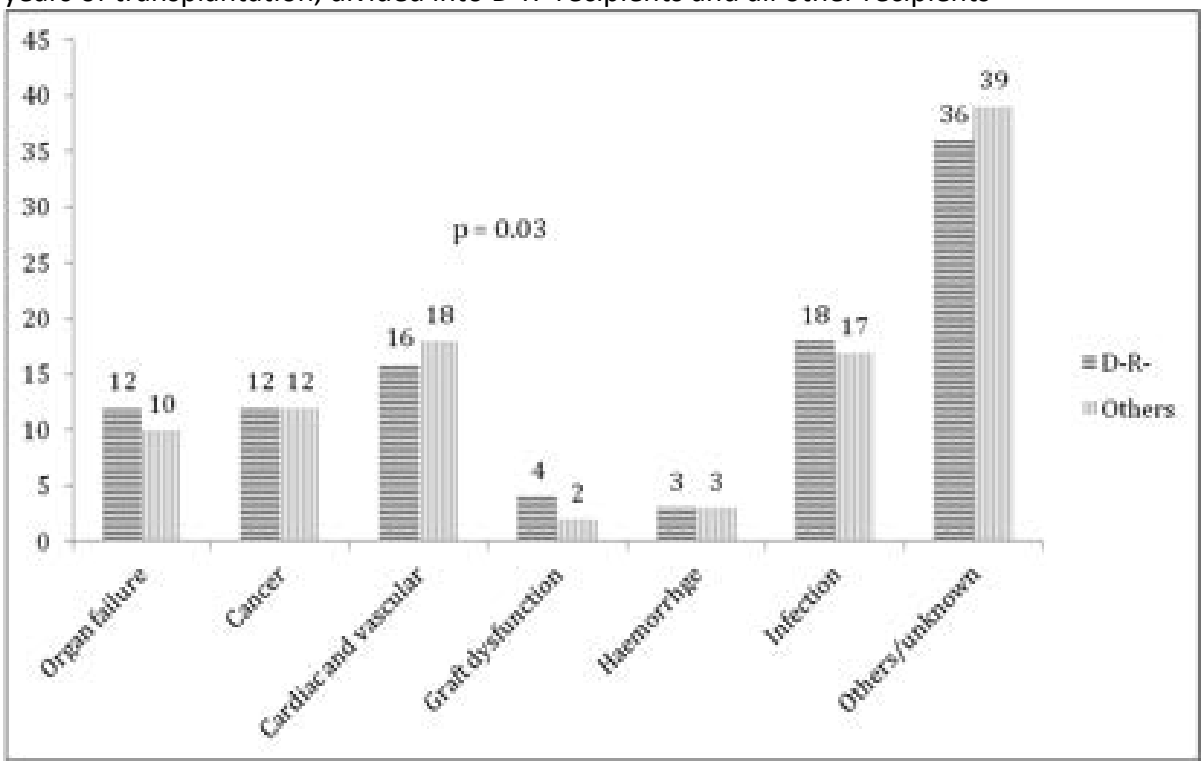
Organ			CMV status				p-value for patient survival
			D+R+	D+R-	D-R+	D-R-	
Heart	N		696	499	789	702	
	1-year survival% ± 95%CL		80.2±3.0	79.1±3.6	84.1±2.6	83.4±2.7	0.037
	Risk adjusted hazard of death within 1 year	HR	1.16 (0.83, 1.61)	1.34 (0.96, 1.87)	0.91 (0.65, 1.27)	1	
		p-value	0.38	0.08	0.57		
	10-year survival% ± 95% CL		55.3±3.8	56.2±4.7	57.6±3.7	64.1±3.8	0.009
	Risk adjusted hazard of death within 10 years	HR	1.31 (1.05, 1.65)	1.34 (1.06, 1.70)	1.09 (0.87, 1.36)	1	
		p-value	0.019	0.014	0.47		
Lung	N		453	328	470	495	
	1-year survival% ± 95%CL		73.6±4.1	69.9±5.0	77.1±3.8	76.8±3.6	0.054
	Risk adjusted hazard of death within 1 year	HR	1.29 (0.93, 1.80)	1.41 (1.02, 1.96)	1.02 (0.73, 1.43)	1	
		p-value	0.12	0.04	0.89		
	10-year survival% ± 95% CL		28.8±4.5	29.9±5.6	34.6±4.8	35.4±4.8	0.01
	Risk adjusted hazard of death within 10 years	HR	1.27 (1.03, 1.57)	1.35 (1.09, 1.68)	1.04 (0.84, 1.29)	1	
		p-value	0.028	0.0058	0.72		

6.4.4 Causes of death among transplant recipients

A total of 6213 recipients died within ten years from transplantation. The recipients who died within 30 days of transplantation (n=897) were excluded, as CMV is not likely to have contributed to death in this group. A majority of these (471, 53%) died within 8 days of transplantation and the cause of death in this group is more likely to be related to peri-operative complications than CMV.

The causes of death were studied in the remaining 5316 recipients after dividing them into D-R- group and 'others' group and the results are shown in Figure 6.4. The cardiac and vascular group included cardiac causes, cerebral causes and thromboembolic causes. Others included miscellaneous, unspecified and unknown causes.

Figure 6.4 Causes of death (in %) among 6213 recipients of all organs who died within 10 years of transplantation, divided into D-R- recipients and all other recipients



6.5 Discussion

This study showed no association between the risk of post-transplant cancer and the CMV status of the organ donor-recipient. However, the study did show an increased mortality among recipients of kidney, heart and lung, exposed to CMV as compared to CMV naïve. Although these results are significant, the limitations of the study must be acknowledged. Further detailed discussion of the strengths and weaknesses of the research presented in this thesis is included in sections 8.2 and 8.3.

6.5.1 Strengths and limitations of this study

Missing data is one of the important limitations of retrospective registry studies. In this study, the CMV data were not available for 12228 (35%) recipients and these were excluded. The CMV status was recorded at the time of transplantation and any recipients with post-transplantation acquisition of de novo CMV infection were not identified. In a significant proportion of patients (35%), no cause of death was specified. The risk of cancer would be underestimated in cases where the recipient had multiple cancers as the data for the first diagnosed post-transplantation cancer only were included. The risk of cancer would also be underestimated, as there may be some recipients with undiagnosed cancer, who may have died of other causes. The cause of death data were obtained from the Office for National Statistics, which is the UK's largest independent producer of official statistics and is the most widely recognised national statistical institute in the UK. Multiple robust internal and external quality control measures are in place, in order to maintain the high quality of data produced by the Office for National Statistics. In spite of this some inaccuracy of data may be inevitable.

6.5.2 Impact of CMV on the risk of post-transplantation cancer

The cancer risk of a transplant recipient is influenced by complex interactions between recipient factors (age, ethnicity, social status, pre-malignant conditions, pre-existing infections, smoking, alcohol intake, possibly genetic factors), donor factors (diseases transmitted from donor organ) and post-transplant factors (the intensity and the duration of immunosuppression, de novo infections, engagement with screening of post-transplant cancer). The recipient factors which are associated with an increased risk of cancer such as age, social status and smoking, are also associated with higher CMV sero-prevalence (Dowd et al., 2009) and it can be difficult to tease out any independent effect exerted by CMV. A higher risk of cancer among CMV positive recipients as compared to D-R- recipients observed on univariate analysis of our cohort may also be explained by the fact that the CMV positive recipients were older than CMV negative recipients. This difference in the risk was not statistically significant following risk adjustment for recipient's age and gender, indicating that the donor-recipient CMV status have no independent association with the risk of post-transplantation cancer in general or with the specific risk of developing 23 types of post-transplantation cancers.

The size of the cohort is likely to be the reason for the differences in findings between the results of the cohort I studied and the two other recent reports assessing a similar question (Couzi et al., 2010, Courivaud et al., 2012). Couzi and colleagues (Couzi et al., 2010) retrospectively studied a cohort of 105 kidney recipients with a median follow-up of 5 years, 23 of whom had developed a post-transplant cancer. They concluded that CMV naïve recipients had a 5·28 times increased risk of post-transplant cancer as compared to recipients exposed to CMV before or after transplantation and attributed this to CMV

mediated increase in the number of a subset of γδ T lymphocytes which possess anti–tumour activity. In contrast, Courivaud and colleagues (Courivaud et al., 2012) reported from a cohort of 455 recipients of kidney transplantation that both pre-transplant exposure (HR = 1·8) and post-transplant replication (HR = 2·17) of CMV were associated with an increased risk of post-transplant cancer as compared to CMV naïve recipients and attributed this to immune exhaustion related to exposure to CMV. Compared to these studies, the cohort I studied was substantially larger resulting in increased statistical power to detect any association between CMV and post-transplantation cancer. As shown in Table 6.2, in spite of the cohort size, the number of individual types of cancers is relatively small; so studies with a smaller cohort would have very small numbers of individual types of cancer and are likely to produce results which cannot be generalised to all transplant recipients.

6.5.3 Impact of CMV on post-transplant recipient survival

This study showed that the use of organs from donors who are CMV positive for recipients who are CMV negative is associated with an increased long-term post-transplant mortality in kidney, heart and lung transplant recipients. In the published literature, the effect of CMV on post-transplant patient survival has been studied among the recipients of different organs with conflicting results. The published reports assessing patient survival after transplantation include studies of kidney recipients (Johnson et al., 2009) (no effect), kidney-pancreas recipients (Kaufman et al., 2001) (no effect), liver recipients (Arthurs et al., 2007) (no effect) and heart recipients (Li et al., 2007) (7·05 times increased hazard of mortality at one year among CMV infected patients). Most of these studies have assessed short-term survival, often limited to less than five years from transplantation. The data assessing the long-term survival are limited. One of the larger reports is the study by

Johnson and colleagues (Johnson et al., 2009), which included 8228 recipients of deceased donor kidney transplantation in the UK between 2000 and 2007, partly overlapping with the cohort I studied. Johnson demonstrated no effect of CMV on the post-transplant patient survival at one, three and five years. In comparison, the results of my study showed an increased risk of patient death at ten years after transplantation among the recipients of kidney as well as heart and lung transplantation. This difference is likely to be due to larger numbers and longer follow-up. A direct comparison between the cohort I studied and the cohort studied by Johnson could not be performed due to inherent differences between the two cohorts, such as different inclusion criteria and unspecified duration of follow up. The results of my analysis showed an increased mortality in the D+R- group at ten years (14% increase in risk of death in comparison to D-R- group among kidney recipients, 34% increase among heart recipients and 35% increase among lung recipients) possibly highlighting the effect of the 'new' CMV infection acquired during transplantation. An increased mortality was also observed among D+R+ group of heart recipients (31% increase) and lung recipients (27% increase).

6.5.4 Possible reasons for increased mortality among CMV exposed recipients

It is difficult to explain the processes by which CMV may be contributing to increased post-transplantation mortality in a retrospective registry study, such as the one I conducted. The most common causes of death within 10 years after transplantation included cardiovascular events, cerebrovascular events, infections and single or multi-organ failure. The analysis of causes of death showed a small (2%) increase in cardiovascular death among CMV-infected recipients, however, it should also be noted that causes of death in more than a third of recipients were unspecified or 'others'. CMV infection has been shown to be associated in

the non-transplantation population with an increased cardiovascular mortality (Blankenberg et al., 2001, Muhlestein et al., 2000, Zhou et al., 1996). Among solid organ transplantation recipients, CMV has been shown to be associated with a variety of conditions such as acute rejection (Nett et al., 2004), tubulointerstitial nephritis and glomerulopathy after kidney transplantation (Rane et al., 2012), hepatic artery thrombosis and accelerated HCV infection (Bosch et al., 2012) after liver transplantation, allograft vasculopathy after heart transplantation and bronchiolitis obliterans after lung transplantation (Thomas et al., 2009), bacterial, fungal and viral infections (George et al., 1997, Arthurs et al., 2008) and new onset diabetes mellitus (Leung Ki et al., 2008). The rates of these complications and their impact on post-transplantation mortality could not be assessed in the present cohort due to lack of relevant data. The increased mortality observed among CMV infected transplantation recipients in the cohort I studied may be interplay of some or all of these diseases.

In the general population, especially the healthy elderly population, CMV is described as a driver of age-associated immune alterations leading to a reduction in naïve T cells (Sansoni et al., 2014). Reactivation of CMV may result in increased levels of pro-inflammatory cytokines such as IL-6 and TNFα. C-Reactive Protein (CRP) levels also increase as a consequence of leakage of the virus from host cells, via the action of IL-6. These inflammatory markers have been linked to both all-cause and cardiovascular disease related mortality. Savva and colleagues (Savva et al., 2013), found in a cohort of 511 healthy individuals aged at least 65 years followed for 18 years, that CMV infection was associated with an increased mortality rate and a near doubling cardiovascular death whereas there was no increase in mortality from other causes. Simanek AM et al. (Simanek et al., 2011), in a large and younger American population, aged 25 and older with up to 18 years of follow-

up, showed that CMV seropositivity was independently associated with an increased all-cause mortality (adjustment for CRP level did not attenuate this relationship). However, after confounder adjustment, they failed to associate CMV serostatus with cardiovascular mortality. Another study by Courivaud et al. (Courivaud et al., 2013) showed that CMV exposure was an independent risk factor for atherosclerotic events whereas post-transplantation CMV replication was independent risk factor for both atherosclerotic events and death in kidney transplant recipients. Their results suggested that CMV was associated with immune exhaustion and inflammation in favour of an indirect effect of CMV on atherosclerotic progression. These results, along with the results of my study provide evidence towards a complex interaction between aging, CMV infection and cardiovascular disease/death both in general population as well as recipients of organ transplantation.

In summary, in this large cohort of solid organ transplant recipients, there was no association between the donor-recipient CMV status and the risk of post-transplantation cancer as a whole, or the risk of 23 individual types of cancers. The results also showed a negative impact of the D+R- CMV mismatch on the long-term survival of the recipients of kidney, lung or heart transplantation but not the recipients of liver transplantation. (Desai et al., 2015)

CHAPTER 7

POST TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS

7.1 Introduction

PTLD include a group of conditions characterised by unregulated proliferation of lymphocytes in the recipients of solid organ or bone marrow transplantation. PTLD, along with non-melanoma skin cancer is one of the two most common cancers after solid organ transplantation (Collett et al., 2010, Buell et al., 2005).

7.1.1 Risk factors and pathogenesis of PTLD

A majority of PTLD are the result of EBV induced proliferation of lymphocytes facilitated by immunosuppression. EBV is an oncogenic Y herpes virus, first discovered in 1964 (Epstein et al., 1964) in Burkitt's lymphoma cells. It was subsequently shown to be associated with nasopharyngeal carcinoma, NHL and HL (zur Hausen et al., 1970, Jones et al., 1988, Weiss et al., 1989). The initial infection with EBV often occurs in the childhood and by the age of 40, about 90%of the population is infected (Cohen, 2000). This initial infection may remain asymptomatic or present with infectious mononucleosis. This is followed by lifelong latent infection, which is kept under control by intact T-lymphocyte mediated immunity. A majority of PTLD involve B lymphocyte proliferation, cases with proliferation of T lymphocyte account for around 15% (Hanson et al., 1996, Ravat et al., 2006, Rajakariar et al., 2004) and cases involving natural killer cell proliferation are rare (Draoua et al., 2004). EBV associated PTLD accounts for more than 80% of PTLD cases involving B-lymphocytes and a smaller proportion of cases involving T-lymphocytes (Caillard et al., 2006). The incorporation of EBV DNA into the lymphocyte genome results in resistance to apoptosis by bcl-2 induction and an unregulated proliferation of lymphocytes. Other viruses such as CMV

and HCV have also been shown to be associated with an increased risk of PTLD in smaller studies but this association has not been conclusively established (Rabkin et al., 2002, Hausfater et al., 2001).

In the immunocompetent, there are several studies showing association between lymphoma and the HLA. Some HLA types are associated with an increased risk: HLA-A68 and DR11(5) (Huang et al., 2011), HLA-A1, B5 and B18 (Hors and Dausset, 1983) and some like HLA-A2, with a reduced risk (Niens et al., 2007). The association between HLA and the risk of lymphoma is further complicated by the EBV status: several HLA types are reported to be associated with an increased risk of Hodgkin's disease and one specific HLA allele has been shown to be protective allele against Hodgkin's disease in EBV negative patients and a susceptibility allele in EBV positive patients (Huang et al., 2012). The association between PTLD and HLA types has not been assessed in larger cohorts.

Immunosuppressive agents increase the risk of post-transplant cancer including PTLD by different mechanisms including reduced immune surveillance and increased risk of infection with oncogenic viruses. Immunosuppressive regimen change continuously as a result of introduction of newer agents, discontinuation of older agents, side effects of a particular agent, comorbidities, preferences of the recipient and the medical team and the availability of new evidence. As a result, it is difficult to tease out the effect of individual agents on the risk of cancer. However, there is good evidence demonstrating the association between more intensive immunosuppressive regimen and an increased risk of cancer including PTLD

(Dantal et al., 1998, Vivarelli et al., 2002, Swinnen et al., 1990). A detailed discussion of the individual immunosuppressive agents and their impact on the risk of PTLD is included in Sections 1.7.1 to 1.7.5 of the thesis and is summarised here. The use of ATG is associated with an increased risk of PTLD, with an odds ratio of 1.6. The use of azathioprine is associated with a four-fold increased risk of PTLD and the risk is enhanced by concomitant use of CNI agents. Several studies comparing the risk of PTLD among the recipients on ciclosporin or tacrolimus have shown an increased risk among recipients on tacrolimus but this difference was only evident among recipients not receiving ATG induction.

7.1.2 Incidence of PTLD

The incidence of PTLD is highest in the first post-transplant year followed by a long tapered incidence rate that continues for decades after transplantation. The incidence is higher in paediatric recipients, EBV negative recipients and recipients of heart or lung transplantation. The cumulative incidence of PTLD after 5 years post-transplantation ranges from 1 to 3% for kidney recipients, 2 to 10% for liver recipients up to 20% for heart or lung transplant recipients (Opelz and Dohler, 2004). The age-gender-year standardised incidence rate of post transplant NHL, compared to matched non-transplant population is 12.5 for kidney recipients, 13.3 for liver recipients, 19.8 for heart and 30.0 for lung recipients. The organ of involvement of PTLD varies among recipients of different organ transplantation with predilection to the transplanted organ. While PTLD can involve different sites such as central nervous system, lymph nodes, gastrointestinal tract or multiple organs, 10 to 30% of kidney recipients, 22 to 33% of liver recipients, 50 to 80% of lung (or heart-lung) recipients and 10% heart recipients have predominant involvement of the transplanted organ (Mucha

et al., 2010). The involvement of tonsils and the Waldeyer's ring is commoner in children than in adults.

7.1.3 Classification of PTLD

The WHO classification of PTLD is most widely used (Campo et al., 2011). PTLD is classified in to four types:

Early lesions – plasmacytic hyperplasia

- infectious mononucleosis like PTLD

Polymorphic PTLD

Monomorphic PTLD (B-cell, T-cell and NK-cell type)

Classical Hodgkin's lymphoma type PTLD

Among these, the early lesions and polymorphic PTLD tend to have the least degree of cellular atypia and are often seen in children and young people with primary EBV infection. These are also often associated with better prognosis. Monomorphic PTLD includes all T-cell, NK-cell lymphomas and a majority of B-cell (non-Hodgkin's) lymphomas. This group also includes less common types of PTLD such as Burkitts lymphoma, multiple myeloma and extra-medullary plasmacytoma.

7.1.4 Clinical features and diagnosis of PTLD

PTLD often presents with varied, non-specific clinical features including graft dysfunction, infections, fever, lymphadenopathy and malaise. The differential diagnoses include a variety of infections, graft rejection, adverse effects of immunosuppressive agents and other dugs, and other types of cancers. While a majority of PTLD present within the first year after transplantation, it can present from weeks to decades after transplantation. The diagnostic work up of PTLD is a multidisciplinary process. The diagnostic tests are histopathological and immunophenotypical tests while clinical examination, endoscopy and cross-sectional imaging can guide in identifying the involved organ. A rising level of EBV in the serum or the presence of EBV in the tissue samples can be a useful circumstantial evidence of PTLD.

7.1.5 Management and prognosis of PTLD

The treatment of PTLD is varied and individualised, depending on the age and comorbidities of the recipient, symptoms, EBV status, organ transplanted, degree of graft dysfunction, location of PTLD, immunosuppressive agents used and the preference of the patient and the medical team. The general principles of management of PTLD include three types of interventions: reduction of immunosuppression, treatment of EBV and tumour reduction interventions, which can be pharmacological or surgical. There is universal agreement with the benefits of reduction of immunosuppression in patients PTLD however substitution of agents is not supported by good evidence. Often azathioprine and MMF are withdrawn and the doses of corticosteroids and CNI agents are reduced. Substitution with the proliferation signal inhibitors such as sirolimus or everolimus is sometimes considered but this is not

based on established evidence. The option of graft excision should be considered in a kidney or pancreas recipient with PTLD localised to the graft but a surgical option for a similar tumour in recipients of liver, heart or lung transplantation is more complicated. The chemotherapy options include CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) and rituximab, an anti-CD20 monoclonal antibody. In those with primary EBV infection and a high EBV titre, treatment with acyclovir or gancyclovir is likely to be beneficial. The immunotherapeutic agents include interferon, anti-IL6 or anti-B-cell antibodies which selectively remove EBV-infected B-cells.

PTLD has a poor prognosis. The one-year mortality following diagnosis of PTLD is 37 to 54% for recipients of kidney or liver transplantation and 50% for recipients of heart transplantation (Opelz and Dohler, 2004, Leblond and Choquet, 2004). Larger studies assessing prognosis of PTLD patients across different eras of transplantation show no significant change in prognosis of PTLD (Opelz and Dohler, 2004).

In this chapter, the incidence of PTLD among recipients of solid organ transplantation across three decades among adult and paediatric recipients, factors associated with development of PTLD including HLA types and recipient survival following diagnosis of PTLD are discussed.

7.2 Aims

The aims of this chapter are:

1. To assess the incidence of PTLD in different eras of transplantation among the recipients of different organs
2. To study the recipient survival following PTLD and compare this in recipients of different organs over different time periods
3. To study the association of PTLD with the immunosuppressive agents
4. To study the association of PTLD with different HLA types

7.3 Methods

7.3.1 Study cohort

Using the data held by the UK Transplant Registry, the recipients of first solid organ (kidney, liver, heart, lung) transplantation performed between 1st January 1980 and 31st December 2007 who were resident in England, Wales or Scotland were identified. This duration was selected, as the availability of PTLD data was limited to this period. Recipients of combined kidney-pancreas transplantation (n=764) were included in the kidney recipient group and the recipients of combined double-lung and heart-lung transplants (n=553) were grouped with the lung recipients.

7.3.2 Data

Transplant data were obtained from the UK Transplant Registry. The data regarding registration of PTLD were obtained from the Office for National Statistics by matching the details of the recipients (name, gender, date of birth/death, address and NHS number). The Office for National Statistics received the PTLD data from the cancer registries in the UK. The

cancer registries did not register lymphoproliferative conditions other than HL and NHL. So the data were unavailable regarding lymphoproliferative disorders other than HL or NHL.

7.3.3 Statistical analysis

The SIR was used to compare the incidence of PTLD in different recipient groups. The SIR for a specific age group and gender is the ratio of the observed number of PTLD cases in that group to the expected number of PTLD cases assuming the incidence rates in the general population prevailed. The Office for National Statistics published incidence rates of cancers in the population of England (ONS, 2014). The same incidence rates were assumed to be applicable to the recipients from Wales and Scotland. For those years where the national incidence rates were not available, the incidence rates were calculated assuming a log linear relationship between the published incidence rates and estimated incidence rates. The expected number of PTLD cases for each age-gender-year group was calculated by working out the number of person-years in each age-gender-year group at risk of developing PTLD in the post-transplant period. Age groups were of 5 years each between 0 and 85 years of age, and a group aged above 85 years. The number of person-years in each age-gender-year group was multiplied by the corresponding incidence rate obtained from the Office for National Statistics publications of incidence rates of cancers in the population of England. This was performed for each year between 1980 and 2007. The recipient survival after the diagnosis of PTLD was assessed using Kaplan-Meier survival curve and compared using the log-rank test. Cox regression analysis was used to assess the risk-adjusted hazard of death.

The analyses of the impact of immunosuppression and HLA type on PTLD were restricted to kidney recipients transplanted after 1st January 2000 as the immunosuppression data and the HLA data were missing in 65% of the recipients transplanted prior to this date. The details of the immunosuppression data were limited to whether a recipient was receiving azathioprine, MMF, tacrolimus and ciclosporin at the time of transplantation, 3 months and 12 months after transplantation. The association of 46 different HLA antigens with PTLD was assessed, including 10 types of HLA-A (A1, A2, A3, A9, A10, A11, A19, A28, A36, A80), 25 types of HLA-B (B5, B7, B8, B12, B13, B14, B15, B16, B17, B18, B21, B22, B27, B35, B37, B40, B41, B42, B46, B47, B48, B53, B70, B78, B82) and 11 types of HLA-DR antigens (DR1, DR2, DR3, DR4, DR5, DR6, DR7, DR8, DR9, DR10, DR103). Logistic regression was used to assess the association of different HLA antigens and PTLD with risk-adjustment for recipient age and gender. While comparing the association of multiple HLA antigens with PTLD, the Bonferroni correction was used to assess the statistical significance in order to avoid inflating the overall type I error above its nominal level for each test. SAS version 9.3 was used for data analysis (SAS Institute, Cary). Person-years at risk and incidence were calculated using SAS Macros function (Macaluso, 1992).

7.4 Results

7.4.1 Recipient characteristics

There were 37617 recipients in the study cohort, including 25104 (67%) kidney, 6846 (18%) liver, 3609 (10%) heart and 2058 (5%) lung recipients. The recipients were divided into three

groups based on their decade of transplantation. Table 7.1 shows the baseline characteristics of these recipients.

Table 7.1. Recipient characteristics in different organ recipients over 3 decades

Transplant Decade		Recipient group				Total
		Kidney	Liver	Heart	Lung	
1980 – 1989	Number	5454	159	401	77	6091
	Mean age at transplant in years (95% CI)	37.1 (36.7, 37.5)	37.2 (34.2, 40.2)	42.8 (41.4, 44.1)	26.2 (23.3, 29.1)	38
	Male %	61	36	85	51	62
	Median follow up in years (95% CI)	16.6 (16.2, 17.0)	18.3 (18.1, 18.6)	17.2 (16.5, 18.2)	14.6 (11.8, 17.2)	
1990 – 1999	Number	11050	3122	2092	1090	17354
	Mean age at transplant in years (95% CI)	43.0 (42.7, 43.3)	41.5 (40.8, 42.1)	45.3 (44.7, 46.0)	40.8 (39.9, 41.6)	46
	Male %	63	48	82	54	62
	Median follow up in years (95% CI)	9.8 (9.7, 9.9)	9.3 (9.1, 9.5)	9.5 (9.3, 9.8)	5.0 (4.5, 5.6)	
2000 – 2007	Number	8600	3565	1116	891	14172
	Mean age at transplant in years (95% CI)	45.2 (44.9, 45.5)	44.7 (44.1, 45.3)	40.1 (39.0, 41.2)	44.4 (43.3, 45.4)	48
	Male %	61	57	73	54	61
	Median follow up in years (95% CI)	3.2 (3.1, 3.3)	3.1 (3.0, 3.2)	3.1 (2.9, 3.4)	2.1 (1.8, 2.4)	

7.4.2 Incidence and SIR of HL and NHL

A total of 620 (1.65%) recipients developed PTLD, including 55 (0.15%) with HL and 565 (1.50%) with NHL. The SIR for NHL was 13.8 (95% CI 12.7, 15.0) and for HL was 7.8 (5.9, 10.2). Table 7.2 shows the observed and expected number of cases of HL and NHL among recipients of different organs and the SIRs. Table 7.3 shows the observed and expected number of cases of HL and NHL among paediatric (under 18 years of age at the time of transplantation) and adult (over 18) recipients of different organs and the SIRs. Table 7.3 also shows the median time from transplantation to the diagnosis of PTLD in each group.

Table 7.2 SIRs for NHL and HL among recipients of different organs

	Non-Hodgkin's lymphoma				Hodgkin's lymphoma			
Organ transplanted	Observed number	Expected number	SIR (95% CI)	p-value	Observed number	Expected number	SIR (95% CI)	p-value
Kidney	353	28.7	12.3 (11.1, 13.7)	<0.001	38	5.2	7.4 (5.2, 10.1)	<0.001
Liver	80	6.2	13.0 (10.3, 16.1)	<0.001	8	0.9	8.6 (3.7, 16.9)	<0.001
Heart	99	5.1	19.5 (15.8, 23.7)	<0.001	8	0.7	11.5 (5.0, 22.7)	<0.001
Lung	33	1.1	31 (21.3, 43.5)	<0.001	1	0.2	4.2 (0.1, 23.5)	0.30

Table 7.3 SIRs for NHL and HL among children and adult recipients

			Non-Hodgkin's lymphoma				Hodgkin's lymphoma			
Organ transplanted	Recipient age-group	Median time to PTLD, days (range)	Observed number	Expected number	SIR (95% CI)	p-value	Observed number	Expected number	SIR (95% CI)	p-value
Kidney	Under 18	3896 (168, 7449)	27	0.3	84.3 (55.5,122.7)	<0.001	2	0.5	4.2 (0.5, 15.2)	0.15
	18 and over	2689 (47, 9280)	326	28.3	11.5 (10.3, 12.8)	<0.001	36	4.7	7.7 (5.4, 10.6)	<0.001
Liver	Under 18	530 (61, 4422)	8	0.1	119.9 (51.6,236.3)	<0.001	1	0.1	10.6 (0.1, 59.2)	0.17
	18 and over	1394 (21, 6692)	72	6.1	11.8 (9.2, 14.9)	<0.001	7	0.8	8.3 (3.3, 17.2)	<0.001
Heart	Under 18	2308 (91, 7805)	18	0.03	523.8 (310.3,827.8)	<0.001	2	0.05	39.5 (4.4,142.5)	0.02
	18 and over	2636 (142, 7751)	81	5	16.1 (12.8, 20.0)	<0.001	6	0.6	9.3 (3.4, 20.3)	<0.001
Lung	Under 18	594 (74, 4020)	5	0.01	470.9 (151.8, 1099.0)	<0.001	0	0.02	0	-
	18 and over	747 (75, 6125)	28	1.1	26.6 (17.6, 38.4)	<0.001	1	0.2	4.6 (0.1, 25.6)	0.29

7.4.3 SIR of lymphoma among transplant recipients over 3 decades

Chronological change in SIR of HL and NHL over three decades was assessed among kidney, liver, heart and lung recipients. The SIRs for kidney recipients and liver recipients are shown in figures 7.1A and B, 7.2A and B. The SIR for heart recipients and lung recipients are shown in Table 7.4.

Figure 7.1A SIR for NHL among kidney recipients (p = 0.20)

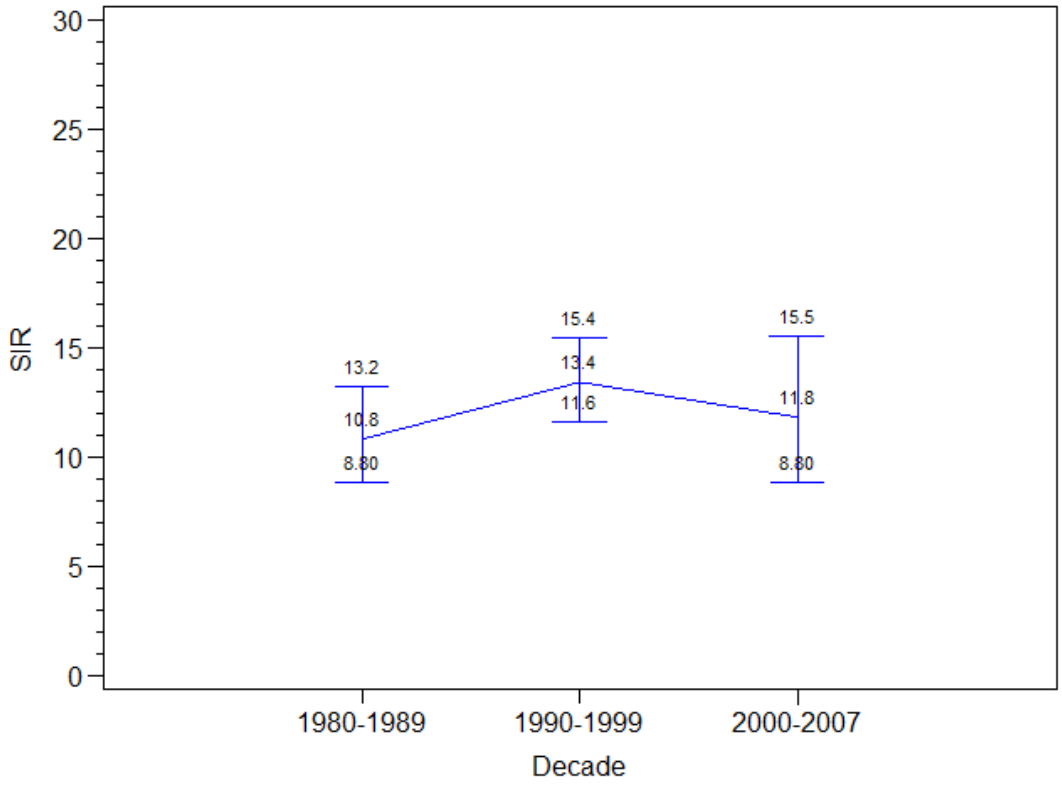


Figure 7.1B SIR for HL among kidney recipients (p = 0.08)

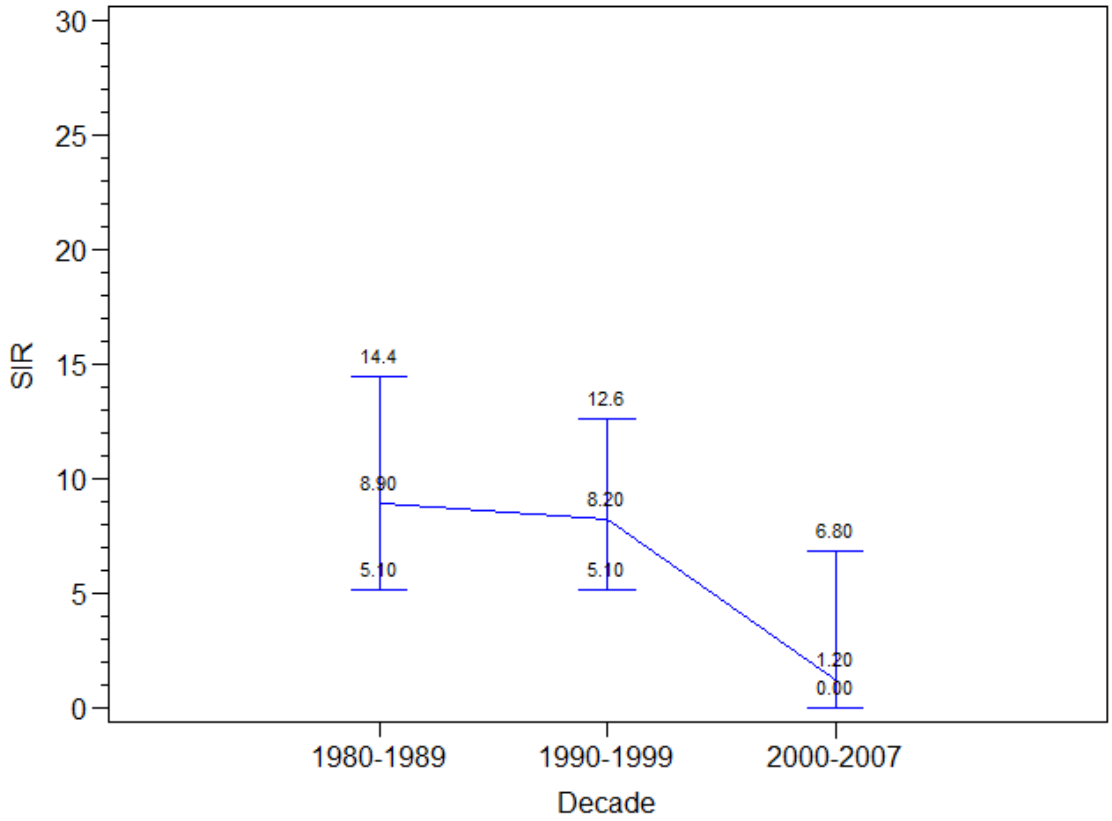


Figure 7.2A SIR for NHL among liver recipients (p = 0.61)

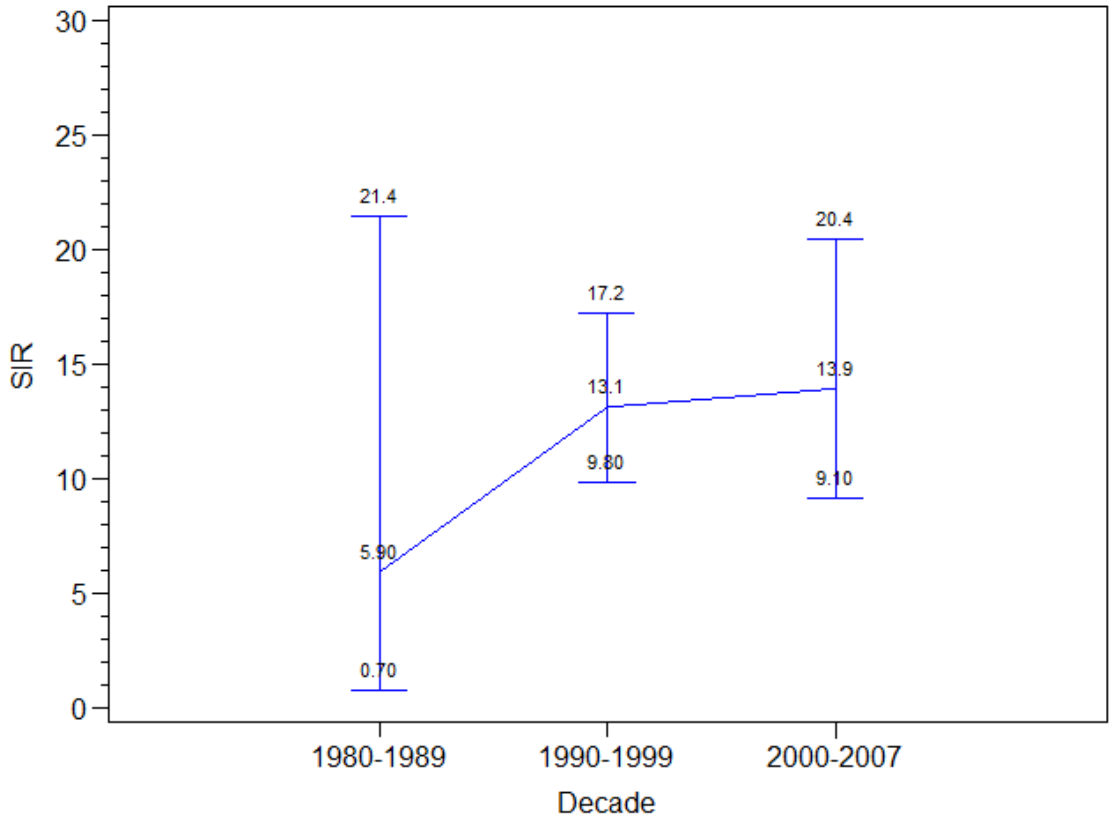


Figure 7.2B SIR for HL among liver recipients (p = 0.70)

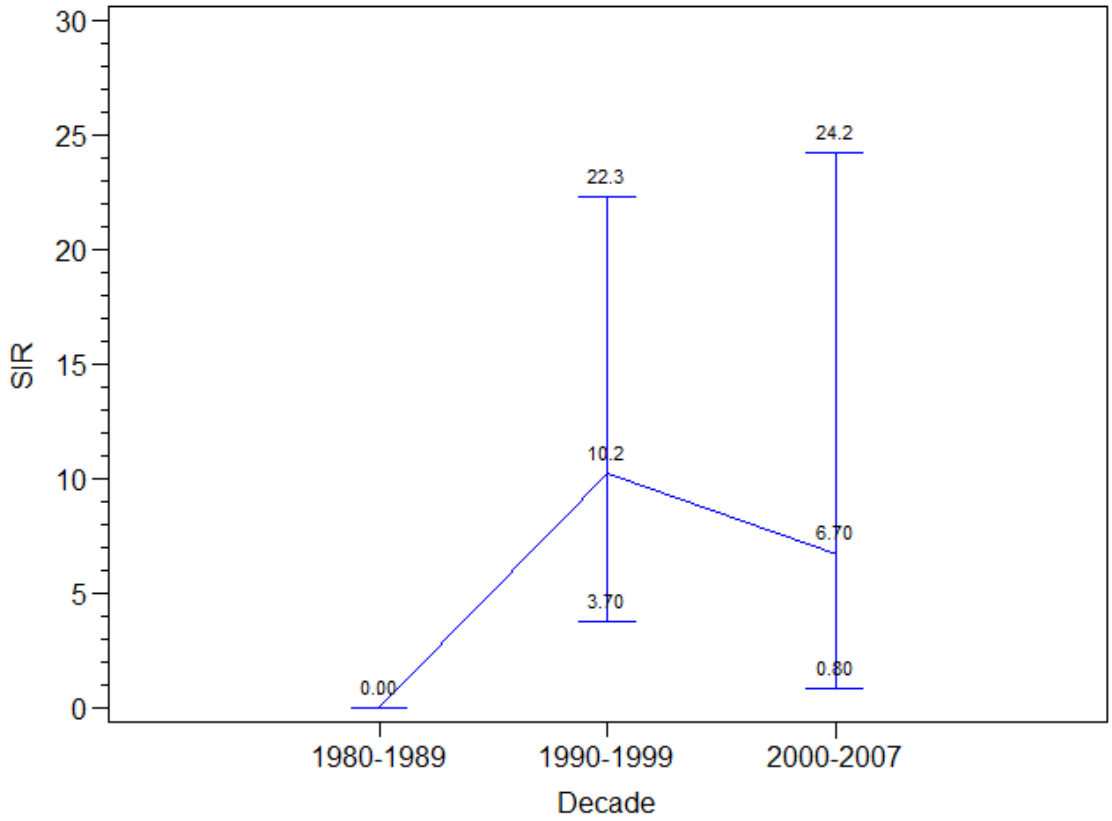


Table 7.4 SIR for HL and NHL among heart recipients and lung recipients

Recipient group		SIR (95% CI)			p-value
		1980 - 1989	1990 - 1999	2000 - 2007	
Heart	HL	13.9 (1.6, 50.3)	13.4 (4.9, 29.1)	0	0.42
	NHL	14.5 (8.4, 23.2)	22.0 (17.3, 27.6)	14.0 (5.6, 28.9)	0.16
Lung	HL	0	6.7 (0.1, 37.3)	0	0.61
	NHL	85 (27.4, 198.3)	28.3 (17.3, 43.8)	26.6 (11.5, 52.4)	0.47

7.4.4 Recipient survival after the diagnosis PTLD

Among the recipients with PTLD, the overall 1-year survival was 52.4% (95%CI 47.3, 57.5) for kidney recipients, 49.1% (95%CI 38.5, 59.7) for liver recipients, 53.4% (95%CI 43.9, 62.9) for heart recipients and 47.1% (95%CI 30.32, 63.88) for lung recipients.

The recipient survival and the risk-adjusted hazard of death after the diagnosis of PTLD were compared among the recipients undergoing transplantation in three decades. Figures 7.3, 7.4, 7.5 and 7.6 show Kaplan-Meier survival curves among kidney, liver, heart and lung recipients respectively. Table 7.5 shows the median recipient survival after the diagnosis of PTLD and the risk-adjusted hazard of death for these recipients.

Figure 7.3 Kidney recipient survival after the diagnosis of PTLD (log rank p=0.84)

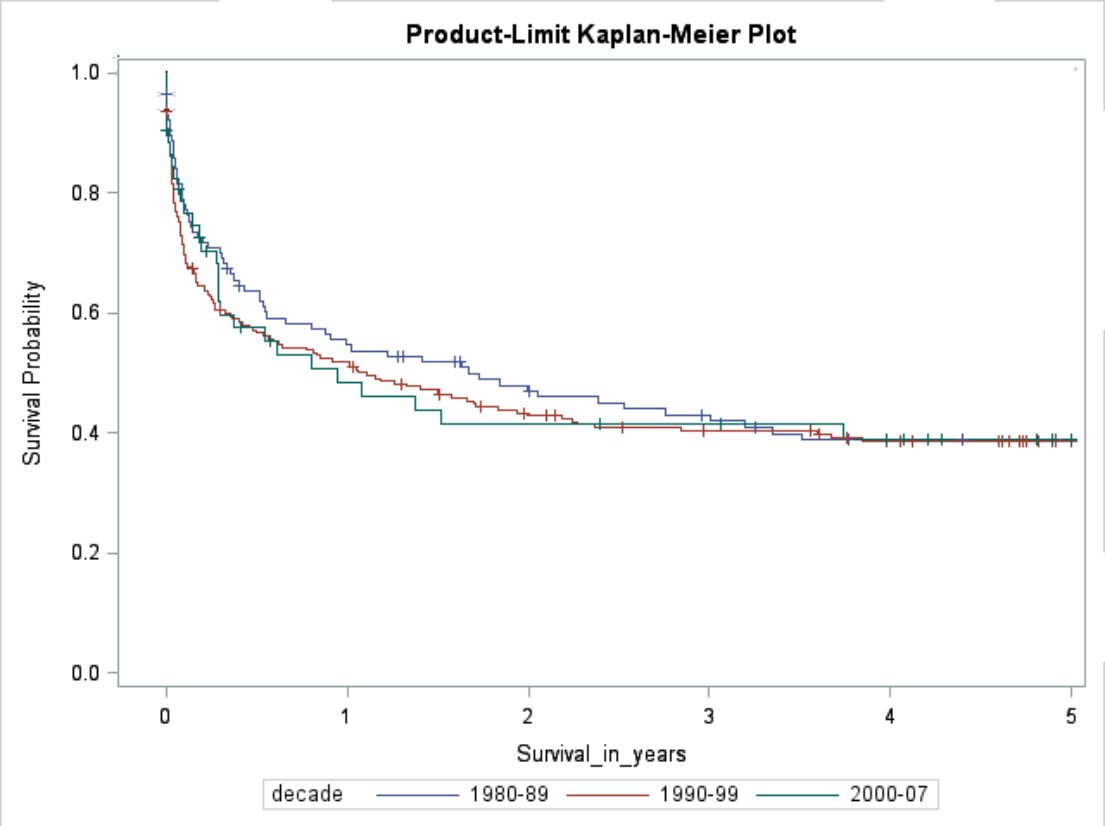


Figure 7.4 Liver recipient survival after the diagnosis of PTLD (log rank p=0.76)

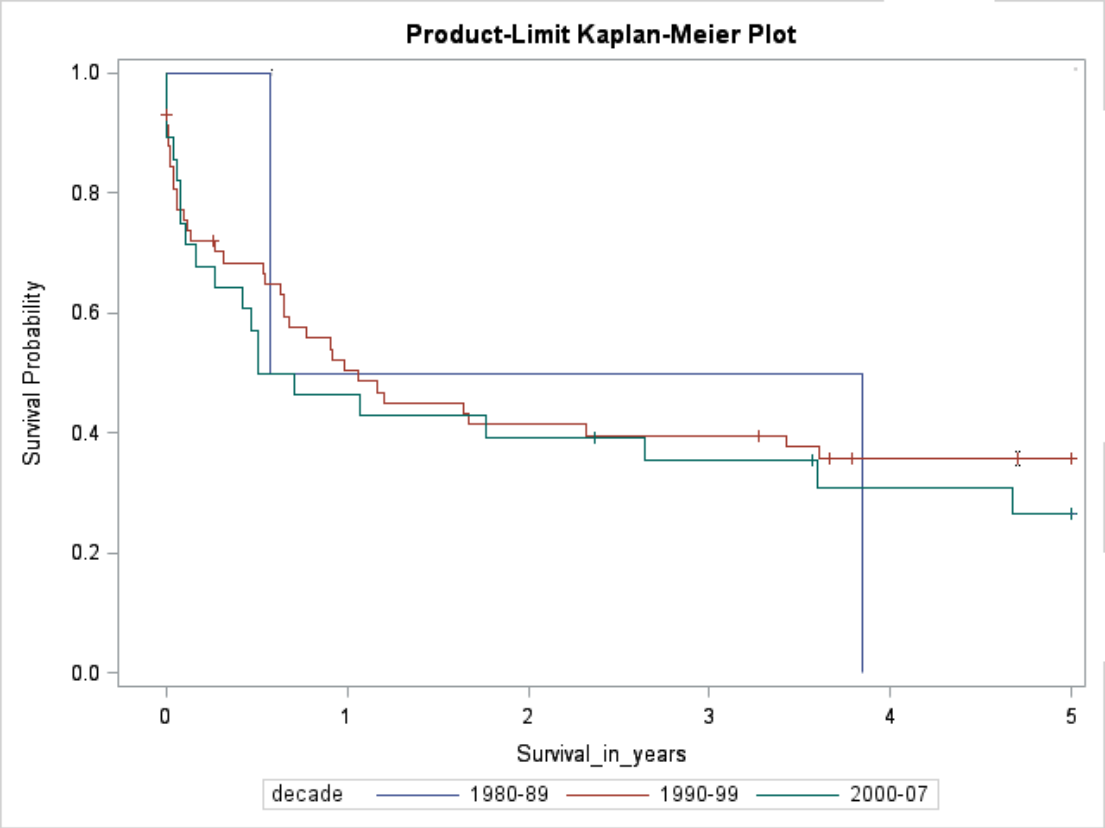


Figure 7.5 Heart recipient survival after the diagnosis of PTLD (log rank p=0.58)

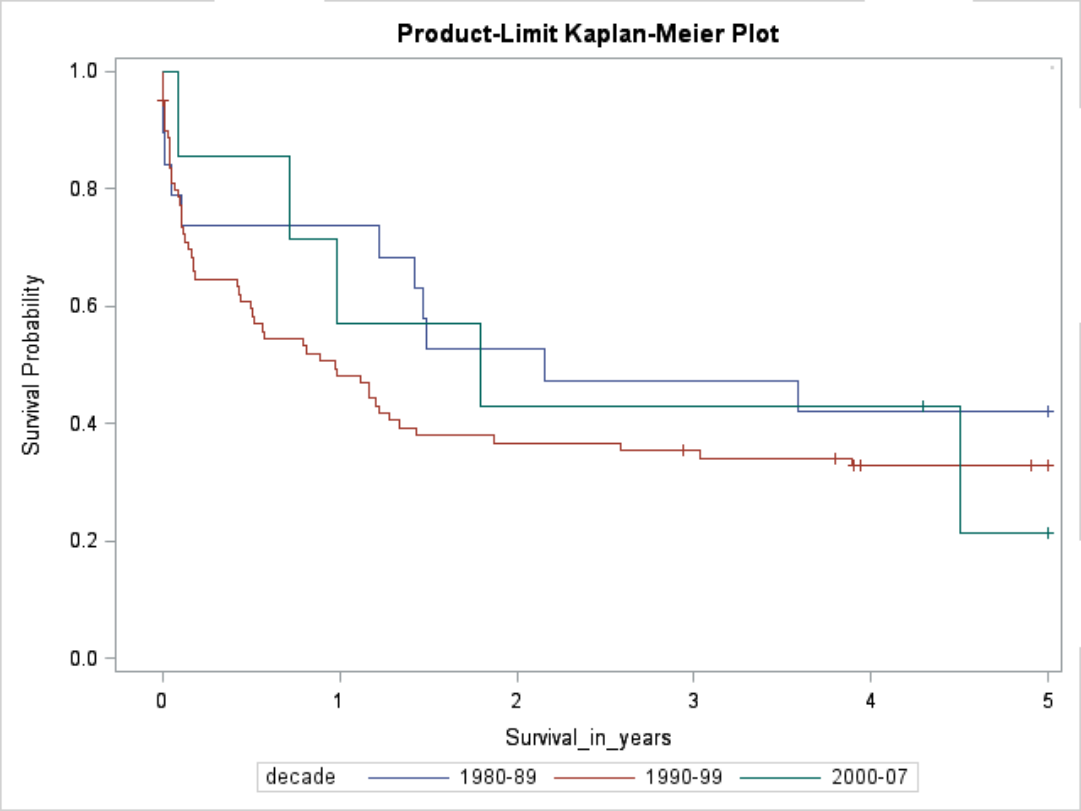


Figure 7.6 Lung recipient survival after the diagnosis of PTLD (log rank p=0.49)

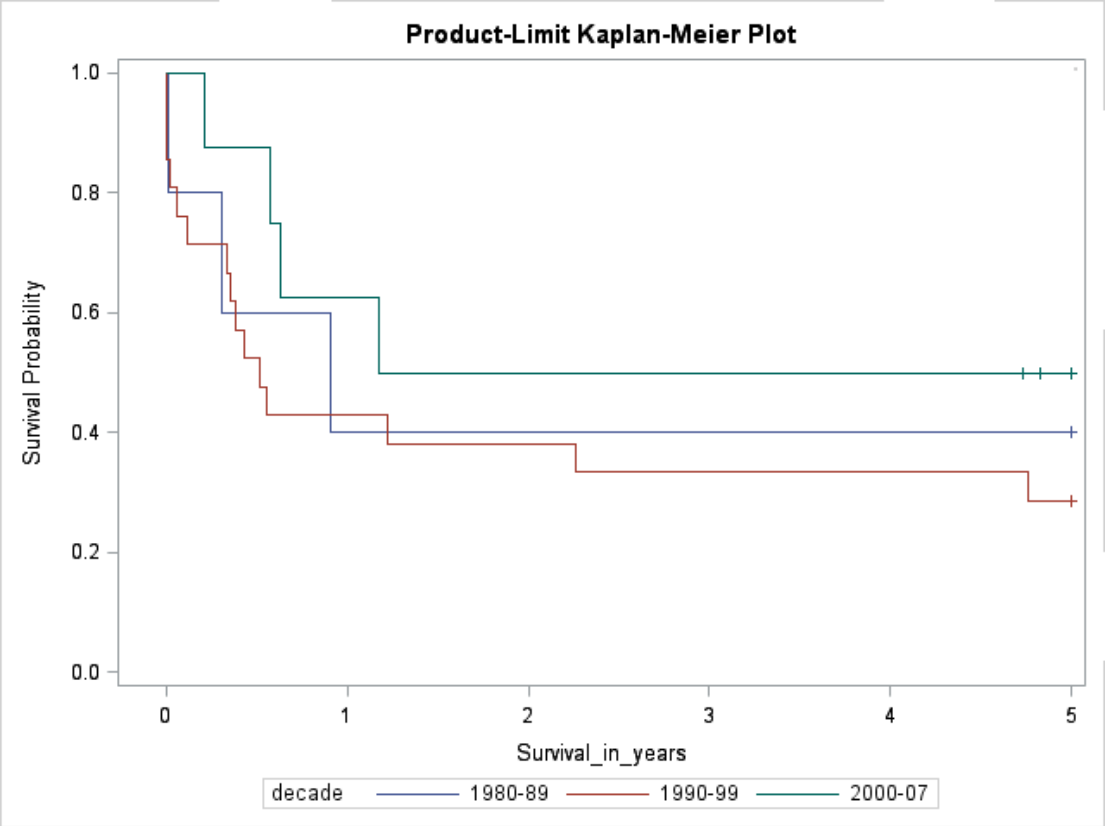


Table 7.5 Recipient survival and risk-adjusted hazard of death among organ transplant recipients with PTLD over three decades

	Decade	N	Median survival in years (95% CI)	Hazard ratio (95% CI)	p-value
Kidney	1980-89	118	1.67 (0.55, 3.35)	1	
	1990-99	221	1.10 (0.50, 1.94)	0.90 (0.61, 1.33)	0.60
	2000-07	52	0.94 (0.29, -)	0.59 (0.33, 1.04)	0.07
Liver	1980-89	2	2.21 (0.57, 3.84)	-	
	1990-99	58	1.06 (0.63, 3.60)	1	
	2000-07	28	0.61 (0.16, 3.59)	0.56 (0.17, 1.85)	0.34
Heart	1980-89	19	2.16 (0.11, -)	-	
	1990-99	80	0.97 (0.44, 1.33)	1	
	2000-07	7	1.80 (0.09, -)	1.45 (0.02, 119.9)	0.86
Lung	1980-89	5	0.91 (0.01, -)	-	
	1990-99	21	0.52 (0.11, -)	1	
	2000-07	8	-	21.85 (0, -)	1.00

7.4.5 Immunosuppression and post-transplant NHL

The impact of immunosuppression on the SIR of NHL was assessed among kidney recipients transplanted between 1st January 2000 and 31st December 2007. There were 8490 recipients in this group after excluding 110 recipients whose immunosuppression data were not available.

7.4.5.1 Impact of induction agent on the SIR of NHL

Of the 8490 kidney recipients, 8326 (98.07%) did not receive any induction agent. Of the remaining 164, ALG only was used in 139 recipients, AKT3 only in 8 recipients and both ALG and OKT3 were used in the remaining 17 recipients. The SIR for NHL among kidney recipients based on their induction agent is shown in Table 7.6.

Table 7.6 SIR for NHL among kidney recipients based on their induction agent

Induction	Number of recipients	Observed number	Expected number	SIR (95% CI)	p-value
Received	164	1	0.08	13.1 (0.2, 72.9)	0.996
Not received	8326	50	4.2	11.9 (8.8, 15.7)	

7.4.5.2 Impact of ciclosporin and tacrolimus on the SIR of NHL

Of the 8490 recipients, 4270 (50.3%) received tacrolimus, 3112 (36.7%) received ciclosporin, 1050 (12.3%) received both ciclosporin and tacrolimus, and the remaining 58 (0.7%) received neither. The SIR for NHL were compared among these four recipient groups and the results are shown in Table 7.7.

Table 7.7 SIR for NHL among kidney recipients on ciclosporin or tacrolimus

	Number of recipients	Observed number	Expected number	SIR (95% CI)	p-value
Ciclosporin group	3112	25	2.1	11.8 (7.7, 17.5)	0.69
Tacrolimus group	4270	21	1.6	13.1 (8.1, 20.1)	
Both	1050	5	0.5	9.4 (3, 21.9)	
Neither	58	0	0.03	0	

7.4.5.3 Impact of azathioprine and MMF on the SIR of NHL

Of the 8490 recipients, 2510 (29.6%) received azathioprine, 3692 (43.5%) received MMF, 1140 (13.4%) received both azathioprine and MMF and 1146 (13.5%) received neither. The SIR for NHL were compared among these four recipient groups and the results are shown in Table 7.8.

Table 7.8 SIR for NHL among kidney recipients on azathioprine or MMF

	Number of recipients	Observed number	Expected number	SIR (95% CI)	p-value
Azathioprine group	2510	18	1.6	11.2 (6.7, 17.7)	0.40
MMF group	3692	18	1.4	13.0 (7.7, 20.6)	
Both	1140	9	0.6	16.1 (7.4, 30.6)	
Neither	1146	6	0.7	8.2 (3.0, 17.8)	

7.4.6 HLA and PTLD

Table 7.9 shows the odds ratios for PTLD among recipients with different HLA antigens. None of the 46 antigens showed a significant association with PTLD, considering a Bonferroni corrected p value of less than 0.001. This p value was calculated using a significance level of 0.05/n, where n is the number of comparisons (n=46 in this instance), to give an overall 5% significance level.

Table 7.9 HLA antigens and their association with PTLD among kidney recipients

HLA	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
A1	1.23 (0.70, 2.15)	0.48	1.24 (0.71, 2.18)	0.45
A2	1.16 (0.67, 2.10)	0.59	1.16 (0.67, 2.00)	0.60
A3	1.15 (0.63, 2.11)	0.64	1.14 (0.62, 2.07)	0.68
A9	1.08 (0.54, 2.16)	0.82	1.10 (0.50, 2.19)	0.78
A10	1.11 (0.44, 2.81)	0.82	1.06 (0.42, 2.67)	0.91
A11	1.75 (0.88, 3.51)	0.11	1.78 (0.89, 3.56)	0.10
A19	0.43 (0.19, 0.95)	0.04	0.42 (0.19, 0.94)	0.03
A28	0.72 (0.22, 2.31)	0.58	0.71 (0.22, 2.28)	0.56
A36	0	>0.99	0	>0.99
A80	0	>0.99	0	>0.99
B5	0.76 (0.27, 2.12)	0.60	0.76 (0.27, 2.12)	0.60
B7	0.93 (0.48, 1.75)	0.83	0.91 (0.49, 1.71)	0.77
B8	1.74 (0.99, 3.07)	0.05	1.82 (1.03, 3.21)	0.04
B12	1.38 (0.79, 2.41)	0.26	1.34 (0.77, 2.34)	0.30
B13	0.47 (0.07, 3.44)	0.46	0.49 (0.07, 3.54)	0.48
B14	1.13 (0.41, 3.13)	0.82	1.12 (0.40, 3.11)	0.83
B15	1.05 (0.47, 2.33)	0.90	1.03 (0.46, 2.29)	0.94
B16	0.35 (0.05, 2.54)	0.30	0.34 (0.05, 2.44)	0.28
B17	0.42 (0.10, 1.74)	0.23	0.44 (0.11, 1.81)	0.26
B18	0.75 (0.23, 2.42)	0.63	0.74 (0.23, 2.39)	0.62
B21	1.25 (0.39, 4.03)	0.71	1.20 (0.37, 3.87)	0.76
B22	1.29 (0.40, 4.14)	0.67	1.22 (0.38, 3.92)	0.74

HLA	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
B27	0.20 (0.03, 1.47)	0.11	0.21 (0.03, 1.49)	0.12
B35	1.49 (0.75, 2.97)	0.26	1.50 (0.75, 2.99)	0.25
B37	0.71 (0.10, 5.15)	0.73	0.70 (0.10, 5.11)	0.73
B40	0.70 (0.28, 1.76)	0.45	0.70 (0.28, 1.76)	0.45
B41	0	>0.99	0	>0.99
B42	0	>0.99	0	>0.99
B46	0	>0.99	0	>0.99
B47	0	>0.99	0	>0.99
B48	0	>0.99	0	>0.99
B53	0	>0.99	0	>0.99
B70	0	>0.99	0	>0.99
B78	0	>0.99	0	>0.99
B82	0	>0.99	0	>0.99
DR1	0.80 (0.39, 1.63)	0.53	0.76 (0.37, 1.57)	0.46
DR2	0.58 (0.29, 1.16)	0.12	0.57 (0.29, 1,14)	0.12
DR3	1.32 (0.73, 2.37)	0.34	1.39 (0.78, 2.49)	0.27
DR4	1.08 (0.62, 1.91)	0.78	1.09 (0.62, 1.92)	0.77
DR5	0.67 (0.29, 1.58)	0.36	0.65 (0.28, 1.54)	0.33
DR6	1.47 (0.82, 2.66)	0.20	1.46 (0.81, 2.63)	0.21
DR7	1.25 (0.69, 2.26)	0.45	1.25 (0.69, 2.25)	0.47
DR8	0	>0.99	0	>0.99
DR9	0	>0.99	0	>0.99
DR10	0	>0.99	0	>0.99
DR103	2.51 (0.90, 7.00)	0.08	2.41 (0.86, 6.74)	0.09

7.5 Discussion

7.5.1 Brief summary of findings

1. The SIRs of NHL were significantly higher among the recipients of kidney, liver, heart and lung transplantation compared with the matched non-transplant population. The SIRs of HL were significantly higher among the recipients of kidney, liver and heart but not lung transplantation.

2. The SIRs of NHL were significantly higher among paediatric transplant recipients than among adult recipients.

3. The SIRs of NHL did not significantly change over the three decades of transplantation among the kidney, liver, heart and lung transplantation recipients.

4. The recipient survival after the diagnosis of PTLD remained poor and did not change significantly over the three decades of transplantation.

5. The use of induction agent, ciclosporin, tacrolimus, azathioprine or MMF was not associated with post-transplant NHL among the recipients of kidney transplantation.

6. Among the recipients of kidney transplantation, none of the 46 HLA antigens tested, showed a significant association with PTLD.

7.5.2 Strengths and limitations of the study

The size of the cohort and the duration of the study are its strengths. The cancer data were obtained from the Office for National Statistics, which in turn received the cancer data from the Cancer Registries. The Cancer Registries have several continuous quality control mechanisms in place to ensure a high degree of completion in registering cases with cancer. These measures are likely to increase the accuracy of the data and the conclusions drawn from the analysis. This study also has several important limitations. The EBV data were not

available resulting in inability to analyse the impact immunosuppression and HLA among EBV positive and negative subgroups. The data regarding the use of EBV chemoprophylaxis were not available. Also, the data regarding the site of involvement of PTLD, histological type or treatment of PTLD were not available. The immunosuppression and HLA data were only available for a subgroup of the cohort. Furthermore, the immunosuppression data were not comprehensive, limited to three time points within the first year after transplantation. The cancer registration data were limited to the first registered cancer after transplantation so in some recipients who may have had another type of cancer first, followed by PTLD, the diagnosis of PTLD would not be captured resulting in an underestimation of the risk of PTLD. Although the Cancer Registries in the UK adopt several internal and external audit mechanisms to maintain a comprehensive registry (as detailed in sections 3.5.2 and 4.5.2) some under-registration is possible.

A further detailed assessment of strengths and limitations of this research is included in sections 8.2 and 8.3.

7.5.3 SIR of PTLD

Overall SIR for NHL of 13.8 in the UK transplant cohort I studied was higher than the rates reported from transplant registries in Sweden (SIR 6.0) (Adami et al., 2003), Finland (SIR 4.8) (Kyllonen et al., 2000) and Canada (SIR 8.8) (Villeneuve et al., 2007). The Swedish study (Adami et al., 2003) included 5931 recipients of kidney, liver, heart, lung and pancreas transplantation performed between 1970 and 1997 whereas the Finnish study (Kyllonen et al., 2000) included 2890 kidney recipients transplanted between 1964 and 1997, and the Canadian study (Villeneuve et al., 2007) included 11155 kidney recipients transplanted

between 1981 and 1988. The reasons for the difference in SIR may include the differences in the prevalence of EBV, the choice and intensity of immunosuppression, cancer registration methods and the geographic variation in the incidence of lymphoma in the non-transplant population.

The data I analysed showed no significant change in the SIR of NHL among transplantation recipients over three time periods, 1980 to1989, 1990 to 1999 and 2000 to 2007. Similar findings were reported from other large studies. Opelz and colleagues studied (Opelz and Dohler, 2004) the Collaborative Transplant Study database which includes data from over 400 transplant centres from 45 countries and analysed the differences in the incidence of PTLD among 195,938 recipients of solid organ transplantation over three time periods, 1985 to 1989, 1990 to 1994 and 1995 to 2001. Similar to the UK data, there was no significant difference in the incidence of PTLD among the kidney recipients.

In the cohort I studied, the SIR of NHL was higher among heart and lung recipients as compared with kidney or liver recipients, and among paediatric recipients than adult recipients. Similar findings of higher incidence of NHL among cardiothoracic recipients and among younger recipients were found in other large national studies from Sweden (Adami et al., 2003) and Canada (Villeneuve et al., 2007).

7.5.4 PTLD and recipient survival

The recipient survival after the diagnosis of PTLD was poor in the cohort I studied. The mortality within the first year of diagnosis of PTLD ranged between 47.6% for kidney recipients and 52.6% for lung recipients. The survival rates did not improve during the three

decades of transplantation. These findings were similar to the findings from the other large registry data (Opelz and Dohler, 2004).

7.5.5 PTLD and immunosuppression

Post-transplant immunosuppression plays a key role in the pathogenesis of PTLD. The analysis of the association of immunosuppression with PTLD faces several challenges in the methodology and statistical modelling. In the post-transplant period, the immunosuppressive agents and their doses vary between the recipients and within an individual recipient, with time. An accurate record of these data is often a challenge to maintain but when maintained, can be critical in reaching useful conclusions. In a large retrospective cohort such as the one I studied, the data are often significantly limited. In this study, the fact the immunosuppression data were limited to 3 fixed time points within the first year after transplantation is likely to be the main reason for the results showing no association between immunosuppressive agents and PTLD. A detailed discussion of the published evidence showing association of various immunosuppressive agents with PTLD is included in sections 1.7.1 to 1.7.5.

7.5.6 PTLD and HLA

T-lymphocytes play a key role in immune-surveillance of cancer cells and EBV-infected cells and protection against PTLD. Effective functioning of T-lymphocytes depends on HLA antigens (discussed in section 1.4.2) and is influenced by several of the immunosuppressive agents used after transplantation (discussed in sections 1.6.1 and 1.6.2). The association of HLA types with PTLD has been studied in few studies. Subklewe and colleagues studied (Subklewe et al., 2006) 155 solid organ transplant recipients with PTLD from eight European

and North American transplant centres and compared them with a control group of 1996 recipients from Berlin. Of the 33 HLA antigens studied, a statistically significant association with PTLD was demonstrated for four antigens - HLA-A03 (OR 0.61, p=0.02), HLA-B18 (OR 1.76, p<0.006), HLA-B21 (OR 2.08, p=0.02) and HLA-DR7 (OR 0.46, p<0.004). There are several important limitations in the methodology used in this study. In spite of including 33 different HLA groups in the analyses, the p-value assumed to indicate statistical significance was not corrected for multiple comparisons. The cohort of PTLD patients was put together by including relatively smaller number of patients from individual centres, ranging from 2 patients from Munich to 40 patients from Paris. These were diagnosed with PTLD over a period of 26 years, between 1977 and 2003. Inherent differences in the risk of PTLD among patients from such diverse background over such a long duration of time were not adjusted during the statistical analysis. The EBV data were available for 144 patients only, 32 from serology and 112 from histology. No data on immunosuppression were included in the analysis. The other large published study (Lustberg et al., 2014) included 106 PTLD cases and 1392 controls from a single centre, Ohio State University. This showed a significant association between PTLD and HLA-B40 (OR 8.38) among EBV negative recipients and HLA-B8 (OR 3.2) among EBV positive recipients. The limitations of this study included lack of immunosuppression data and the single centre nature of the study. The discordance between the results from the two studies discussed here and the results from the cohort I analysed highlight the importance of further data from large multicentre prospective studies including all the relevant confounding factors.

In summary, the incidence of PTLD among the recipients of solid organ transplantation in the UK and their survival following the diagnosis of PTLD showed no statistically significant

change between the time periods of 1980-89, 1990-99 and 2000-07. This study showed no association between the risk of PTLD and the immunosuppressive agents or HLA antigens. However, significant limitations detailed in Section 7.5.2 and later in section 8.3 must be considered before drawing conclusions from this study. Further work from larger prospective multicentre cohorts with comprehensive data are needed to verify the conclusion of this study.

CHAPTER 8

SUMMARY AND CONCLUSIONS

(Some data and text from this chapter have been published

(Desai et al., 2012, Desai et al., 2014, Desai et al., 2015))

8.1 Summary of research findings

In this chapter, a summary of the findings discussed in the previous chapters is made and the strengths and weaknesses of this research are discussed.

Cancer is one of the important complications of solid organ transplantation. Along with infection and cardiovascular disease, cancer is one of the three common causes of death among long-term survivors of organ transplantation (USRDS, 2012, Pruthi et al., 2001, Rabkin et al., 2001, Jung et al., 2011). Cancer in the organ transplant recipient could be classified as:

donor origin cancer (including donor-derived cancer and donor-transmitted cancer)

de novo cancer

recurrent cancer

8.1.1 Setting the scene

Chapter 1 included a brief overview of the history of solid organ transplantation, the development of surgical and anaesthetic techniques, experimentation with xenotransplantation and finally the successful human allotransplantation.

The challenges that arose following the technical success of transplantation related to maintaining the health of the allograft and the recipient such that the graft continued to function and the recipient benefitted with improved length and the quality of life. Perhaps the greatest advance in the long-term post-transplant management was the development of effective immunosuppression. Whilst the immunosuppression improved the graft function by reducing the consequences of rejection, new challenges arose in the form of

adverse effects immunosuppression including agent-specific side effects, increased rates of infection and cancer. At present in the UK, 5-year post-transplant patient survival rates range from 88 to 96% (depending on the type of the donor) for kidney recipients, 80% for liver, 78% for heart and 55% for lung recipients (NHSBT, 2014b). The incidence of cancer is increased in the UK transplant recipients compared with the matched non-transplant population by 2.2 times in the liver recipients, 2.4 times in the kidney recipients, 2.5 times in the heart recipients and 3.6 times in the lung recipients (Collett et al., 2010). The highest increased risk is noted for NMSC (6 to 16 times increased risk depending on the type of transplant), cancers of the lip (20 to 65 times increased risk), the anus (3 to 20 times increased risk) and non-Hodgkin's lymphoma (12 to 30 times increased risk). It should be noted, however, that for some of these cancers, such as anus, the absolute risk remains very low.

Cancer transmission from donors has been reported since early years of transplantation (Martin et al., 1965, Wilson et al., 1968). Major published reports assessing the burden of DTC include the reports from the IPITTR (Penn, 1997) and OPTN/UNOS (Myron Kauffman et al., 2002). The IPITTR report (Penn, 1997) included 117 recipients with 13 types of transmitted cancers. Of the 117 recipients, the cancer was localised to the allograft in 45 recipients (6 died due to the transmitted cancer), locally spread in 6 recipients (no deaths due to cancer) and had distant metastasis in 66 recipients (44 deaths due to cancer). The OPTN/UNOS study (Myron Kauffman et al., 2002) reported 15 (0.01%) cases of DTC among 108,062 recipients. Since the OPTN/UNOS report in 2002, the donor profile has changed (NHSBT, 2014b). The donors are older and have higher rates of obesity. The proportion of

DCD donors has increased. It is likely that these changes in donor characteristics may have an impact on the risk of cancer in the donor and its transmission by transplantation.

The main reason why I chose this topic for research is its potential to improve the clinical practice of transplantation. Every organ offered for transplantation carries some risk of cancer transmission. When an organ is offered, the transplant surgeon, in discussion with the prospective recipient and their family, assesses the risks of accepting the organ for transplantation and compares this with the risks of not accepting. So far, there had not been a national study of the organ donors and the recipients in the UK to assess the extent of cancer transmission. The results of this research, in addition to enabling the estimation of the risk of cancer transmission, have also provided data on the risk factors associated with cancer transmission and the outcome of the recipients with transmitted cancer. Using the data from this research, I have contributed to the development of national guidelines for stratification of the risk of cancer transmission from organ donors. These guidelines are now published (SABTO, 2014).

8.1.2 Donor-transmitted cancer in the transplant recipient

In Chapter 3, the data from a nationwide survey of all the transplant recipients assessing the donor-origin cancer were presented. This survey covered a total of 30765 transplant recipients undergoing transplantation between 1st January 2000 and 31st December 2010. In this group, 18 (0.06%) cases of donor origin cancers were identified, including 3 (0.01%) DDC and 15 (0.05%) DTC. Three DDC included one transitional cell cancer in a kidney recipient, one renal cell cancer in a kidney recipient and one lymphoma in a liver recipient. Of the 15 cases of DTC, 6 were renal cell cancers (all in kidney recipients), 5 were lung cancers (one

lung recipient and 4 kidney recipients), two were lymphoma (both kidney recipients) and one each of neuroendocrine tumour (liver recipient) and colon cancer (liver recipient).

The rate of cancer transmission to the recipients was 0.05% (15 of 30765 recipients). These 15 recipients had received organs from 13 donors. The rate of cancer transmission from the donors was 0.09% (13 of 14986 donors resulted in cancer transmission). Among the donors resulting in transmission of cancer, at the time of transplantation, none of the donors were known to have cancer or a past history of cancer. According to the guidelines from the Council of Europe (COE, 2010) which classify the donors based on their risk of cancer transmission (summarised in Table 1.7), the donors with no known cancer are classed as standard risk donors. So the transmission of cancer had exclusively occurred from standard risk donors.

As none of the donors resulting in cancer transmission had a history of cancer, the risk of cancer transmission cannot be eliminated by strict adherence to these guidelines. This research has established that a small risk of cancer transmission persists despite all precautions. This emphasizes the need to include an explanation of this unavoidable but small risk of cancer transmission whilst taking consent from a prospective recipient.

In this study, among the donor factors, older age was significantly associated with the risk of cancer transmission. Donors older than 45 years of age at the time of donation had a 9 times higher risk of cancer transmission than the donors younger than 45 years. The mean age of the donor in the UK has been increasing and at present 59% of the donors are older than 50 years of age (NHSBT, 2014b). A higher proportion of older donors is likely to

translate into a higher risk of cancer transmission to the recipients from these donors, although it must be noted that the absolute risk for all the donors remains very small at 0.09% (13 of 14986 donors resulted in cancer transmission).

A diagnosis of the transmitted cancer within 6 weeks of transplantation was associated with localised disease, suitability for curative treatment and no deaths attributable to transmitted cancer. On the other hand, later diagnosis of transmitted cancer was more likely to be associated with disseminated disease and death due to transmitted cancer.

Individual cases of cancer transmission often receive coverage in the media (BBCNews, 2011, MailOnline, 2013, CNN, 2009) but these do not help in the assessment of the risk for the patients considering a transplantation. The results of this national survey provide a context to the extent of the problem and enable explanation of the actual risk of transmission of cancer to the prospective recipient and its comparison to the risk of death on the waiting list if the prospective recipient wishes to decline the offer of an organ. An explanation of risks and benefits, as accurately as possible, is an essential component of informed consent. Therefore, the data from this study provide important additional information which can be explained to the prospective recipients while consenting them for transplantation.(Desai et al., 2012)

The data discussed in chapter 3 showed that the donors resulting in cancer transmission were not known to have cancer at the time of accepting the organs for transplantation. This led to the next research question: what is the outcome of the transplantation from the donors with a previous history of cancer? This was discussed in chapter 4.

8.1.3 Donors with a history of cancer

The guidelines from the Council of Europe (Table 1.7) classify the risk of transmission of cancer from the donor, based on the donor's history of cancer. The guidelines, being revised at this time, divide the donors in to three categories: standard risk, non-standard risk and unacceptable risk. While the effort to stratify the risk among the donors is worthwhile, the terminology used for the donor risk categories is misleading. In particular, the 'unacceptable risk' seems to indicate that the donors in this category pose a risk of cancer transmission that is not acceptable for transplantation regardless of the risk of non-transplantation to the prospective recipient. Considering that the evidence supporting this classification comes not from high quality evidence but from case reports and retrospective registry reports, such categorical terminology used to classify the risk among donors appears to be potentially misleading. For example, in a patient with acute liver or heart failure listed for transplantation on super-urgent priority, the risk assessment would be considerably different from another patient needing transplantation for chronic organ failure. Whilst the annual rates of removal from and death on the waiting list are as high as 4% and 2% for kidney, 10% and 6% for heart, 5% and 10% for lung and 8% and 5% for liver transplant lists respectively (NHSBT, 2014b), the consequences of not accepting an organ must be carefully considered particularly when the actual risk of cancer transmission posed by an organ is likely to be very small.

Thus, strict non-critical adherence to the guidelines may result in non-availability of organs for transplantation to some critically ill patients and also may result in wastage of some donor organs. To my knowledge, in the published literature, there has not been a study of

organ donors based on their classification of the risk of cancer transmission and the assessment of outcomes of the recipients of such organs.

Over a period of 19 years (1990 - 2008), 17639 actual organ donors from England were assessed for a history of cancer diagnosed before organ donation. A total of 202 (1.15%) donors had a history of cancer diagnosed prior to organ donation including 61 (0.35%) donors belonging to the types classed as 'unacceptable risk' of cancer transmission by the Council of Europe guidelines. The cancer was diagnosed at the time of organ retrieval in 13 (0.07%) donors. The cancers diagnosed at retrieval included renal cell cancer (5 donors), NHL (2), unspecified (2), metastatic adenocarcinoma, sarcoma, cancer of the pancreas and lung (1 each). Of these, the cancer of the pancreas was transmitted to the kidney recipient. The recipient was treated with excision of the transmitted cancer and was alive at 1 year following excision.

From these 61 donors with cancers belonging to the types classed as 'unacceptable risk' of cancer transmission, 140 organs had been transplanted into 133 recipients. The survival analysis confirmed no significant difference in the recipient survival between the recipients from the donors with an 'unacceptable risk' and the recipients from donors with standard/non-standard risk. At 10 years of follow-up, transplant recipients had benefitted by an additional 944 person-years of survival as a result of using organs from the 'unacceptable risk' donors. None of the recipients from the donors with an 'unacceptable risk' of cancer transmission developed a transmitted cancer.

After assessing the features of these donor cancers which did not transmit and similar reports in the literature of cancer non-transmission, I made the recommendations that the organs from a sub-group of the donors with a history of cancer may be considered for transplantation after careful assessment of risks to the recipient and an informed consent.

The factors associated with caner non-transmission are:

cutaneous melanoma, curative treatment with a cancer-free period of more than 5 years,

stage 1 breast cancer with curative treatment and a cancer-free period of more than 5 years,

ovarian cancer with curative treatment and a cancer-free period of more than 10 years,

colon cancer with curative treatment and a cancer-free period of more than 5 years.

It is important that these recommendations should be used with careful risk assessment of the recipient and an informed consent. These recommendations have been included in the UK national guidelines for classification of cancer transmission risk from organ donors (SABTO, 2014) (Desai et al., 2014).

8.1.4 Recurrent cancer after transplantation

The outcome of the recurrence after transplantation of a cancer treated prior to transplantation is poor, often fatal (Penn, 1993). So the assessment of the risk of such recurrence is one of the important factors considered while listing patients for transplantation. The largest published report assessing this risk (Penn, 1993) has several limitations including reporting bias due to voluntary reporting, incomplete denominator due to non-inclusion of all cases of transplantation and lack of differentiation of recurrent

cancers from de novo post-transplant cancers. In chapter 5, the data from 4835 solid organ transplant recipients from the West Midlands region of the UK were presented. These recipients were assessed for a history of cancer prior to transplantation and a recurrence of cancer after transplantation. Of the 4835 recipients, 64 (1.32%) recipients had a history of cancer prior to transplantation. There were five cases of recurrence of cancer after transplantation including 3 cases of melanoma, one case each of leiomyosarcoma and testicular germ cell cancer. In all the five cases, the recurrent cancer proved fatal. Of the 59 recipients who did not develop a recurrence of cancer, 50 had been transplanted at least 2 years following the diagnosis of cancer. There were no significant associations between individual immunosuppressive agents and the risk of recurrence of cancer, although the effect may not be apparent due to small numbers.

Although the results indicated a favourable outcome for the patients transplanted following a minimum of 2-year wait after the diagnosis of cancer, these outcomes should be considered with caution. The number of patients transplanted with a previous history of cancer was small and the numbers of patients with individual types of cancer were very small indicating a high degree of selection of recipients. So the outcomes noted in this study may not be generalised to all patients undergoing transplantation. These limitations are discussed further in section 8.2.3.

8.1.5 CMV and the risk of post-transplant cancer

There is conflicting evidence in the published literature assessing the impact of CMV on the risk of cancer after transplantation. Couzi and colleagues followed up a cohort of 131 recipients of kidney transplantation for 8 years and reported a 5-fold higher risk of cancer

among CMV naïve recipients (Couzi et al., 2010). In contrast, Courivaud and colleagues reported from a cohort of 455 kidney transplant recipients, an increased risk of cancer among the recipients exposed to CMV before transplantation (HR 1.83, p=0.009) and among the recipients with post-transplant CMV replication (HR 2.17, p=0.044) (Courivaud et al., 2012). A common limitation of both these studies is small cohort size.

In chapter 6, I presented the risk of post-transplant cancer in a cohort of 22461 solid organ transplant recipients over a period of 10 years. The recipients were divided into four groups based on the donor and recipient CMV IgG status at the time of transplantation: D-R-, D-R+, D+R+ and D+R-. There was no significant difference in the risk of cancer between these four groups. Furthermore, no significant difference in the risk of developing 23 different types of cancer was noted. The survival analysis showed that as compared to the other groups, the 10-year recipient survival was significantly lower (and the risk-adjusted hazard of death was higher) among D+R- recipients of kidney, lung and heart but not the liver transplantation. The analysis of the cause of death showed that the proportion of recipients with cardiovascular death was significantly higher among the D+R- recipients. Although it was not possible to assess the mechanisms by which CMV may be increasing the mortality, the discussion of the chapter 6 included several reports from the published literature where CMV has been shown to be associated with increased rates of graft dysfunction, atherosclerosis and cardiovascular disease. (Desai et al., 2015)

8.1.6 Post-transplant lymphoproliferative disorders

PTLD, along with non-melanoma skin cancer is one of the two most common cancers after solid organ transplantation (Collett et al., 2010, Buell et al., 2005). In chapter 7, an

assessment was made of the incidence of PTLD, survival of the recipients after the diagnosis of PTLD and the factors influencing the incidence and the survival. A cohort of all the recipients of first solid organ transplantation in the UK between 1980 and 2007 included a total of 37617 transplant recipients. Among these, 620 (1.65%) cases of PTLD were identified. SIR was used to compare the risk-adjusted incidence rates in different subgroups. The SIR for NHL was 12.3 among kidney recipients, 13.0 among liver recipients, 19.5 among heart recipients and 30.0 among lung recipients. Chronological changes in the incidence were assessed over 3 decades: 1980 to 1989, 1990 to 1999 and 2000 to 2007. Over these three decades, there was no significant change in the SIR of NHL or HL among the kidney, liver, heart or lung recipients. The recipient survival following the diagnosis of PTLD was poor: among the recipients with PTLD, the overall 1-year survival was 52.4% for kidney recipients, 49.1% for liver recipients, 53.4% for heart recipients and 47.1% for lung recipients. The recipient survival following the diagnosis of PTLD did not change significantly over the three decades. The impact of various immunosuppressive agents and HLA antigens on the incidence of PTLD was assessed among 8490 recipients of kidney transplantation. No significant association with PTLD was found for any of the immunosuppressive agents (induction agent, ciclosporin, tacrolimus, azathioprine or MMF) or the HLA antigens. The limitations of the immunosuppression data, discussed in section 8.3 must be considered while interpreting these results.

8.2 Strengths of this research

Much of this research is based on a collaboration of the data from two comprehensive national databases: the UK Transplant Registry and the Cancer Registries. Additional data supplementing these are from the recipient databases maintained at the individual

transplant centres and the Office for National Statistics. This research draws its strengths from the direct impact of the new evidence identified, on the clinical practice of transplantation and from the strengths of the data utilised in this research.

8.2.1 New evidence with impact on clinical practice

This research presents the results of the first national comprehensive survey of all organ recipients to identify cases with donor-transmitted cancer. The survey involved searching for the cases of transmitted cancers from multiple sources including patient databases at transplant centres across the country, the UK Transplant Registry and the clinical governance records at NHSBT. The detailed nature of this search is likely to have resulted in identification of most of the cases of cancer transmission by transplantation in the UK.

The results of this survey have enabled the calculation, for the first time in the UK, of the rate of transmitted cancer among the recipients of solid organ transplantation. This rate of cancer transmission has provided vital information for the transplant team and for the prospective recipient to understand the extent of the risk of cancer transmission. Apart from improving clinical management, the understanding of the risk of cancer transmission has also enabled informed consent to be more comprehensive.

This study provides some data regarding the management and outcome of the recipients with transmitted cancer. It also identified the differences between the clinical features, management and the outcomes of recipients with early DTC compared against the recipients with late DTC. The differences highlighted by this study, between the recipients diagnosed with a DTC soon after transplantation as opposed to those with a late diagnosis

of DTC, in terms of the extent of cancer, amenability to curative excision and also differences in DTC related mortality, will provide guidance for the management of the recipients with DTC.

A higher risk of DTC from older donors was identified by this research. This is likely to forecast an increased risk of cancer transmission in the coming years, in view of the increasing average donor age in the UK. However, it must be noted that the absolute risk of cancer transmission is very low.

The study of the donors with a history of cancer (chapter 4) demonstrated non-transmission of cancer from such donors in a substantial cohort of recipients. As a result of this research a sub-group of donors with a previous history of certain type of cancers with a very low risk of cancer transmission has been identified. This evidence has contributed to the development of national guidelines for transplantation of organs from deceased donors with cancer or a history of cancer (SABTO, 2014). These guidelines are now in use and have the potential to increase the number of organs used for transplantation resulting in valuable additional survival for the recipients.

A common limitation of the published studies assessing the impact of CMV on the risk of post-transplant cancer is the small number of recipients included. With a cohort size of 22461, which in my knowledge is the largest study assessing this question, my research overcomes this limitation. Consequently, the absence of association between CMV and the risk of post-transplant cancer shown in this research is likely to be a reliable result as opposed to the conflicting associations between CMV and cancer shown in studies with

smaller cohorts. In addition, this research showed a poorer long-term post-transplant survival among the CMV negative recipients of kidney, heart or lung transplantation who received an organ from a CMV positive donor. These results provide evidence for matching the CMV status of the donor and the recipient.

8.2.2 Quality of data: the UK Transplant Registry

The UK Transplant Registry is a comprehensive database, which records the data from all organ donation and transplantation activity in the UK. Data are regularly collected and included to the UK Transplant Registry by a variety of professionals including Specialist Nurses for Organ Donation, National Organ Retrieval Service personnel, transplant doctors, recipient transplant coordinators, data managers at individual transplant centres and other hospital staff. Maintenance of a reliable database is a high priority and a dedicated Information Services team oversees the accuracy of the data. The Information Services team runs a process called 'Stats for Verification' which checks, at quarter-yearly intervals, that the organ usage is recorded correctly on the registry. The CUSUM analysis is used to check allograft failure and recipient deaths. There is regular cross verification of the transplant registry data against the independent recipient follow-up data held by the transplant centres and any discrepancies identified are rectified.

The procedures of data management adopted by the Information Services team are regularly audited internally to ensure high degree of accuracy. The UK Transplant Registry practices double-data entry enabling comparison and validation of data entry processes to ensure accurate input.

In accordance with the specification of the Human Tissue act, all retrieved organs are tracked, accounted for and signed for at the point of retrieval and the point of use/non-use. These forms are used to crosscheck the data on the UK Transplant Registry.

As a consequence of these comprehensive and continuous quality control interventions, the data held by the UK Transplant Registry achieves a high degree of accuracy. The conclusions drawn from the analyses of such high-quality data, such as the conclusions of my research are likely to be valid although, as discussed below in section 8.3, there are caveats.

8.2.3 Quality of data: the cancer registries

The UK Association of Cancer Registries is widely regarded to maintain a highly reliable database (UKACR, 2013). Cancer registries in the UK collect a wide range of data items including patient demographics, tumour details, treatment modalities and death details. These records are coded by experienced registrars trained to the UK Association of Cancer Registries standards, using internationally recognised ICD10 topography and ICD-O-3 morphology codes. All data are captured locally and inputted into regionally held databases that are then merged to form the National Cancer Data Repository. The quality of the data held by the cancer registries is rigorously verified to maintain the accuracy, both prior to and after combining of these local databases. Cancer registries make every effort to record all malignancies by use of a range of data sources, in order to ensure that the most accurate information is captured. The data sources that are commonly used by cancer registries include hospital patient information systems, hospital episode statistics, cancer waiting time data, pathology reports, medical records departments, radiotherapy systems, hospices,

general practices, private hospitals, cancer screening programmes, nursing homes, autopsy reports and death certificates.

The number of cancer registrations that each registry records is closely monitored for discrepancies between the actual number of registrations and the expected number of registrations. The results of such comparison are released internally usually, and occasionally in the published literature. One such study assessed the national cancer registration data for breast cancer and compared these to independently collected data held within the General Practice Research Database and showed no significant difference between the rates of registration (Kaye et al., 2000). Another study to test the hypothesis that under-registration of malignancies in England and Wales was associated with poorer survival following a cancer diagnosis in England and Wales compared to other European countries, noted that it was implausible that under-registration occurred to a significant level, and to an extent that would adversely affect the reported survival rates (Woods et al., 2011).

The quality control measures undertaken by the cancer registries would improve the quality of these data and consequently, strengthen the reliability of the conclusions drawn from the research detailed in this thesis.

8.3 Limitations of this research

This research has some important limitations. The reported incidence of DTC must be an underestimate. DTC were identified retrospectively and only those cases were included where donor origin was confirmed or suspected. It is probable that in some cases of cancers

in the recipient, a donor origin was not suspected or investigated. In spite of my exhaustive efforts in searching databases at individual transplant centres to identify all cases of DTC, it is probable that not all cases were identified. (Desai et al., 2012)

The history of cancer in the donors was obtained from the cancer registries. The efforts undertaken by the cancer registries in order to maintain an accurate record of all cases of cancer diagnosed, have been detailed in section 8.2.3. All these measures would have contributed to minimization of missed cases. However, it is possible that there may be some under-registration affecting the accuracy of the conclusions drawn from this research.

Although the increased donor age was the only donor factor associated with an increased risk of cancer transmission, the effect of small numbers must be noted. There may be other donor factors associated with increased cancer transmission risk, which did not reach statistical significance due to the small number of donors who transmitted cancer.

Therefore the estimated risk of transmission of cancer from the donors with a previous history of cancer is likely to be an underestimate. Because of the limitations of the data recorded by the registry, I was able to assess only the risk of cancer transmission to recipients resident in England: among the recipients from the donors with a high risk of cancer transmission, 133 (86%) recipients (residents of England) were included in my study; from the same donors, there were 22 (14%) other recipients who lived outside England and cancer transmission to these recipients was not assessed. An occult transmitted cancer may have gone undiagnosed in cases where the recipient died soon after transplantation. Extending the recurrence rates of dormant cancers from the immunocompetent population

to recipients of non-renal transplants (where stopping immunosuppression is not usually a viable therapeutic option) is also likely to result in imprecise risk estimation. For these reasons, this study will underestimate the cancer transmission risk. (Desai et al., 2014)

The teams facilitating donation-transplantation applied a high level of screening in donor selection by carefully assessing the donor factors and balancing them with the clinical situation of the recipients. The acceptance and the use of organs from a donor with a history cancer was assumed to imply that the tumour was correctly treated, appropriately followed-up, and that the retrieving surgeon performed thorough laparotomy and thoracotomy looking for evidence of recurrence. For these reasons, the donors in this study represent a carefully selected cohort and caution must be used while extrapolating the conclusions of this research to all potential donors with a history of cancer. (Desai et al., 2014)

While assessing the risk of recurrence of cancer treated prior to transplantation (chapter 5), despite the reassuring results showing low rates of recurrence, the limitations of the data must be considered. Numbers are relatively small so misleading conclusions may be drawn. In spite of a large initial cohort, the number of recipients who had a history of cancer was small indicating a high degree of selection. Moreover, the patients who underwent transplantation were carefully evaluated prior to transplantation and so represent a carefully selected cohort and any conclusions drawn from this analysis will not be directly applicable to all candidates. It is therefore difficult to develop robust evidence-based guidelines to help identify patients with pre-existing cancer who may not benefit with transplantation because of lack of data, with small number of patients reported,

inconsistency of reporting, the diversity in the type, stage and treatment of cancer and the immunosuppressive regimen. It is difficult to confirm if the lack of association between the risk of cancer recurrence and the immunosuppressive agents is real because of the relatively small number of recipients and also because the immunosuppression data were not comprehensive as they were limited to the agent at three time points within the first year of transplantation.

Missing data is another important and inevitable limitation encountered whilst assessing the data retrospectively from a large national transplant registry. The CMV data were not available for a large proportion (35%) of recipients and these were excluded. The CMV status was recorded at the time of transplantation and any recipients with post-transplantation acquisition of CMV infection were not identified. Furthermore, in a significant proportion (36% of the 6213) of patients, the cause of death was not specified. The data regarding pharmacological prophylaxis against CMV infection were not available. The risk of cancer would be underestimated in cases where the recipient had multiple cancers, as the data for the first diagnosed post-transplantation cancer only were included. (Desai et al., 2015)

With regards to the data assessing the incidence and survival of the recipients with PTLD several important limitations are likely to influence the conclusions drawn. EBV is one of the important risk factors associated with the development of PTLD. The EBV data were not available for the entire cohort, resulting in inability to analyse the impact immunosuppression and HLA among EBV positive and negative subgroups. The data regarding the use of EBV chemoprophylaxis were also not available. Also, the data regarding

the site of involvement of PTLD, histological type or treatment of PTLD were not available. The immunosuppression and HLA data were only available for a subgroup of the cohort. Furthermore, the immunosuppression data were not comprehensive, limited to three time points within the first year after transplantation. The cancer registration data were limited to the first registered cancer after transplantation so in some recipients who may have had another type of cancer first, followed by PTLD, the diagnosis of PTLD would not be captured resulting in an underestimation of the risk of PTLD.

Finally, the practice of donation-transplantation is evolving: the profile of the donor is changing, with more donors becoming older and heavier; both factors are likely to increase the risk of cancer. The evaluation of the potential donor is improving so cancer and other risks are becoming better identified; the improved training of the retrieval teams is likely to lead to a more systematic examination of the abdomen and chest, so possibly identifying more cancers in the donor. The immunosuppressive regimens are also changing: some of the newer agents, such as mTOR inhibitors, have an anti-neoplastic effect, and so may modify the likelihood and impact of cancers. Finally, the greater awareness of cancer in the allograft recipient may lead not only to earlier diagnosis but also greater emphasis on reducing cancer risk, such as reinforcing the need to stop smoking or avoiding excess alcohol.

Thus conclusions based on historical data must be extrapolated with caution.

8.4 Conclusions

The research detailed in this thesis provides new evidence with a direct impact on the clinical practice of transplantation. Donor-transmitted cancer is a rare complication of solid organ transplantation but frequently results in graft loss and death. The risk of cancer transmission cannot be completely eliminated because the transmission occurred from standard-risk donors. This information should be included in informed consent for prospective recipients. The recipients with a transmitted cancer that is localised to the graft are likely to benefit with explantation or excision but in transplants other than kidney or pancreas, the benefits of explantation should be balanced against the risks of retransplantation.

Organs from carefully selected donors with a history of cancer can be used for transplantation with a low risk of cancer transmission, whilst providing valuable additional survival benefit to the recipients. Strict implementation of present guidelines is likely to result in overestimation of cancer transmission risk in some donors. (Desai et al., 2014)

Recurrence after transplantation of cancers treated prior to transplantation is a rare complication among the recipients selected after careful assessment of risks, after a minimum of 2-year wait between the diagnosis of cancer and transplantation. The outcome of cancer recurrence is poor, frequently fatal.

CMV does not influence the risk of post-transplant cancer. There is no chronological change in the incidence of or the survival after a diagnosis of PTLD among the recipients of solid organ transplantation in the UK.

CHAPTER 9

FUTURE WORK

(Some data and text from this chapter have been published

(Desai et al., 2012, Desai et al., 2014, Desai et al., 2015))

Future developments in several areas have the potential to contribute towards better estimation of the risk of cancer transmission from organ donors, reducing the risk of post-transplant cancer and improving the management and outcomes for the recipients with cancer. These are discussed here.

9.1 Improvements in data

There are several areas related to DTC where there is a scarcity of good quality evidence. The fact that several large national cohorts have found a small number of cases of DTC highlights the importance of international collaboration. Data from larger cohorts of recipients with DTC are likely to enable identification of trends, which can guide the management of future cases of DTC, both in terms of risks/benefits of surgical resection and the choice of immunosuppression. It is also useful to identify the donor characteristics associated with cancer transmission. The risk of cancer transmission is different from donors with different types of cancers and also depends on the duration between successful cancer treatment and organ donation. These characteristics can be more reliably assessed in a larger cohort. (Desai et al., 2014)

The outcomes for the recipients of organs from donors with a history of cancer were not routinely reported to the UK Transplant Registry. Since the development of the guidelines to which this research has contributed, it is now recommended that NHSBT should maintain a register of the outcomes of such recipients (SABTO, 2014). Mandatory reporting of all cases of DTC is now required under each Transplant Unit's licence from the Human Tissue Authority. This reporting is crucial in creating a comprehensive database which can provide evidence for the selection of donors with lower risk of cancer transmission, exclusion of

donors with a higher risk, specific transmission rates of different types of donor cancers and the management of other organ recipients from the same donor when recipient of one organ develops a DTC. (Desai et al., 2014)

My research centred around a collaboration of the data from the UK Transplant Registry and the data from the cancer registries in the UK. An important limitation of the methods used was that the data were matched between the two databases, at one point of time. Conclusions were drawn and recommendations were made for the patients undergoing transplantation in future, based on the historical data. Further analysis of similar data in future transplant recipients is necessary to confirm the findings and improve the validity of the conclusions. A regular and ongoing linkage (annual, for example) between the transplant and the cancer databases will have several advantages. Such linkage would facilitate regular assessment of the incidence and types of cancer in the organ donors and transplant recipients. This linkage will also enable identification of DTC. Changing trends in the incidence, outcomes and transmission risks of different cancers would be identified and this information would contribute towards improving the recommendations. The US Transplant Cancer Match Study (Transplantmatch, 2015) is one such example of ongoing linkage between the national transplant registry data in the USA and the cancer registration data from 16 states of the USA.

The NOTIFY project is an important initiative in collaborating international data regarding multiple outcomes following transplantation with a common theme of improving safety and reducing the risks (NOTIFY, 2010). The NOTIFY project is a joint venture of WHO and CNT, which aims to improve the donor and recipient safety and increase the transparency in the

practice of transplantation. Started in 2010, this project aims to collect data from 36 countries on various complications of transplantation such as transmitted cancer, infection, clinical errors and adverse reactions, with an intention provide evidence to facilitate risk reduction. Data collated from several countries are more likely to increase the robustness of the study and the power of the statistical analysis. However the limitations of such multi-national projects would include diverse demography of donors and recipients, varying inclusion/exclusion criteria for donors with known cancer and genetic differences which may result in heterogeneity in the types of cancers and their biological behaviour. The Council of Europe guidelines for the classification of donor's risk of cancer transmission (COE, 2010) are currently under review. The next edition is likely to include the results of the NOTIFY project as well as the results of the research detailed in this thesis. (Desai et al., 2012)

9.2 Improvements in donor selection and assessment

Whilst assessing the potential donor's suitability for safe organ donation, several additional interventions such as cross-sectional imaging of the donor, urgent histological assessment of any suspicious lesions, urgent autopsy and tumour markers can be considered in order to improve the detection of occult cancers. The detection of occult cancers enables risk assessment and informed decision regarding the use or non-use of the donated organ. The other advantage of using additional interventions to detect and confirm occult cancers would be to avoid inappropriate non-acceptance of donors who may be classed as high-risk of cancer transmission by conventional assessment whereas additional investigation may indicate that the risk of cancer transmission is low. However, along with the advantages, the disadvantages of such interventions must also be considered. These are discussed here.

9.2.1 Cross-sectional imaging

The gap between the supply and the demand for donor organs continues to increase resulting in search for avenues to find additional organs. In recent years, the organs from older donors and donors with co-morbidities have been accepted for transplantation and this trend is likely to continue. The rising age of the organ donor is likely to increase the chances of a donor organ carrying an occult cancer, resulting in transmission of cancer to the recipient. At present in the UK, it is not a mandatory practice to perform cross-sectional imaging of the donor prior to donation. Cross-sectional imaging is more likely to find an occult cancer, facilitating a thorough assessment of the donated organ and non-use of organs considered to be at high-risk of containing a transmitted cancer. There are advantages of identifying the occult cancer in the donor, even after the donated organ has been transplanted. The recipient will be informed, investigated and additional interventions such as excision of the tumour from the allograft, reduction or cessation of immunosuppression, explantation or close monitoring can be considered.

There are several challenges and disadvantages in implementing a routine use of cross-sectional imaging during donor assessment. Most hospitals in the UK have access to CT scan, in working hours as well as out-of-hours, however access to other types of imaging may be limited. In some cases when a lesion is identified on a CT scan, it may need further characterisation by a magnetic resonance imaging (MRI) scan or a positron emission tomography (PET) scan before its malignant nature is ascertained. Availability of these specialised imaging modalities is limited particularly in smaller peripheral hospitals, particularly during out-of-hours period. Even if a scan can be performed out-of hours, the

on-call radiologist may not have the expertise necessary to report a MRI or a PET scan with a degree of accuracy needed to make a decision regarding accepting the organ for donation.

A routine use of cross-sectional imaging in the assessment of all organ donors is likely to be inappropriate and impractical. The use of cross-sectional imaging needs to be targeted to high-risk donors such as older donors, donors with significant risk factors such as smoking, alcohol use and infection with viruses known to predispose to cancer. The routine use of cross-sectional imaging in low-risk donors (such as children or young victims of traffic accidents) is likely to be counter-productive and burden the health care system with wastage of financial and technical resources and the donor's family with avoidable anguish.

9.2.2 Histopathology: biopsy and autopsy

In cases where a suspicious lesion is identified during the assessment of a potential donor, the availability of an expert histopathology opinion on an urgent basis can make a significant difference. Such histopathology opinion, in combination with cross-sectional imaging and blood test results, has the potential to enable the transplant team to differentiate benign lesions from malignant ones with a high degree of accuracy. However, at present in many hospitals in the UK, the availability of histology services is limited to daytime working hours. The Royal College of Pathologists which monitors and regulates the pathology services in the UK, has set out key performance indicators (RCPath, 2010) to provide a direction for future development of pathology services. This document listed out a number of targets to be achieved by the pathology services in the coming years. According to this report, by April 2014, a target of 90% of the diagnostic biopsy samples should be reported within 7 days of the biopsy. There is no target set for providing urgent histopathology services, in cases such

as diagnosis of a possible cancer identified during the assessment of a potential donor. While such a service is likely to be invaluable in deciding the safety of the donor organ and reduce wastage of organs, setting up urgent histopathology services in hospitals across the UK is a significant challenge. This involves major re-structuring of pathology workforce, enabling on-call availability of the biomedical scientists to prepare the histopathology slides and the pathologists to report the samples.

Autopsy of the donor following organ donation is also likely to increase the chances of identification of occult cancers. At present in the UK, donor autopsy is not routinely performed. The advantages of donor autopsy and the challenges in implementing it routinely to all organ donors are similar to the advantages and the challenges of cross-sectional imaging, discussed in section 9.2.1. The availability of urgent histopathology services is also likely to expedite the reporting of autopsies resulting in early management of recipients of organs from donor with cancer.

9.2.3 Tumour markers

None of the tumour markers in clinical use at present have the levels of sensitivity or specificity to be suitable for screening for cancer in the general population (NCI, 2011). For the same reason, a routine use of tumour markers cannot be recommended for screening for cancer in organ donors. Tumour markers under development include proteomic-based or genomic-based markers which are expected to have higher sensitivity and specificity. Examples of such tumour markers under development include markers for prostate cancer (pro-prostate specific antigen (pro-PSA), prostate cancer antigen-3 (PCA3)), ovarian cancer (OVA1 and ROMA) and hepatocellular carcinoma (Des-gamma-carboxy prothrombin (DCP)

and alpha-fetoprotein-L3 (AFP-L3)) (NCI, 2015). At present, these biomarkers are approved by the United States Food and Drug Administration (USFDA) for clinical use in specific situations for diagnostic purposes, but not for screening of cancer. Development of markers for screening of cancer in the future would be of interest to transplant specialists as these markers may be of use in identifying occult cancers in the organ donors and reduce the likelihood of inadvertent transmission of cancer to the transplant recipient.

9.3 Improvements in the recipient management

9.3.1 Lifestyle changes

Post-transplant recipient management should have an emphasis on a healthy lifestyle. Providing guidance and advice on smoking cessation, alcohol moderation and weight management should start when the patient is listed for transplantation and continue throughout the post-transplant period. Transplant centres should develop close links with their local addiction services and nutrition/obesity specialist teams. Specialists such as dietitians, physiotherapists and nurses/doctors specialising in addiction medicine should be involved at an early stage, in the management of selected patients. Many transplant centres already have such facilities, however, with an increasing transplant activity in the UK it is likely that these services will be burdened with an increasing demand. It is imperative that the transplant centres recognise the need for adequate number of specialists and resources to be able to meet the needs of their patients.

The UK national policies on harmful drinking (Alcoholpolicy, 2013) and smoking (Smokingpolicy, 2013) emphasised the ill-effects of excessive alcohol intake and smoking, and the interventions undertaken by the UK government at various levels to reduce the

burden of smoking and harmful drinking. The interventions against smoking include restrictions on sale and promotion of tobacco, implementation of tobacco taxes, anti-smoking campaigns and regulation of e-cigarettes. The interventions against harmful drinking include Change4life campaign which focuses on provision of information, inclusion of an alcohol risk assessment as a routine within the NHS Health check, restriction on advertising alcohol to young people, cutting down the availability of cheap alcohol and a commitment to additional expenditure to be able to meet these services. The rates of smoking (ONS, 2013b) and harmful consumption of alcohol (ONS, 2013a) among adults in the UK are dropping and with these additional efforts it is likely that these trends will continue. Although it is difficult to predict the impact of these interventions on the outcomes after transplantation, the lower rates of tobacco and alcohol consumption will likely have a favourable impact on the risk of post-transplant cancer and cardiovascular disease, and consequently, on post-transplant recipient survival.

9.3.2 Vaccination against oncogenic viruses

The recipients of organ transplantation endure an increased risk of many types of cancers including some cancers in which the risk is increased by a viral infection. These include cancer of the cervix, vagina, vulva, anus, oral cavity (all predisposed by HPV), hepatocellular carcinoma (predisposed by HBV, HCV), NHL (predisposed by EBV) and Kaposi's sarcoma (predisposed by HHV-8). Another intervention with a potential to reduce the risk of post-transplant caner is vaccination of the recipients against oncogenic viruses. At present, among these viruses, effective vaccines are available against HPV and HBV.

In the UK, routine vaccination against HPV for girls aged between 11 years and 14 years was introduced in 2008 as a part of the national vaccination programme (NHSChoices, 2014). This is an important intervention because, vaccination as a part of the national vaccination programme is likely to reach large proportion of schoolgirls in the UK and provide protection against HPV. As a secondary effect of routine vaccination against HPV, in the coming years the proportion of transplant recipients who have been vaccinated against HPV is likely to increase. This is likely to have an impact on the incidence of post-transplant cancer, in particular, cancers predisposed by HPV.

At present, routine vaccination against HBV is limited to individuals considered to be at high-risk of HBV, such as close contacts of a patient with HBV infection, people who are prone to occupational or lifestyle related exposure to HBV and patients listed for liver transplantation. Whilst routine use of HBV vaccination has the potential to reduce the risk of HBV infection and the consequent risk of hepatocellular carcinoma, the disadvantages of this strategy would include the side effects and the risk of vaccine failure along with the impact on healthcare expenditure and resources.

At present, there are no vaccines available for clinical use against HHV-8, CMV, HCV or EBV. Advances in the development of these vaccines would be of interest to selected sub-groups of patients undergoing organ transplantation.

9.3.3 Immunosuppressive agents with anti-neoplastic properties

Post-transplant immunosuppression contributes significantly to the increased risk of cancer after transplantation. Some mTOR inhibitors such as sirolimus and everolimus have, in

addition to immunosuppressive effect, anti-neoplastic properties. Sirolimus is shown to be associated with a lower incidence of cancer, in particular NMSC, in several studies (Campbell et al., 2012, Hoogendijk-van den Akker et al., 2013, Euvrard et al., 2012, Gu et al., 2012). An important challenge in assessing the long-term impact of sirolimus on the risk of post-transplant cancer is the lack of record of comprehensive immunosuppression data. Like the UK Transplant Registry, many large registries record immunosuppression data comprehensively during the initial post-transplant period. During long-term post-transplant follow-up, the degree of detail of immunosuppression data recorded by the registry is reduced significantly. Even the studies from large well-managed national transplant registries have limited the follow-up period to under 3 years whilst assessing the impact of sirolimus on the risk of post-transplant cancer (Kauffman et al., 2005). Sirolimus is often not a preferred first-line immunosuppressant in the early post-transplant period due to its side effects such as delayed wound healing and hepatic artery thrombosis among liver recipients, and is introduced later during long-term post-transplant follow-up. This highlights the importance of an accurate record of the long-term immunosuppression data by large transplant registries to enable assessment of the impact of sirolimus on post-transplant cancer. Other mTOR inhibitors such as temsirolimus have exclusive anti-cancer activity but development of agents with anti-cancer as well as immunosuppressant activity would be of interest in the management of future transplant recipients.

9.3.4 Cancer screening after transplantation

The guidelines recommending cancer screening among transplant recipients include the European best practice guidelines (Europeanguidelines, 2002) and the American Society of Transplantation guidelines (Kasiske et al., 2000). These recommend screening for breast

cancer (annual or biennial mammography for women over 50 years of age), colorectal cancer (annual faecal occult blood test and/or 5-yearly flexible sigmoidoscopy for patients over 50 years), cervical cancer (annual cervical smear and pelvic examination once sexually active), prostate cancer (annual digital rectal examination and PSA measurement for men over 50 years) and skin cancer (monthly skin self-examination and 6 to 12 monthly examination by physician/dermatologist). These recommendations are adapted from the recommendations for screening for cancer in the non-transplant population. There are no published data demonstrating the survival benefit to the transplant recipients undergoing cancer screening or the cost-effectiveness of screening (Wong et al., 2008). Considering the increased risk of several cancers among the transplant recipients and also the impact of the cancer on the survival of the immunosuppressed recipient, future research assessing the risks, benefits and cost-effectiveness of cancer screening will provide valuable evidence.

9.3.5 Surveillance for cancer treated prior to transplantation

The rates of recurrence after transplantation of cancers treated prior to transplantation are shown to be low in several national transplant registry data. However, the outcome of the recipients with cancer recurrence remains poor with limited survival. There are no data assessing the benefit of cancer surveillance in such recipients. Considering the small number of transplant recipients with a previous history of cancer, any research assessing the impact of cancer surveillance on the recurrence of cancer will need international collaboration.

9.3.6 Role of CMV and EBV in post-transplant cancer

There are several limitations in the data presented in this thesis, assessing the impact of CMV on the risk of post-transplant cancer, the most important ones being the incomplete

data and relatively small number of patients with individual types of cancer. The EBV data were not available resulting in significant limitation in the analyses and interpretation of the PTLD data. Several improvements in the recording of the data by the transplant registry would be necessary to undertake an assessment of the interplay of multiple risk factors involved in the development of post-transplant cancer. Future studies will need to be planned prospectively with comprehensive data from larger cohorts of transplant recipients. In such studies, individual types of cancer will likely be represented in bigger numbers and fewer patients will be excluded from the study for lack of record of CMV data, resulting in increased reliability of results and the conclusions. Comprehensive data will also enable an assessment of the incidence and survival rates in the PTLD cohort and in EBV positive and negative sub-groups. The additional data needed would include accurate record of the viral serological status at the time of transplantation and update at regular intervals in the post-transplant period, comprehensive record of immunosuppression and anti-viral prophylaxis and treatment.

CHAPTER 10

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APPENDIX 1

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS WORK

PUBLICATIONS – ORIGINAL ARTICLES

DESAI R, COLLETT D, WATSON CJ, JOHNSON PJ, MOSS P, NEUBERGER J. Impact of Cytomegalovirus on long-term mortality and cancer risk after organ transplantation. Transplantation 2015 Sep; 99(9): 1989-94. PMID 25706273.

DESAI R, COLLETT D, WATSON CJ, JOHNSON PJ, EVANS T, NEUBERGER J. Estimated risk of cancer transmission from organ donor to graft recipient in a national transplantation registry. Br J Surg 2014 Jun; 101(7): 768-74. PMID 24771410.

DESAI R, COLLETT D, WATSON CJ, JOHNSON PJ, EVANS T, NEUBERGER J. Cancer transmission from organ donors-unavoidable but low risk. Transplantation 2012 Dec 27; 94(12): 1200-7. PMID 23269448.

PUBLICATION – REVIEW ARTICLE

DESAI R, NEUBERGER J. Donor transmitted and de novo cancer after liver transplantation. World J Gastroenterol 2014 May 28; 20(20): 6170-6179. PMID 24876738.

PUBLICATION – NATIONAL GUIDELINES

Guidance on Safety of Organs for Transplantation [Online]. Organ Donation and Transplantation Website. Available: http://www.odt.nhs.uk/transplantation/guidance-policies/sabto/

ORAL PRESENTATIONS AT LEARNED SOCIETIES

1. British Transplant Congress, Glasgow, March 2014

Presentation title: Cytomegalovirus is associated with reduced long-term post-transplant survival of renal and cardiothoracic transplant recipients

2. UK and Eire Liver Transplant Annual Congress, January 2014

Presentation title: Which donors with cancer can we use?

3. American Transplant Congress, Seattle WA, May 2013

Presentation title: Death on Wating-List and Risk of Transmission of Cancer: Where Is the Right Balance?

4. American Transplant Congress, Seattle WA, May 2013

Presentation title: Risk of Recurrence of Pre-Existing Cancer in Organ Recipients

5. British Transplant Congress, Bournemouth, March 2013

Presentation title: Risks and Benefits of using Organs from Donors with known Cancer

6. British Transplant Congress, Bournemouth, March 2013

Presentation title: Changing Profile of Organ Donor and its Impact on the Risk of Cancer Transmission

7. British Transplant Congress, Bournemouth, March 2013

Presentation title: Risk of Post Transplant Cancer: Does Cytomegalovirus Play a Role?

8. European Society for Organ Transplantation meeting, Vienna, September 2013

Presentation title: Donor transmitted cancer in kidney recipients: UK experience

9. European Society for Organ Transplantation meeting, Vienna, September 2013

Presentation title: Cancer transmission from organ donors

10. European Society for Organ Transplantation meeting, Vienna, September 2013

Presentation title: De novo post transplant lung cancer: UK experience

11. European Society for Organ Transplantation meeting, Vienna, September 2013

Presentation title: Role of Cytomegalovirus infection in de novo cancer after organ transplantation

12. European Society for Organ Transplantation meeting, Vienna, September 2013

Presentation title: Recurrence of pre-existing cancer following kidney transplantation

13. European Transplant Fellow Workshop, Vienna, September 2012

Presentation title: Cancer transmission risk in organ donors

POSTER PRESENTATIONS AT LEARNED SOCIETIES

1. American Transplant Congress, Seattle, May 2013

Presentation title: Cytomegalovirus and Post-Transplant Cancer: Protection, Predisposition or No Effect?

2. American Transplant Congress, Seattle, May 2013

Presentation title: Lung Cancer in organ transplant recipients

3. American Transplant Congress, Seattle, May 2013

Presentation title: Can the Risk of Cancer Transmission from Organ Donors Be Eliminated?

4. International Liver Congress, Amsterdam, April 2013

Presentation title: Recurrence of pre-existing extra-hepatic cancers following liver transplantation

5. International Liver Congress, Amsterdam, April 2013

Presentation title: Donors with known cancer: an under-used source of additional livers

6. British Transplant Congress, Bournemouth, March 2013

Presentation title: Should a history of cancer preclude transplantation?

7. British Transplant Congress, Bournemouth, March 2013

Presentation title: Lung Cancer in organ transplant recipients

APPENDIX 2

AWARD AND DISTINCTIONS

1. Elizabeth Watson Davidson Best Abstract Award and Travel Bursary, awarded by the University of Birmingham, UK, March 2013.
2. Finalist, 3-Minute Thesis presentation competition, University of Birmingham, September 2013.
3. Posters of Distinction awarded to three posters, American Transplant Congress 2013.

APPENDIX 3

PUBLISHED MANUSCRIPTS

Cancer Transmission From Organ Donors—Unavoidable But Low Risk

Rajeev Desai,[1,5] Dave Collett,[1] Christopher J. Watson,[2] Philip Johnson,[3] Tim Evans,[4] and James Neuberger[1]

Background. Donor origin cancer (DOC) in transplant recipients may be transmitted with the graft (donor-transmitted cancer [DTC]) or develop subsequently from the graft (donor-derived cancer [DDC]).
Methods. Recipients with DOC between January 1, 2001, and December 31, 2010, were identified from the United Kingdom Transplant Registry and database search at transplantation centers.
Results. Of 30,765 transplants from 14,986 donors, 18 recipients developed DOC from 16 donors (0.06%): 3 were DDC (0.01%) and 15 were DTC (0.05%). Of the 15 DTCs, 6 were renal cell cancer; 5, lung cancer; 2, lymphoma; 1, neuroendocrine cancer; and 1, colon cancer. Recipients with DTC underwent explant/excision (11), chemotherapy (4), and radiotherapy (1). Of 15 recipients, 3 (20%) recipients with DTC died as a direct consequence of cancer. Early DTC (diagnosed ≤6 weeks of transplantation) showed a better outcome (no DTC-related deaths in 11 cases) as opposed to late DTC (DTC-related deaths in 3 of 4 cases). Five-year survival was 83% for kidney recipients with DTC compared with 93% for recipients without DTC (P=0.077). None of the donors resulting in cancer transmission was known to have cancer at donation.
Conclusions. DTC is rare but frequently results in graft loss and death. The risk of cancer transmission cannot be eliminated because, in every case, the presence of cancer was not known at donation. This information will allow informed consent for prospective recipients. Explantation/excision is likely to benefit recipients with localized cancer, but in transplants other than kidney/pancreas, the benefits should be balanced against the risks of retransplantation.

Keywords: Organ transplantation, Transmitted cancer, Donor assessment, Cancer transmission risk.

(Transplantation 2012;94: 1200–1207)

Original article

Estimated risk of cancer transmission from organ donor to graft recipient in a national transplantation registry

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Correspondence to: Dr R. Desai, NHS Blood and Transplant, Fox Den Road, Stoke Gifford, Bristol BS34 8RR, UK (e-mail: rajeev.desai@nhs.net)

Background: Transplanted organs carry the risk of inadvertent donor cancer transmission. Some cancers in organ donors have been classified as being associated with a high or unacceptable risk, but the evidence for such recommendations is scanty.

Methods: The risk of cancer transmission from donors characterized as high or unacceptable risk was studied by analysing transplant and cancer registry data. Donors and recipients from England (1990–2008) were identified from the UK Transplant Registry. Cancer details were obtained from cancer registries and classified using guidelines from the Council of Europe and Organ Procurement and Transplantation Network/United Network for Organ Sharing.

Results: Of 17 639 donors, 202 (1·1 per cent) had a history of cancer, including 61 donors with cancers classed as having an unacceptable/high risk of transmission. No cancer transmission was noted in 133 recipients of organs from these 61 donors. At 10 years after transplantation, the additional survival benefit gained by transplanting organs from donors with unacceptable/high-risk cancer was 944 (95 per cent confidence interval (c.i.) 851 to 1037) life-years, with a mean survival of 7·1 (95 per cent c.i. 6·4 to 7·8) years per recipient.

Conclusion: Strict implementation of present guidelines is likely to result in overestimation of cancer transmission risk in some donors. Organs from some donors with cancers defined as unacceptable/high risk can be used safely.

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Impact of Cytomegalovirus on Long-term Mortality and Cancer Risk After Organ Transplantation

Rajeev Desai,[1] Dave Collett,[1] Christopher J. E. Watson,[2] Philip J. Johnson,[3,4] Paul Moss,[5,6] and James Neuberger[1]

Background. There is conflicting evidence of the effect of cytomegalovirus (CMV) infection on survival and the risk of cancer after transplantation. **Methods.** All recipients of kidney, liver, heart, and lung transplants in the United Kingdom between 1987 and 2007 with known CMV immunoglobulin G status were identified from the U.K. Transplant Registry. Based on the donor-recipient CMV status, recipients were grouped into: donor (D) negative recipient (R) negative (D– R–), D–R+, D + R+ and D + R–. Cancer data were obtained from the Office for National Statistics. The impact of CMV infection on survival and cancer incidence was assessed. **Results.** The 10-year posttransplant survival in D–R– recipients (73.6% [95%CI, 72.3, 74.9]) was significantly higher ($P < 0.0001$) than in other recipients (66.1% [65.3, 66.9]). Compared with the D– R– group, the risk-adjusted hazard of death within 10 years of transplantation for D+ R– group was 14% higher for kidney recipients ($P = 0.0495$), 13% higher for liver recipients ($P = 0.16$), 34% higher for heart recipients ($P = 0.01$), and 35% higher for lung recipients ($P = 0.006$). The proportion of recipients with a cardiovascular cause of death was higher ($P = 0.03$) among the recipients exposed to CMV (18%) as compared to the D– R– recipients (16%). The CMV status was not associated with an increased risk of cancer. **Conclusions.** The results from this large study demonstrate that CMV is associated with a significantly increased long-term mortality in kidney and cardiothoracic transplant recipients and an increased risk of cardiovascular death but not of posttransplant cancer.

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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (7): Liver transplant

Donor transmitted and *de novo* cancer after liver transplantation

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Abstract

Cancers in solid organ recipients may be classified as donor transmitted, donor derived, *de novo* or recurrent. The risk of donor-transmitted cancer is very low and can be reduced by careful screening of the donor but cannot be abolished and, in the United Kingdom series is less than 0.03%. For donors with a known history of cancer, the risks will depend on the nature of the cancer, the interventions given and the interval between diagnosis and organ donation. The risks of cancer transmission must be balanced against the risks of death awaiting a new graft and strict adherence to current guidelines may result increased patient death. Organs from selected patients, even with high-grade central nervous system (CNS) malignancy and after a shunt, can, in some circumstances, be considered. Of potential donors with non-CNS cancers, whether organs may be safely used again depends on the nature of the cancer, the treatment and interval. Data are scarce about the most appropriate treatment when donor transmitted cancer is diagnosed: sometimes substitution of agents and reduction of the immunosuppressive load may be adequate and the impact of graft removal should be considered but not always indicated. Liver allograft recipients are at increased risk of some *de novo* cancers, especially those grafted for alcohol-related liver disease and hepatitis C virus infection. The risk of lymphoproliferative disease and cancers of the skin, upper airway and bowel are increased but not breast. Recipients should be advised to avoid risk behavior and monitored appropriately.