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Ziki, Joyce Tukayi

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MALIGNANCY IN RENAL TRANSPLANT RECIPIENTS AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL: 1990-2010

Dr Joyce Tukayi Ziki

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in the Department of Internal Medicine

Johannesburg, August 2016

DECLARATION

I, Joyce Tukayi Ziki declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the Department of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

……. (Signature of candidate)

……day of August , 2016

DEDICATION

This work is dedicated to my husband -Desmond Ziki, who has unconditionally supported me through my academic endeavors' and to my parents Butty and Beauty Jumira, who have always pushed me to academic excellence.

ABSTRACT

Introduction

Post transplant malignancy (PTM) is a recognized long term complication in renal transplant recipients. Many studies have been conducted on this group of patients over the last 50 years to assess the impact of various immunosuppressant drug regimens, geographical locations, ethnicity, and age at the time of transplant on the risk of developing a PTM. The incidence of PTM has been shown from these studies to vary from 3% to 11%. Many inconsistencies exist in these studies, but the one common finding is that the incidence of malignancy is increased in renal transplant recipients compared to the general population.

Aims and Objectives

The objectives of this study were to determine the incidence of PTM at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in the period from 1990 to 2010; to calculate the mean time to diagnosis of PTM; determine the association of PTM and immunosuppressive drug regimens and identify risk factors associated with developing a malignancy post renal transplant.

Methods

The study design was a retrospective review of the medical records of patients transplanted between 01/01/1990 and 31/12/2010 at CMJAH, South Africa. All recipients above 18years of age transplanted during this study period were included in the review. All recipients who rejected, died or were transferred to other centres within six months of transplantation were excluded. A total of 668 records were included in this study for analysis. Information retrieved from the files included patient demographics (age at transplantation; gender; ethnic group, year of transplantation), aetiology of end-stage renal disease, the source of graft, the number of times treated for rejection, oncogenic viruses diagnosed, immunosuppressant regimens and outcomes of the recipients. For those recipients who developed a malignancy,

the time from transplantation to diagnosis of cancer was calculated and the histological diagnoses documented.

Results

The incidence of PTM in this study was 7.0% (95% CI 5.2-9.4) for the era under review. The cumulative incidence of cancer from transplantation increased with follow-up time. The mean time to diagnosis of malignancy was: 3.4 years, 6.6 years, 7.4 years and 8.1 years for Kaposi Sarcoma (KS), post transplant lymphoproliferative disorder (PTLD), skin and solid organ malignancy, respectively**.** The distribution of post transplant malignancy (PTM) was skin cancers 44.7%; KS 23.4%; PTLD 14.9%; solid organ tumours 17.0 %. The recipients who developed cancer were significantly older at transplantation with a mean age of 42.9 years compared to those without PTM whose mean age was 36.3 years. Age and year of transplantation period 1996-2000 were independent risk factors for developing a malignancy in this cohort.

Discussion

There was no change in the incidence of PTM at CMJAH, occurring in 7% of the transplant recipients in the period of review (1990-2010) compared to 7.0% reported for the period 1966-1989, despite the change in the demographic patterns of the patients, immunosuppressive regimens and improved surveillance for cancers. No individual immunosuppressant drug appears to pose a risk for cancer significantly, instead, the prolonged general state of immune suppression in this group of patients seems to be the main risk factor of note. Recipients transplanted at an older age and those with long post renal transplantation follow-up should be closely monitored and routine surveillance for cancers done.

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LIST OF ABBREVIATIONS

HIV AIDS	- Human Immunodeficiency Virus-Acquired Immunodeficiency Syndrome
PTM	-Post Transplant Malignancy
RRT	- Renal Replacement Therapy
RLD	-Related Living Donor
UNRLD	-Unrelated Living Donor
HLA	-Human Leukocyte Antigen
PD	-Peritoneal Dialysis
HD	-Haemodialysis
ESRD	-End Stage Renal Disease
CKD	-Chronic Kidney Disease
CMJAH	-Charlotte Maxeke Johannesburg Academic Hospital
SA	- South Africa
MESOT	- Middle East Society of Organ Transplantation
BCC	- Basal Cell Carcinoma
SCC	- Squamous Cell Carcinoma
NHL	- NonHodgkin's lymphoma
MMF	- Mycophenolate Mofetil
CNI	-Calcineurin Inhibitors

M-TOR	-Mammalian Target of Rapamycin
CYA	- Cyclosporine
IL-2	- Interleukin 2
FK	- Tacrolimus
OKT3	- Anti-cluster of differentiation 3 antibody
ALG	- Anti-Lymphocyte Globulin
ATG	- Anti-Thymocyte Globulin
KS	- Kaposi Sarcoma
PTLD	–Post Transplant Lymphoproliferative Disorder
CMV	-Cytomegalovirus
EBV	-Epstein Barr Virus
HHV 8	-Human Herpes Virus 8

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CHAPTER 1 - INTRODUCTION

1.1 BACKGROUND

Kidney transplantation is the preferred treatment modality of renal replacement therapy (RRT) to date ineligible recipients for the management of end-stage renal disease (ESRD) [1, 2].Transplantation has been shown to reverse many of the complications of chronic kidney disease (CKD) and thus has led to improvement in the quality and length of life in these patients [2, 3].

Currently, the sources of kidney grafts are related living donors (RLD), unrelated living donors (URLD) and cadaveric donors. These donors have Human Leukocyte Antigen (HLA) serotypes that are often different from that of the recipient to varying degrees and hence the need for individualised immunosuppression protocols to prevent rejection of the graft by the recipient. Usually, two to three different classes of immunosuppressants with different mechanisms of action are used for induction and maintenance in the recipient. The rational use of immunosuppressants and good clinical practice ensures normal functioning of the graft and its prolonged survival. In 1996, a renal allograft was estimated to have a half-life of approximately 21.6 years when received from a living donor and 13.8 years when obtained from a cadaveric donor in the United States [4].

The leading causes of death with a functional renal graft are cardiovascular diseases, infections and post transplant malignancy (PTM), respectively [2, 5].Numerous studies postulate that with improved patient care, the leading cause of death with a functioning renal graft in the 21st century will be PTM [6].

In a retrospective study, Howard *et al.* showed that PTM was a rapidly rising cause of mortality in the renal transplant population in the USA. These results are summarised in Table 1.1 below. This rise in mortality from PTM is likely due to longer patient survival post-transplant, older age at transplant recipients, and the newer immunosuppressive drugs in use [7].

Table 1.1 – Causes of Death Post Kidney Transplant during 1970-1999 by Transplant Era

Cause of death	**Transplant Era**		
	1970-1979	**1980-1989**	**1990-1999**
Infection (%)	42	42	28
Cardiac (%)	9.6	23.8	30.2
Neurologic (%)	2.4	5.2	8.5
Cancer (%)	1.2	5.2	13.2

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Findings from retrospective and prospective studies in various countries of diverse geography and population groups have been inconsistent with regards to the incidence of PTM and the impact of the various risk factors on the incidence thereof [8]. This indicates the need to evaluate PTM in each transplant centre, at different time periods and to make comparisons with other centres [9].

1.2 LITERATURE REVIEW

1.2.1 Definition of Post-Transplant Malignancy

Post transplant malignancy refers to a malignancy that develops in an organ transplant recipient [10, 11]. The time from transplantation to diagnosis varies depending on malignancy type and the risk factors at play in each recipient [10]. The malignancy may arise as a result of the transmission of the recipient of undiagnosed cancer in the donor, recurrent cancer in the recipient or it may develop *de novo* [5, 12].The risk of *de novo* PTM is 0.2% while that of donor-derived PTM is 1.3 % [7].

1.2.2 Epidemiology of PTM in Kidney Transplant

The risk of developing malignancy has been shown to be increased in the post transplant population has been shown to be 3-5 times that of non- transplant population [12]. The risk is higher for skin cancers, lymphomas, Kaposi sarcoma (KS) and epithelial cancers[10]. The incidence of PTM varies in different parts of the world due to the impact of various risk factors on a recipient. These include environmental and population-related risk factors (the latter including racial and genetic factors) the type of cancers endemic in the region (e.g. gastrointestinal in Asia), and the local availability of screening tests for cancer [12]. The incidence ranges from 1.6 -11% with an average of about 6% [13-15]. Given the varied incidence of PTM across transplant centres, the epidemiology is best discussed geographical regions and reference made to the cancer registries for renal transplant patients in the different regions [9, 16].

<u>Africa</u>

In South Africa (SA), the incidence of PTM ranges from 3.4% to 8.1% in studies conducted in Johannesburg, Durban and Cape Town [17-20]. These studies were performed at different immunosuppressants and political eras in SA, between 1966 and 2009. In all these studies, skin cancer was most prevalent among the Caucasian recipients, accounting for

over 80% of PTM in this population group. On the other hand, KS was most common among the black recipients and was not observed in the Caucasian population[19].

CMJAH is one of 6 centers in SA offering renal transplantation to patients in the public health sector. Moosa *et al.* from Stellenbosch reviewed a cohort of patients transplanted between 1976 and 1999 and found Kaposi sarcoma (KS) to be the most prevalent PTM while Margolius *et al* found skin cancers to be the commonest PTM in Johannesburg before 1989 [18, 21, 22]. Maharaj and Assounga in Durban found PTLD to be the commonest PTM between 1982 and 2009 [20].

In Egypt, the incidence of PTM in a cohort followed up for 18 years was 2.3% and after 30 years of follow-up, the incidence increased to 3.97% [14, 23].Kaposi Sarcoma was the commonest cancer, accounting for over 50% of the malignancies. In the study by Bakr *et al.*, bladder cancer constituted 14% of the PTM and was related to schistosomiasis which is endemic in this area [14].

Middle East

The Middle East Society for Organ Transplantation (MESOT) Transplant Registry has noted the incidence of PTM to be 1.8 -2.2% with KS and skin cancers, especially squamous cell carcinoma (SCC), being most common [11, 15]. A multicentre study conducted in Iran showed the incidence of PTM to be 2.17%, with skin cancer contributed over 50% of the post transplant cancers [8]. In this study, more males than females were affected, and older patients were at higher risk.

Asia

Studies conducted in Asian countries have shown the incidence of PTM to range from 3.5% to 11% and the cumulative incidence of cancer to increase with increasing the time from date of transplantation [24]. Renal and gastrointestinal malignancies are more common in China, Taiwan, and Tokyo compared to other regions of the world [25].Post-transplant

lymphoproliferative disease (PTLD) is the most prevalent cancer among Indian renal transplant recipients. In a cohort from northern India followed up for 30 years,72.5% of the cases of PTM were PTLD [26].

ANZDATA (Australia and New Zealand Dialysis and Transplant Registry)

Australia and New Zealand with a climate which is predominantly sunny and a population mainly composed of the Caucasian race, have a 6.3-12% incidence of PTM [27]. Skin cancer is the most common PTM with an incidence as high as 24% [15]. Kaposi Sarcoma is also very common in the renal recipients with 40-fold risk compared to the normal population [28].

The United States of America

A review of the Cincinnati Transplant Tumor Registry (CTTR) has shown the most frequent PTM to be PTLD and squamous cell carcinoma of the lip, skin, cervix and vulva, and KS [12].

Europe

The European Dialysis and Transplantation Association and European Renal Association (EDTA-ERA) registry confirms an increased incidence of KS, skin cancers and, and non-Hodgkin's lymphoma (NHL) among the renal transplant recipients, compared to the non-transplanted population [29]. A retrospective study from Ireland between 1994 and 2001 showed skin cancer and Kaposi sarcoma to be more prevalent among the renal transplant recipients, compared to the normal population [30].

Table 1.2 below summarises the incidence of PTM in different parts of the world and shows the most prevalent PTM in the respective regions.

Table 1.2 –Summary of PTM in the World

Region	Incidence of PTM	Most Common PTM
Africa – South Africa **Egypt**	3.4- 8.1% 3.97%%	Skin cancer and KS [17-20, 31] Kaposi sarcoma [23]
Middle East (MESOT)	0.75% -2.17%	Kaposi Sarcoma Skin cancers [10, 15]
Europe – (Portugal; United Kingdom)	1.6 %-3.5%	Colorectal cancer- Lymphoma [32]
Asia (Korea, Taiwan, India)	1.8 % - 8.4%	PTLD; renal and gastric cancers [12, 24-26]
America (Cincinnati Transplant Tumor Registry –CTTR)	6-8%	PTLD; Squamous carcinoma of the lip; cervix; skin; vulva [11].
Australia	6.3-12%	Skin cancer [28]

1.2.3 Spectrum of Cancers in Post-transplant recipients

Skin cancers

Skin cancers have been noted in most studies from renal transplant units to be the most common cancer worldwide among the Caucasian population [7, 19, 31]. Non-melanoma skin cancers are the commonest, of which squamous cell carcinoma is the most prevalent subtype among renal transplant recipients, whilst in the non-transplanted population, basal cell carcinoma is the most prevalent [5, 11]. In this population group, skin cancers occur at a younger age, are more aggressive, have an increased risk of metastasis and recurrence after treatment [7]. Melanomas and Merkel's cell carcinoma also more commonly occur in these immunosuppressed patients compared to the normal population [11].

Kaposi Sarcoma (KS)

Kaposi sarcoma is a common malignancy among immunocompromised patients. It is one of the three common PTMs reported in the literature, together with skin and PTLD. The risk of developing KS is 500 times more in the post-transplant population compared to the non-transplanted population [33].Kaposi sarcoma is most common among males, patients exposed to cyclosporine and azathioprine, and people of Mediterranean origin[2, 33, 34]. In retrospective studies from South Africa, KS was shown to have an incidence of 6% in Johannesburg and 3.4% in Cape Town [18, 21].

Kaposi sarcoma is a tumour of the blood vessels that is usually seen as hyper-pigmented skin lesions although at times, it presents with disseminated disease, which carries a high mortality [2]. Common sites of dissemination are the mouth, mucous membranes, lungs, lymphoid tissue and the gut. Histology shows a proliferation of endothelium-derived spindle cells. Human herpes virus-8 is known to cause KS, but a prospective study in France found no difference in survival or risk of graft loss in recipients who were seropositive for HHV8 pre-transplant [2, 33, 35].

Post-Transplant Lymphoproliferative Disorder (PTLD)

This post-transplant lymphoproliferative disorder is a heterogeneous group of malignancies that arises as a result of lymphoid proliferation in recipients of a solid organ transplant in the presence of immunosuppression [26]. These lymphoproliferative disorders are Epstein-Barr virus (EBV) associated in 80% of cases in transplant recipients [36] Posttransplant lymphoproliferative disorder is the second most common PTM after skin cancer [10]. The incidence of PTLD is highest within the first year of transplantation and falls progressively with time from transplantation [7].This is postulated to be as a result of the high doses of immunosuppressants and anti-lymphocyte treatment given during the 1st year post transplantation. Post-transplant lymphoproliferative disorder in renal transplant recipients is usually NHL with extra nodal involvement and is usually of the large B-cell subtype [5, 10, 37].

The World Health Organisation (WHO) has classified these lymphoproliferative diseases into three categories based on cytogenetics, clonality, and genetic rearrangements. Table 1.3 shows the most recent classification released in 2008.

Table 1.3 **-** World Health Organisation classification of PTLD

Category	
Early lesions	Reactive plasmacytic hyperplasia Infectious mononucleosis-like lesion
Polymorphic PTLD	
Monomorphic PTLD	B-cell lymphomas Diffuse large B-cell lymphoma Burkitt lymphoma Plasma cell myeloma Plasmacytoma-like lesions T-cell lymphomas Peripheral T-cell lymphoma Hepatosplenic T-cell lymphoma
Classical Hodgkin lymphoma –type PTLD	

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Solid tumours

These are not as common as skin cancers and KS but have been shown to be more prevalent in the renal transplant population as compared to the normal population. They have been described in all organs and tend to be more aggressive with increased mortality [38]. The risk of breast cancer in post -transplant recipients is lower than the normal population [10].

1.2.4 Risk Factors for developing a Post -Transplant Malignancy

Since the first renal transplant in 1956, various risk factors have been associated with the development of PTM in the different continents [9]. The role of immunosuppressant's appears to be pivotal in the development of PTM coupled with other risk factors [28, 39]. A number of risk factors are implicated in the development of each of the various types of malignancies encountered in the post renal transplant period.

Table 1.4 below summarises the risk factors associated with the common PTM described to date.

Table 1.4 - Summary of the risk factors for developing PTM (compiled from Sheik *et al.* [11]

Cancer	Risk Factors
Skin	Older age at transplantation Increasing time from transplantation Gender: Male Race: Caucasian HLA A11; B27; DR7 Human Papillomavirus (HPV) infection Use of cyclosporine (CYA), azathioprine, corticosteroids[2] Sun exposure -ultraviolet radiation[2] Geographic location CD4 lymphopenia [2]
Kaposi Sarcoma	Geographic location – Africa, the Mediterranean, the Caribbean and the Levant Human Herpesvirus (HHV) 8 infection [2] Epstein-Barr Virus (EBV) infection Hyperpigmented skin
PTLD	EBV is associated with Hodgkin's Disease and NHL [2] Cytomegalovirus(CMV) infection in the donor graft Polyclonal or monoclonal antibodies [2] OKT3 antibody and anti-thymocyte globulin(ATG) Cyclosporine
Solid Organ	Traditional risk factors such as: smoking genetic predisposition family history Older age at the time of transplantation Race: Caucasians

1 Immunosuppressant Drugs

The immunosuppressant drugs used post organ transplantation are a double-edged sword in that they are crucial in preventing graft rejection, but also pose a high risk for developing a malignancy. The risk for malignancy posed by immunosuppressant drugs has been shown to be related to the following factors.

a). Type of Drug

Azathioprine and MMF are anti-metabolites that are used for induction and maintenance therapy post renal transplantation. Mycophenolate mofetil is associated with a reduction in acute rejection and an increase in graft survival. Meta -analysis of the research done on the effects of these two drugs on PTM show that MMF has anti-proliferative activity against lymphomas and leukaemias [6].Maintenance therapy with MMF was associated with significantly reduced risk of PTLD compared with azathioprine[6, 7].

The antibody therapies used as induction treatment and in the management of rejection, are associated with an increased incidence of PTLD [6].The depleting anti -T cell antibodies (muronomab CD3 and ATG) are associated with an increased risk of all cancers in the post-transplant recipients when compared to the recipients who received the non-lymphocyte depleting agent, basiliximab (IL-2 receptor antagonist) [6]. Muronomab is no longer used in induction therapy as it is no longer manufactured. According to the findings from ANZDATA, the use of depleting anti-lymphocyte antibodies is associated with an increased incidence of skin cancers especially non melanomas[2, 7]. Recent collaborative studies have shown an increased incidence of lymphomas, non-melanoma skin cancers, carcinoma of the cervix, vulva and vagina[7]

The use of corticosteroids was noted to be associated with an increased incidence of basal cell and SCC in a population-based study of prescriptions for steroids [6].Corticosteroids are

never used alone in the management of post-transplant recipients hence its effect on PTM is difficult to elucidate.

Calcineurin inhibitors (CNIs),were introduced in the 1980s and they brought a drastic reduction in acute graft rejection [39]. Azathioprine and CYA are associated with an increased incidence of skin cancers, lymphomas, KS, breast cancer, brain tumours and bladder cancers while the use of MMF and tacrolimus has been shown to be protective of PTM in most meta-analysis of studies done to date [1, 8, 33].

Sirolimus (rapamycin), an M-TOR-I (mammalian target of rapamycin -inhibitor), is associated with a decrease in the incidence of KS, and its regression in post renal transplant recipients [7, 33, 40].

b). <u>The dose</u>

Retrospective and prospective studies have shown that heart transplant recipients are at a higher risk of PTM compared to renal allograft recipients because they receive higher doses of immunosuppressants [5]. The risk of developing PTLD is most significant during the first year post-transplantation as the doses of immunosuppressants are at their highest and monoclonal and polyclonal antibodies are used for induction during this period [5, 10]. Dantal *et al.* showed in their randomized comparative study that increasing the dose of CYA is associated with an increase in the risk of malignancy but decreasing the dose predisposed the recipient to rejection [41].

c). <u>Duration of exposure</u>

The higher the cumulative time of exposure to immunosuppressants the greater the risk of PTM [6].This then poses a challenge as the goal of the transplant nephrologists is to ensure many years of graft survival.

2. Oncogenic Viruses

There are 3 possible routes of infection with oncogenic viruses:

a). From the donor

b). Re-activation of latent infection in the recipient

c). *De novo* infection in the recipient [6, 12].

Kaposi Sarcoma is strongly associated with HHV8. Human Herpes Virus 8 is also associated with multiple myeloma. A study from France showed that infection with HHV8 is not a contraindication to renal transplantation as the risk of developing an HHV8 infection, and ultimately KS is very low [35].Kaposi sarcoma has been predominantly seen in the black transplant population and in regions with high sero prevalence of HHV8 which include sub Saharan Africa. The areas in Europe and America were such epidemiological studies have been done have had much lower sero prevalence of HHV8.In SA HHV8 sero prevalence in blood donors showed higher levels in the blacks compared to the Caucasians [21].

Epstein-Barr virus has been linked to the development of PTLD, nasopharyngeal cancers and leiomyosarcomas. Human Papillomavirus is associated with squamous cell carcinoma of the skin, cervix, anus, mouth, vagina, penis and Bowen's disease [6].Hepatitis B and C viruses are linked to hepatocellular carcinoma [6]. Donors and recipients are usually screened for Hepatitis B and C before surgery and vaccination given for Hepatitis B to the recipient if they are negative.

Cytomegalovirus (CMV) is associated with PTLD but y since the 1990s CMV prophylaxis has become standard of care. This saw a drastic reduction in the incidence of CMV disease in transplant recipients as observed at CMJAH in a review of the transplant registry between 2000 and November 2004[42]. .

Human Immunodeficiency Virus (HIV) is an oncogenic virus that was discovered in the early 1980s, and currently, some centres offer renal transplantation for virally suppressed patients on antiretroviral therapy. HIV is associated with various cancers which include KS, squamous cell carcinoma, lymphomas and an increased incidence of solid organ cancers. To date, no study has reported the impact of HIV infection on the development of PTM in transplanted patients.

Human Papillomavirus serotypes 16 and 18 are associated with epithelial cancers of the skin, cervix, penis and the anogenital area in post-transplant recipients[12].The human polyomavirus has recently been implicated in tumourigenesis through the transformation of somatic cells. The associated malignancy is a skin cancer called Merkel cell carcinoma [12].

3**.** Environmental Factors

Skin cancers are mainly seen in the Caucasian population with higher incidences being seen in the temperate climates of Australia, Africa, and America. Kaposi sarcoma tends to occur in geographic areas in which HHV8 is an endemic infection; these areas include Africa, the Mediterranean, the Caribbean, and the Levant. The descendants of populations originating in these regions living in other locations are also at increased risk of KS [7].

4. Traditional Factors

These are not unique to the transplant population alone. They include advanced age, smoking, analgesic abuse, race and a genetic predisposition to malignancy [12]. Skin cancers are more prevalent in older male recipients who are Caucasian and above 50yrs of age [2, 7, 8, 22].

1.2.5 Pathophysiology of PTM

The theories related to the pathogenesis of PTM are varied, and no one process can explain the increased incidence of malignancy in this population of patients. The most likely scenario is an interplay of these various mechanisms on a background of individual recipient and geographically-related environmental risk factors seen in the different patients and environmental factors as posed by the varied geographical locations [2].Below is a discussion of the various mechanisms that have been postulated to result in malignancy in the post-transplant population.

Immune Paresis

The immunosuppressant drugs prescribed to renal transplant recipients result in immune paresis to varying extents [6]. The depressed immune system increases recipient vulnerability to infections allows for the reactivation of latent infections and creates an environment that allows the oncogenic virus to thrive [5]. The paralysed T cell-mediated immune response fails to rid the body of virally infected cells and allows the incorporation of oncogenic viral genes into host DNA resulting in abnormal cell proliferation. Such processes have been implicated in EBV-associated PTLD and HHV 8-related KS [10, 12].

The weakened T cell-mediated immune response then provides poor tumour surveillance and thus allowing tumour growth to continue unchecked. The host of cancerous cells allows for uncontrolled cell division with the failure of the processes involved in apoptosis. Corticosteroids and cyclosporine are pro–oncogenic and have also been shown to decrease tumour surveillance [12, 43]. Cyclosporine and Azathioprine impair the ability of the body to repair damaged DNA [6].

The use of immunosuppressive drugs has been seen to increase the proliferation of growth promoting cytokines such as TGF-B1; VEGF; IL-10 and their receptors. In animal studies, cyclosporine was seen to increase angiogenesis and facilitate tumour growth through the increased release of VEGF and TGF-B from activated lymphocytes [43]. However, studies

by Gallagher *et al.* show no increase in malignancy in patients on CNIs [1].m-TOR-I (sirolimus and everolimus) have been shown to regress tumour growth by decreasing the transcription enzyme p70 S6 kinase, IL-10, cyclins and VEGF from lymphocytes [7]. The anti-proliferative properties of sirolimus were shown in the study by Campistol *et al.* on patients with KS [40].

Prolonged Uraemia

Chronic uraemia is an immune suppressing state and most patients on RRT awaiting renal transplantation have urea levels above normal despite dialysis. A multicentre study in the United States of America (USA), Europe, Australia and New Zealand showed that patients on dialysis had an increased incidence of developing malignancy compared to the non-transplanted population [44]. Increased duration of dialysis before renal transplantation, female sex, and younger age group have been linked to cancers of the kidney and the urogenital system in dialysis patients. The mode of dialysis appears not to affect the risk of malignancy [6, 44].

Environmental Factors

Ultraviolet light destroys DNA and disrupts the DNA repair mechanisms in cells. The damaged DNA forms thymidine dimers which lead to inactivation of the tumour suppressor gene p53 [12].This is a strong risk factor in the development of skin cancer with both pre and post-transplant exposure to sunlight being significant [7]. The interplay of UV radiation, white skin pigmentation, male gender, type of immunosuppressant used and the age of the patient ultimately determine the overall risk of skin malignancy.

1.2.6 Average time to diagnosis of PTM

The interplay of various risk factors and different mechanisms of oncogenesis in the post renal transplant patients result in the development of PTM at different times post-transplant. The average time to diagnosis of cancer post renal transplantation is five years [10].The table below summarises the time frames to the diagnosis of various PTMs as observed in different studies.

Table1.6 - Average Time to diagnosis of PTM

Cancer Type	**Average time to diagnosis post-transplant**
Skin **Non-Melanoma** **Melanoma**	4-9 years Eight years below 40 years and Three years in those above 60 years Not known[11]
Post-Transplant Lymphoproliferative Disease (PTLD)	Biphasic: 0-12 months After 5years [10]
Kaposi Sarcoma (KS)	13-22 months [11]
Solid Organ	Not known

1.2.7 Outcome of patients with Post Transplant Malignancy

Outcomes of PTM depend on the type of malignancy, histology and extent of disease at the time of diagnosis. In general PTMs are more aggressive and often have metastasised by the time of diagnosis [11, 45]. These factors result in poor survival rates of 25-35% and very high mortality rates , especially in PTLD and solid organ malignancies [12]. Metastatic disease at presentation is usually associated with high mortality rates.

Management of KS and PTLD in renal transplant recipients involves various modalities, though the universal approach is to decrease the dose of the immunosuppressants and/or change to a regime with decreased risk of PTM e.g. sirolimus, tacrolimus, MMF [7, 45]. A change of immunosuppressant to sirolimus has been shown to regress the lesions of KS [33]. Dose reduction is an effective treatment modality in recipients with PTLD and KS [12, 45]. Excision of localized KS lesions, radiotherapy, laser, and chemotherapy, especially for disseminated disease, usually results in disease remission [34].. Most types of PTLD are sensitive to chemotherapy, though the challenge is reducing chemotherapy-related toxicity. Current recommendations favour rituximab over CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) [45].

Most skin cancers are diagnosed early and respond to excision and immunosuppressant dose reduction [13]. The challenge with dose reduction is the risk of rejection. The therapies for skin cancer include photodynamic therapy, cryotherapy, superficial ablative therapy and Moh's micrographic surgery [45].

A combination of surgery and chemotherapy has been employed successfully with solid organ cancers and lymphomas [12].

1.2.8 Prevention of Post-Transplant Malignancy

The risk of developing a post-transplant malignancy is inherent in every recipient and measures must always be taken to prevent these cancers throughout the recipient's life.

Many transplant nephrologists have suggested various steps both pre and post-transplant have been suggested to reduce morbidity and mortality from post-transplant malignancy among these patients.

Recommended Pre-transplant Measures

These measures are targeted at the risk factors for developing PTM.

Table 1.7 below summarises these measures.

Table 1.7 – Measures to reduce PTM Pre-Transplant

Risk Factor	**Possible Intervention**
Age	Avoid transplanting patients above 65 years of age
Sex	Screen for malignancy related to sex e.g. prostate, cervix, breast
Obesity	Avoid transplanting patients with BMIs above 35
Oncogenic Viruses	Screen, prevent and treat for oncogenic viruses in donors and recipients [6]
Premalignant lesions	Screen and treat for e.g. CIN, hyperkeratosis, renal cysts [5]
Previous diagnosis of cancer	Transplantation must be delayed for two years after remission of cancer[12]

The challenge with pre-transplant screening is most patients remain on the waiting list for many years and , some patients may be transplanted with pre-malignant lesions or may contract oncogenic viruses while waiting [12].

Table 1.8 below summarises the recommended post-transplant measures that should be taken to prevent PTM.

Table 1.8- Recommended Screening for Post-Transplant Malignancy

Cancer	Demography	Recommendations
Breast	Women > 50 years Women <50 years at high risk (family history or prior cancer)	Mammogram every 1-2 years Mammogram every 1-2 years
Cervical/Uterine/ peri-anal	Women >18years	Annual gynaecological examination and pap smear
Prostate	Men >40years	Rectal exam and PSA every year
Colorectal	Recipients > 50 years	Faecal blood test yearly Flexible sigmoidoscopy every five years
Skin and KS	All recipients High risk of skin cancer Low risk	Annual self-exam and biopsy of all suspicious lesions Six monthly dermatologist examination Annual examination by dermatologist Routine use of sunscreens and reducing sun exposure.
PTLD	All ages	Three monthly history and examination for feature of PTLD –in the first year of transplantation Annually intervals after the 1st year [12]
Carriers of Hep B or C virus	All ages	Annual alpha-fetoprotein level and abdominal sonar

Table is adapted from Morath *et al.* and Kasiske *et al.* [12, 46]

Immunosuppressant drugs should be kept at a minimum number and at a dosage to achieve normal graft function without rejection and with minimal side effects. Drugs with low potential to tumour genesis e.g. m-TOR inhibitors can be considered [2]

1.3 RATIONALE OF THE STUDY

This study was conducted as a follow-up to the work of Margolius in which PTM in renal transplant recipients between August 1966 and November 1989 at Charlotte Maxeke Johannesburg Academic Hospital (CMAJH) was reviewed [18, 31]. This current study will allow us to compare the findings of the two unique transplant eras and thus evaluate the effects of immunosuppressants and the different risk factors posed by the various demographic factors in the two periods, as described below.

This study reviews malignancies post renal transplant in patients transplanted in the era 1990 to 2010.This is a post-apartheid era in South Africa (SA) where the healthcare delivery system was improved and extended to the previously marginalised majority (non-white population -Indians, Blacks, and Mixed race). Thus, this study will include a more diverse group of transplant recipients which is more representative of the SA population. Literature strongly supports the theory that PTMs are related to immunosuppressant drugs and their total dose exposure in recipients. It is postulated that the current regimens are more potent and have increased the risk of PTM. Immunosuppressants used post renal transplantation have changed over the years, with steroids remaining in use since 1966 to the current day, albeit at lower doses for maintenance at CMJAH. Azathioprine, steroids, cyclosporine and a monoclonal antibody OKT3 were the drugs used before 1990 for induction and maintenance therapy. Since 1990 azathioprine has been replaced by MMF. Tacrolimus and sirolimus were introduced into the maintenance treatment of recipients of renal grafts in 1999 at CMJAH. Antibodies against Interleukin 2 (IL-2) receptors were introduced in 1999 for induction.

Most of the currently available literature is based on Asian, European, American, Australian and Middle East studies from the last decade whose demographic, environmental and carcinogenic exposures are different to those found in southern Africa.

The CMJAH renal transplant cohort has a significant population size and fairly well kept patient records which provide for a good data source to undertake this review. These patients have been followed up for a long enough period- 20years in this study- which is adequate to enable us to describe PTM in this cohort.

1.4 AIMS AND OBJECTIVES OF THE STUDY

This study seeks to assess the extent to which PTM have affected renal transplant patients in the last 20 years and to identify the possible risk factors in comparison to previous reports locally and internationally. This will assist in improving patient care and thus reduce the number of recipients dying of malignancy with functioning grafts at CMJAH.

Objectives

1. Describe the incidence of malignancy among the renal transplant recipients during the study period.

2. To determine the time from transplantation to diagnosis of cancer.

3. To investigate the association between immunosuppressive regimens and risk of PTM.

4. To identify other risk factors for developing PTM.

5. To characterize the histological features of the different cancers in the study cohort.

2. CHAPTER 2- METHODS

2.1 STUDY DESIGN

This was a retrospective chart review of renal transplant recipients transplanted between 01/01/1990 and 31/12/2010.

2.2 STUDY SITE

The study was conducted at CMJAH in the renal transplant unit. CMJAH is a quaternary academic hospital in central Johannesburg, SA. It is one of 6 centres in SA offering renal transplantation in the public sector.

2.3 STUDY POPULATION AND SAMPLE

The study population included all patients transplanted at CMJAH during the study period: 1990-2010.The study sample includes all recipients who developed a PTM during the study period.

2.4 ETHICAL APPROVAL

Ethical approval was granted by the University of the Witwatersrand Human Research Ethics Committee (Medical) protocol number **M120642** (Appendix A)

2.5 ELIGIBILITY CRITERIA FOR THE RENAL PROGRAMME

The CMJAH transplant unit has standard guidelines on eligibility criteria for renal transplant recipients. These guidelines exclude patients with malignancy and other risk factors for malignancy such as active Hepatitis B and C. These pre -transplant selection criteria ensure that patients who are transplanted have very low-risk profiles for the development of malignancy.

Inclusion criteria

All patients are transplanted between 01/01/1990 and 31/12/2010 and above 18 years of age at that time of transplantation.

Exclusion criteria

1. All recipients who died; transferred or rejected within six months of transplantation.

2. Recipients transferred in from other centres after transplantation.

2.6 STUDY VARIABLES

1. Age at the time of transplantation

2. Gender

3. Ethnicity /Race

4. Aetiology of ESRD

5. Source of the graft

6. Number of grafts received

6. Mode of dialysis and duration on dialysis before transplantation

7. Immunosuppressant exposure history

8. Oncogenic viruses diagnosed post-transplant

10. Number of times the patient was treated for rejection

11. Outcome of the recipient

12. Malignancy diagnosed

13. Features of malignancy from histology reports

i. Histological findings

ii. Sites of metastases

14.Duration from transplant to diagnosis of cancer

2.7 DATA HANDLING AND ANALYSIS

Recipient information was collected from each patient file onto a data collection sheet created on Epi Info version 3.4.3. (See Appendix C). Each recipient was given a unique study number linked to their file. The study numbers and recipient file numbers were kept separately. Data was analysed using STATA version 13.

2.7.1 Descriptive analysis

The demographic and clinical characteristics of all renal transplant recipients, of those who did not develop PTM and those who developed PTM, were described using proportions for categorical variables and mean and standard deviation for continuous variables (Table 1). Student t-test was used to compare mean age at transplantation for those who developed PTM with that of those who did not. The spectrum of PTM was described using a bar chart for all recipients and males and females (Figure 3.1). Time to cancer diagnosis was described regarding mean and standard deviation for specific cancers (Table 3.4). The p – value was set at 0.05 for significance testing.

2.7.2 Cancer Incidence Analyses

Time-to-event analysis was the primary method of analysis. Time started to the date of transplantation and ended in the last month of follow-up (measured as the last date of receipt of prednisone) or date of cancer diagnosis, or 31 December 2010 (date of database closure), whichever came first.

A cancer event was defined as the first cancer diagnosis made from the date of transplantation. Cancer incidence was calculated by dividing the number of cancer events by the person-time and reported per 100 000 person-years. Kaplan-Meier curves were plotted to show cumulative cancer incidence in males and females.

Cancer incidence was also calculated by dividing the number of first cancer events by some renal transplant recipients and expressed as a percentage to allow for comparability with the Margolius study.

2.8 RISK FACTOR ANALYSIS

Unadjusted and adjusted Cox proportional hazards models were fitted to identify factors associated with the development of PTM in renal allograft recipients.

3. CHAPTER 3 - RESULTS

A total **959** patient records were reviewed, and **281** records were excluded as they did not meet the inclusion criteria of this study, **668** records were therefore considered for statistical analysis for this research report.

3.1 DESCRIPTIVE SUMMARY OF THE DEMOGRAPHIC STATISTICS

Table 1A- Summary of Descriptive Characteristics (Demographic data)

Variable	**All Recipients**	**No PTM**	**PTM**	**p-value**
Demographic Characteristics	n= 668 % (n)	n = 621 % (n)	n =47 % (n)	
Sex				
Females	36.8 (246)	37.2 (231)	31.9(15)	0.469
Males	63.2 (422)	62.8 (390)	68.1(32)	
Ethnicity				
Black	50.6 (338)	(51.9)322	34.0(16)	
Caucasian	41.0 (274)	(39.3)244	63.8(30)	0.014
Indian	6.1 (41)	(6.4)40	2.1 (1)	
Mixed race	2.3 (15)	(2.4)15	0	
Year of Transplantation				
1990-1995	275 (41.2)	235(37.8)	40(85.1)	
1996-2000	141 (21.1)	139(22.4)	2(4.3)	<0.001
2001-2005	142 (21.3)	139(22.4)	3(6.4)	
2006-2010	110 (16.5)	108(17.4)	2 (4.3)	
Age at Transplantation	*Mean (S.D)*			
Males	*37.4 (12.5)*	*36.9 (12.5)*	*42.9(11.6)*	*0.009*
Female	*35.6 (12.1)*	*35.2 (12.2)*	*42.8 (7.5)*	*0.003*
Overall	*36.7 (12.4)*	*36.3 (12.4)*	*42.9 (10.4)*	*0.001*

n= number; PTM-Post transplant malignancy

Table 1B- Summary of Descriptive Characteristics (Clinical Variables)

Variable	All Recipients	Non PTM	PTM	P value
Clinical Characteristics	n =668	n=621	n=47	
Source of Graft				
Cadaver	505 (75.6)	466(75.3)	39 (83.0)	
RLD	138 (20.7)	130(21.0)	8 (17.0)	0.412
NRLD	23 (3.4)	23 (3.7)		
Missing data	2 (0.3)			
Number of Grafts received	609 (91.2)	567 (91.3)	42 (89.4)	
1	27 (4.0)	24 (3.9)	3 (6.4)	
2	9 (1.4)	9(1.50		0.499
>3	23 (3.4)	21 (3.4)	2 (4.3)	
Missing data				
Number Rejection Treatments				
0	498 (74.6)	455 (73.3)	43 (91.5)	0.043
1	135 (20.2)	132 (21.3)	3 (6.4)	
2	29 (4.3)	28 (4.5)	1 (2.1)	
>3	6 (0.9)	6 (0.9)		
Aetiology ESRD				
Hypertension	220 (32.9)	202 (32.5)	18 (38.3)	
Diabetes Mellitus	29 (4.3)	29 (4.7)	0	
APCKD	22 (3.3)	17 (2.7)	5 (10.6)	
Glomerulonephritis	96 (14.4)	87 (14.0)	9 (19.2)	0.048
Ig A Nephropathy	8 (1.2)	7 (1.1)	1 (2.1)	
Analgesic Nephropathy	13 (1.9)	12 (1.9)	1 (2.1)	
Reflux Nephropathy	37 (5.5)	37 (6.0)	0	
Other	111 (16.6)	99 (15.9)	12 (25.5)	
Missing data	132 (19.8)	131 (21.1)		
Mode of dialysis				
Haemodialysis	103 (15.4)	103 (16.6)	0	
Peritoneal Dialysis	133 (19.9)	126 (20.3)	7 (14.9)	0.021
Both	15 (2.3)	14 (2.3)	1 (2.1)	
Missing data	417 (62.4)	378 (60.9)	39 (83.0)	
Oncogenic viruses				
Yes	91 (13.6)	87 (14.0)	4 (8.5)	0.203
Types of virus diagnosed	*N=91*	*N=91*	*N=91*	
CMV	65 (71.4)	63 (69.2)	2 0.02	0.039
HIV	13 (14.2)	13 (14.2)	0	
Hepatitis B	8 (0.1)	8 (0.1)	0	
Hepatitis C	2 (0.02)	1 (0.01)	1 (0.01)	
Other	4 (0.04)	3 (0.03)	1 (2.1)(0.01)	
Outcome of patient				
Alive and in care	207 (30.9)	203 (32.7)	4 (8.5)	
Death	182 (27.3)	159 (25.6)	23 (48.9)	<0.001
Rejected	140 (20.9)	134 (21.6)	6 (12.8)	
Lost to follow up	86 (12.9)	76 (12.2)	10 (21.3)	
Transferred	51 (7.6)	48 (7.7)	3 (6.4)	
Missing data	2 (0.3)	1 (0.2)	1 (2.1)	
Immunosuppressants				
Azathioprine	428 (64.1)	387 (62.3)	41(87.2)	0.001
Cyclosporine	575 (86.1)	529 (85.1)	46(97.9)	0.006
Tacrolimus	93 (13.9)	92 (14.8)	1 (2.13)	0.006
MMF	302 (45.2)	291 (46.9)	11 (23.4)	0.002
Sirolimus	114 (17.1)	108 (17.4)	6 (12.8)	0.0416

The study population had more males than females and among those who developed a malignancy, 68.1% were males. Overall the age at transplantation was 36.7 years but the recipients who developed a malignancy were older at transplantation with an average age of 42.9 years old (p= 0.001).

This cohort of renal transplant recipients comprised predominantly of Blacks and Caucasians who contributed 50.6% and 41.0% respectively; the Indian and the mixed race recipients formed 8.4% of the study population. Of those who developed a PTM, 63.8% were Caucasian while 34% were blacks and no mixed race recipients developed cancer (p=0.014).

The number of patients transplanted between 1990 and 2010 decreased gradually over the 20 years of the study with the highest number of renal transplants occurring during the period 1990-1995 (41.2%), and the least between 2006-2010 (16. 5%).Most of the recipients who developed a PTM were transplanted between1990-1995 (85.1%), and this was statistically significant (p=<0.001).

The commonest source of renal grafts was from cadaveric donors (75.6%). Thirty- nine of the 47 recipients who developed a malignancy received their grafts from cadaveric donors compared to 17% of recipients of RLD grafts who developed PTM were linked to RLD grafts (p=0.412). No cancer was diagnosed in NRLD recipients.

In this cohort, 91.2% of the recipients were transplanted once, and 74.6% were never treated for rejection. Among those who developed cancer, 10.7% received two or more grafts and 8.5% were treated for rejection.

Hypertension and glomerulonephritis were the commonest causes of end-stage renal disease in this population. The aetiology of renal failure was not documented in almost 20% of the files and 16.6% was captured as “other”. The conditions under the category “other” included congenital causes and unknown aetiology. Among the recipients who had ADPKD and analgesic nephropathy as an aetiological factor, 12.7% of them developed a

malignancy. A quarter of the recipients whose aetiology was documented as “other” developed a malignancy. No transplant recipient whose cause of renal failure was diabetes mellitus (DM) or reflux nephropathy or missing developed cancer.

The mode of dialysis the recipients were on before transplantation was poorly documented in the files with 62.4% of the records having no documentation of this variable. The mode of dialysis is unknown in 83% of those who developed a PTM.

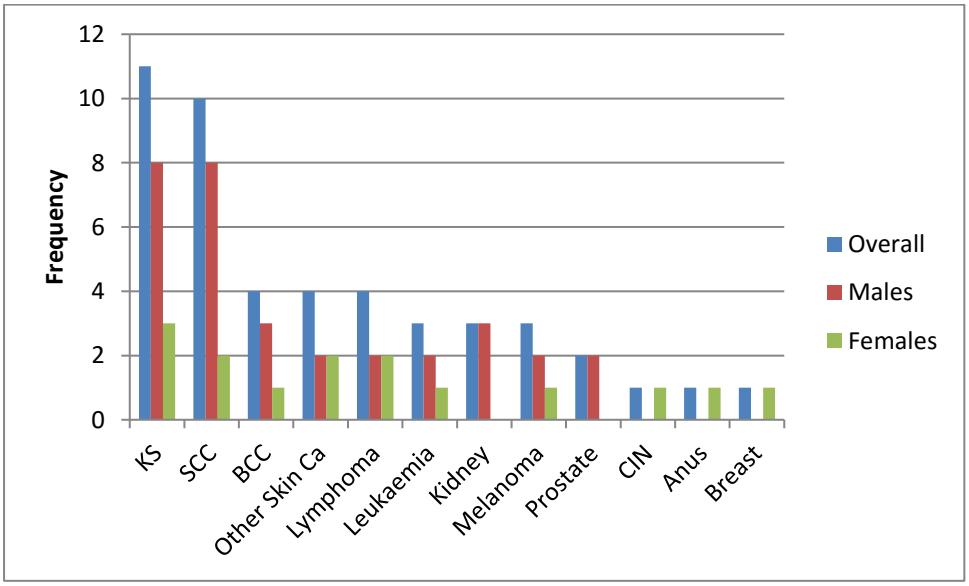
Oncogenic viruses were not present in 84.1% of the study population and of the recipients who had an oncogenic virus, four developed cancer. The viruses diagnosed were CMV, Hepatitis B and C and HIV.

A third of the recipients are still alive and in care while 69% of the cohort had adverse outcomes.

3.2 SPECTRUM OF PTM AT CMJAH

The bar graph below summarises the spectrum of malignancies diagnosed among the recipients or renal transplants at CMJAH in the era under review. The cancers are shown about gender.

Figure 3.1 Spectrum of PTM at CMJAH



Skin cancers (SCC, BCC, other skin cancers, melanoma) are the commonest type of PTM at CMJAH contributing 44.7% of the cancers. Non-melanomas are more predominant while squamous cell carcinoma is the most prevalent histological diagnosis among the recipients who developed skin cancers. More males than females are affected by skin cancer in this cohort. Of the 13 recipients who had analgesic nephropathy as the aetiology of ESRD, one recipient developed skin cancer.

Kaposi Sarcoma is the second commonest cancer affecting 23.4% of the recipients and was seen mostly in black male recipients. Two recipients who self-identified themselves as Caucasian had KS.

Post-transplant Lymphoproliferative Disorder comprised mainly of lymphomas and leukaemias with a ratio of 4 males to 3 females. The one Indian recipient who developed a malignancy had a lymphoma.

Anal cancer, breast, and cervical carcinoma were seen in females only while the renal cancers were diagnosed in 3 black males.

3.3 **HISTOLOGICAL CHARACTERISTICS OF THE CANCERS DIAGNOSED AT CMJAH**

Table 2 below shows the histological diagnosis of the four main classes of cancers diagnosed in this cohort.

Table 2 – Histological Characteristics of the Cancers diagnosed at CMJAH

Type	**Histological Diagnosis**	**Frequency n=47**	**Incidence**
Skin	Melanoma	3	4.97/1000
	Basal Cell carcinoma	4	(CI 3.21-7.70)
n=21	Squamous cell carcinoma	10	
	Unspecified	4	
KS	Disseminated KS	7	2.73/1000
n=11	Localised KS	4	(CI 1.51-4.92)
PTLD	Large B cell NHL	3	
	T cell lymphoma	1	
	Refractory anemia blasts in	1	1.72/1000
n=7	transformation	1	(CI 0.82-3.61)
	Acute Myeloid Leukaemia	1	
	Chronic myeloid leukaemia		
Solid	Breast -Adenocarcinoma	1	
Organ	Prostate -Adenocarcinoma	2	
	Kidney –Papillary renal cell	3	1.97/1000
n=8	carcinoma	1	(CI 0.99-3.95)
	Anus	1	
	CIN		

n = number

Seven of the eleven recipients diagnosed with KS had disseminated disease. One of the recipients had KS of the ureters, and he is still alive after chemotherapy and a switch to sirolimus. According to the information in the hospital records, none of the recipients with KS were ever tested for HHV 8 virus.

Post-transplant lymphoproliferative disorder was diagnosed in 14.9% of the recipients who developed a malignancy and the histology was predominantly that of large B-cell NHL. One patient had a histological diagnosis of RAEB-T (refractory anemia with excess blasts in transformation) on bone marrow aspirate and trephine diagnosed in 1995.This is now considered as acute myeloid leukemia in the new WHO classification. Mortality was 100% among the recipients diagnosed with PTLD. All the recipients who developed PTLD were transplanted once, had never been treated for rejection and

Solid organ malignancies were the least common type of PTM encountered.

3.4 AVERAGE TIME TO DIAGNOSIS OF PTM

Table 3 below summarises the average time from transplantation to diagnosis of cancer as calculated for this cohort.

Table 3 – Average time to diagnosis of PTM

Malignancy	**Median (Interquartile Range) years**
Skin	7.3 (4.0 – 8.8)
Melanoma	7.6 (2.8 – 10.5)
Basal Cell carcinoma	7.6 (2.3 – 8.6)
Squamous cell carcinoma	5.2 (3.4 – 7.8)
Kaposi Sarcoma	2.1 (0.8 – 5.9)
PTLD	3.8 (1.9 – 14.3)
Solid Organ	5.9 (4.1 – 11.9)

Kaposi Sarcoma was diagnosed earliest at median time of 2.1yearsyears post transplantation. Non-melanoma skin cancers were seen earlier than the melanomas with squamous cell carcinoma being diagnosed at a median time from transplantation of 5.2 years. Solid organ cancers were diagnosed later at a median time of 5.9years post transplantation.

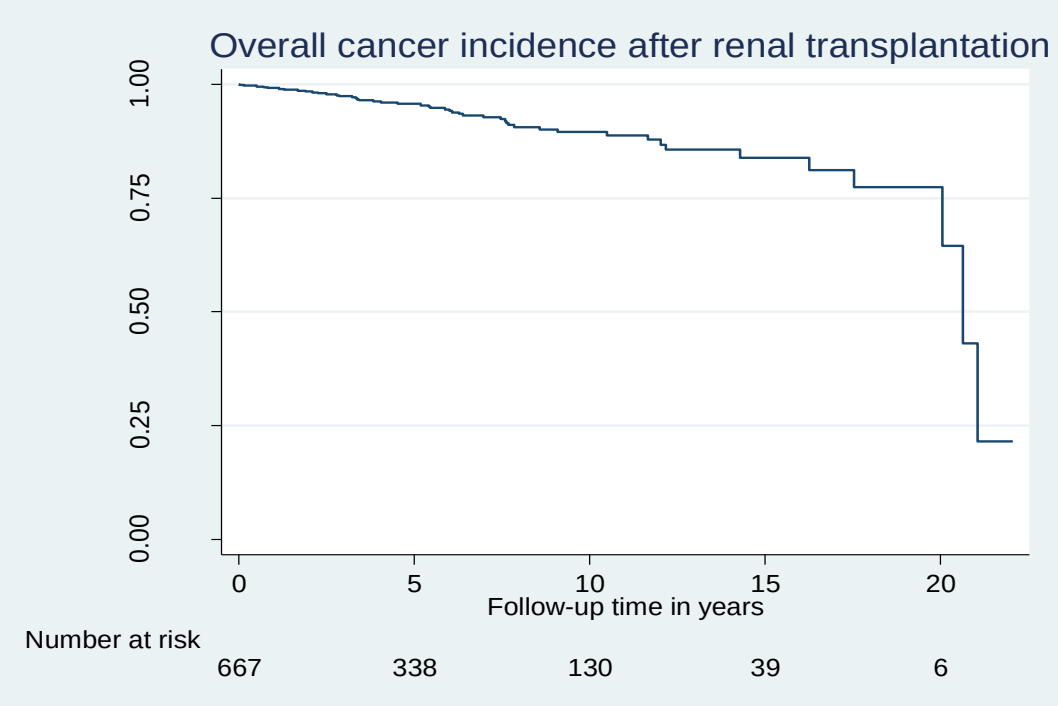
3.5 INCIDENCE OF PTM AT CMAJH

In this study, 47 recipients developed a post-transplant malignancy, and 668 recipients were included for statistical analysis. The incidence of malignancy at CMJAH during the study period 1990-2010 is 7.0 % (95% CI 5.2-9.4).

The median follows up time was five years (IQR 2.0-8.6) and mean follow-up time was 5.9 years (STD 4.9). 667 recipients were included in the incidence analysis and contributed to a total of 3997 person-years. Overall cancer incidence was 1176 (95% CI 883-1565) per 100 000 person years. In males cancer incidence per 100 000 person-years was 1249 (CI 883-1766) and in females, it was 1045 (CI 630-1733).

Below is the Kaplan Meier curve summarizing the overall cancer incidence in this cohort.

Figure 3.2 Kaplan-Meier curve of the cumulative incidence after renal transplantation by gender



3.6 **RISK FACTORS OF DEVELOPING PTM**

Table 4 – Univariate and Multivariate Analysis of the Risk factors of developing a PTM

Characteristic	**Unadjusted HR (95%CI)**	**P value**	**Adjusted HR (95%CI)**	**P value**
Age	1.06 (1.03 -1.08)	**<0.001**	1.05 (1.03-1.08)	**<0.001**
Gender				
Female	1		1	0.361
Male	1.12 (0.60 -2.08)	0.720	1.35 (0.71-2.59)	
Ethnicity				
Black	1			
Caucasian	1.77 (0.97-3.26)	0.064		
Mixed Race/Indian	0.30 (0.04-2.25)	0.240		
Year of Transplant				
1990-1995	1		1	
1996-2000	0.11 (0.03-0.45)	**0.002**	0.12 (0.03-0.53)	**0.005**
2001-2005	0.19 (0.06-0.63)	0.006	0.15 (0.02-1.28)	0.083
2006 -2010	0.55 (0.13-2.40)	0.424	0.51 (0.05-5.11)	0.0566
Graft Source				
Cadaver	1			
NRLD/RLD	0.53 (0.25-1.13)	0.099		
No of Grafts received				
1	1			
>2	0.65 (0.19-2.19)	0.488		
Ever treated for Rejection				
No	1			
Yes	0.38 (0.13-1.05)	0.062		
A etiology				
Other	1			
Hypertension	1.07 (0.56-2.05)	0.830		
Glomerulonephritis	1.27 (0.57-2.82)	0.557		
Oncogenic virus				
Yes	0.68 (0.24-1.90)	0.459		
Immunosuppressants Exposure				
Azathioprine	2.17 (0.90-5.19)	0.083	0.39 (0.06-2.39)	0.307
Cyclosporine	5.49 (0.75-39.95)	0.093	2.92(0.32-26.49)	0.341
Tacrolimus	0.13 (0.02-0.98)	**0.0047**	0.21 (0.02-2.01)	0.176
MMF	0.35 (0.18-0.69)	**0.002**	0.58 (0.22-1.56)	0.282
Sirolimus	0.54 (0.23-1.26)	0.154	1.06 (0.38-2.97)	0.915

We fitted unadjusted and adjusted Cox models to identify independent risk factors for cancer in renal transplant patients. Factors explored for their association with cancer in unadjusted analysis were age, gender, ethnicity, year of transplant, source of graft, number of grafts received, number of times the patient was treated for rejection, aetiology of renal disease, the presence of a diagnosed oncogenic virus and exposure to the immunosuppressant drugs azathioprine, cyclosporine, tacrolimus, MMF, and sirolimus.

In unadjusted analysis, increasing age was significantly associated with developing cancer. Patients transplanted in the period of transplant 1996-2000 and 2001-2005, had a lower risk of developing cancer than those transplanted in the period 1990-1995, HR 0.11 (0.03-0.45) and 0.19 (0.06-0.63) for 1996-2000 and 2001-2005, respectively. Patients who received the immunosuppressants tacrolimus HR 0.13 (0.02-0.98) and MMF HR 0.35 (0.18-0.69) had a lower risk of developing cancer compared to those who did not.

The multivariable Cox model adjusted for age, gender, year of transplant and exposure to the immunosuppressant drugs azathioprine, cyclosporine, tacrolimus, MMF, and sirolimus. In adjusted analyses, the association of tacrolimus and MMF and cancer was lost. Age and the period of transplant were the only factors with a significant association with cancer. Older age at transplant predicted cancer development, with a 5% increase in the risk of cancer of each additional year of age at transplant, HR (1.05 (1.03-1.08). Patients transplanted in the period of transplant 1996-2000 had a lower risk of developing cancer than those transplanted in the period 1990-1995 HR 0.12 (0.03-0.53).

CHAPTER 4 - DISCUSSION

This study was conducted to assess the extent to which post-transplant malignancy affected the renal transplant recipients at CMJAH over 20years (1990-2010) and to compare the findings with the first 23 years (1969-1989) of renal transplantation at CMJAH, and with other centres or registries in the world.

4.1 SPECTRUM AND HISTOLOGY OF MALIGNANCIES DIAGNOSED

Skin cancer was most prevalent in this study contributing 44.7% of the malignancies reported and the non- melanoma types were more common with the histological diagnosis of squamous cell carcinoma being the most predominant. This is consistent with other studies reported in Cape Town and the other registries from the developed countries. [11, 22, 46] The number of Caucasians transplanted at CMJAH in the last 20 years has dropped significantly, but skin cancer remains the most prevalent malignancy. This suggests that the Caucasian population is at high risk for skin cancer. In the early 1980s, the routine use of UV light blockers was introduced as routine care to decrease the incidence of skin cancer which was 41.5/1000 transplanted cases [47]. In this study, the incidence has dropped to 4.97/1000.

Pre-1990, KS was the 4th commonest cancer at CMJAH possibly because fewer blacks were previously transplanted, but with a doubling of the number of blacks transplanted in this study, it is now the 2nd commonest cancer. Other studies in Africa and Mediterranean areas have shown that KS is the second commonest PTM [15, 19, 21]. Kaposi sarcoma was diagnosed mostly in the non-Caucasian population in the studies done in Africa. In Cape Town Moosa *et al* found that most of the recipients who developed KS were of the mixed race group [21].From the MESOT registry, KS was the most predominant skin cancer with PTLD in the second position. In the developed world KS is not common.

PTLD is the 3rd commonest PTM in the developing countries and the 2nd commonest in developed countries[10, 11]. In developing countries PTLD is seen mainly in the Indian

population and this is possibly so in the study done in Durban where PTLD and non-melanoma skin cancers were equally common[20, 26]. The registries in the United States America and Europe show lymphomas to be the most predominant PTM in some centres while in others, it is second to skin cancer [48]. Presentation is usually in the early post-transplant period and most recipients have extra nodal disease at diagnosis.

Solid organ malignancy appears not to be common in the renal transplant population than that seen in the non-transplanted population[10, 15, 31]. Most studies in the developed and developing world have small numbers of recipients developing solid organ cancers. There is not much in the literature regarding these cancers. Some solid organ tumors in the post-transplant population follows the pattern of the endemic cancers in the region e.g. bladder cancer in Egypt; gastrointestinal in Asian countries (Taiwan and Korea) [14, 24, 25]

4.2 TIME FROM TRANSPLANTATION TO DIAGNOSIS OF PTM

The risk of developing a malignancy increases with increasing time from transplantation. This has been confirmed in most studies on the risk of developing PTM [2, 6, 7, 12, 31].Decreased mortality from infections and improved healthcare systems have seen patients surviving longer and the traditional risk factor for malignancy – age, becomes a significant risk factor.

The time at which a PTM is diagnosed varies with the different cancers. KS seems to be diagnosed the earliest with a median time to diagnosis of 2.1 years (IQR 0.8-5.9) in this study and has been diagnosed in other centres as early as 13 months after transplantation[11] .

4.3 INCIDENCE OF PTM

CMJAH

The incidence of PTM at CMJAH between 1990 and 2010 was 7%. Margolius *et al.* found the incidence to be 7% between 1966 and 1989, and Disler *et al.* found the incidence to be

7.3% among the first 200 renal transplant recipients at CMJAH [18, 47].This may support the notion that the main risk factor for developing a malignancy is the overall immunosuppression in these patients from drugs and uraemia rather than specific drug classes [47].

Most researchers in the area of PTM have postulated the risk of PTM to rise in the 21st century, but this appears not to be the case at CMJAH given the findings from this review compared to the previous retrospective reviews at CMJAH[7]. This constant incidence of PTM at CMJAH could be due to the fact that the number of recipients exposed to the newer potentially more immunosuppressive drugs like MMF (45.2%); Sirolimus (17.1%), Tacrolimus (13.9%) is small compared to those on the older drugs Azathioprine (64.1%), cyclosporine (86.1%). The cumulative dose exposure of the newer drugs is also small in the era 1990-2010.

Africa

The transplant centres in Africa that have conducted studies related to PTM are Egypt, South Africa (Johannesburg, Durban and Cape Town). In the study done by Maharaj and Assounga in Durban, with a mainly Indian population and sunny climate found that 5.4% of their recipients had PTM after an average follow up time of 12years; PTLD and skin cancer were the commonest[20].

The studies done in Cape town have incidences of PTM ranging from 3.35% to 7.56% and the recipients are mainly of the mixed race population[19]. Bakr et al found the incidence of PTM in their cohort of 95 recipients to be 3.97% and KS was the most common PTM among the recipients.

MESOT

The studies done in Iran and the findings from the MESOT registry show that the incidence of PTM in this region is lower than that found in our study and in western countries. [8, 11,

15].The incidence in some countries in this region are as low as 1.6% as reported in Iran[49]. The reasons why this is so being not clear but may be due to the fact that most grafts are not cadaveric and hence the amount of immunosuppression given is less.

Western Counties

In the western countries, the incidence of PTM is higher than that seen in the other regions in the world. Australia has the highest incidence with 26% being recorded in 2006 while in United Kingdom and US, the incidence are between 5-10%. Canada had an incidence of 12.2% in 2002[19].

4.4 RISK FACTORS FOR DEVELOPING A PTM

In this study, more males than females were transplanted and the average age at the time of transplantation was 36. 7years.Thus, the transplant recipients in this cohort were young. Recipients in the MESOT region especially Iran are mostly less than 30years of age[49].

The average number of patients transplanted per month decreased from about 5 to 2 in 2010 due to a drop in donor availability. The study number reflects some selection bias as 288 recipients were excluded from the study as they did not meet the inclusion criteria.

Most recipients received their renal allograft from cadaveric donors, and 24.1% obtained them from RLD and NRLD. Cadavers are the most common source of grafts in most transplant centres in South Africa [31]. During the study period 1990 -2010, 5.4% had received more than two allografts, and 25.4% were noted to have been treated for more than one episode of rejection. Records of the MESOT registry show that 85% of the graft sources are from RLD and NRLD [11, 49].

Recipients of multiple grafts and those treated for rejection on multiple occasions are exposed to higher doses of induction therapy which is associated with PTLD [11]. In contrast in this study, all the recipients who developed PTLD were transplanted in the era 1990-1995, had not had a previous transplant and received an allograft from a deceased donor and were

never treated for rejection. In this study, these possible reasons for increased exposure to induction therapy had no significant impact on the risk of developing PTLD.

Hypertension was the leading cause of renal failure among the black population, and this has been seen in numerous studies among this population of patients especially among the African population [50]. Among the recipients who were diagnosed with an oncogenic virus, 8.5% had a PTM, but none of them developed an oncogenic virus-related malignancy.

4.5 LIMITATIONS

The main limitation of this study was missing information in the patient records especially the mode of dialysis before transplantation and aetiology of the end-stage renal disease. Naicker *et al* reported similar difficulties in reviewing the database of the South African Dialysis and Transplantation Registry (SADTR) [50]. Some of the information which was absent in the file was considered as negative during data collection e.g. oncogenic viruses diagnosed in the recipients and number of times recipients were treated for rejection. This introduced information bias into the data and hence some causal relationships may not be correct, such as the finding that all recipients who developed KS were never diagnosed with HHV8 or all patients who had PTLD were never treated for rejections.

The duration of follow up of some of the recipients was less than 20 years (the total study period) and those transplanted after 2005 were followed up for less than 5 years, this could have biased the analysis of cancer types, time from transplant to diagnosis and the calculation of the incidence of cancer.

The impact of each immunosuppressive drug on the risk of developing a PTM could not be analysed as the numbers of patients exposed to the drugs was small.

Recipients documented as lost to follow-up are those who did not return for a review, and their actual outcome is not known as they might have died or been transferred.

Some viruses such as HHV8, HIV, EBV, and HPV are not routinely tested for post-transplantation at CMJAH and only being tested for when the clinical symptoms suggest its necessity. The routine use of this test may be limited by cost.

CHAPTER 5 - CONCLUSIONS AND RECOMMENDATIONS

Conclusions

This study shows that the clinical practice in the renal transplant department in the last 20 years has not had an impact on the incidence of PTM at CMJAH.

The recipients transplanted at an older age, those who have been on immunosuppressants for a longer duration and those awaiting transplantation beyond two years must be closely monitored and surveillance for malignancy undertaken routinely.

No specific immunosuppressant drug appears to pose a risk for PTM, thus suggesting that decreased immunity is the main risk factor for the pathogenesis of malignancy post renal transplantation.

Recommendations

The development of an electronic database will improve the quality of record keeping by ensuring that all the relevant patient information is kept in one record – dialysis history, donor information, clinical notes and results of all investigations done.

Kaposi sarcoma is a common PTM at CMJAH; routine HHV8 testing must be considered for the blacks and any recipients of Mediterranean origin.

HIV must become a routine test annually post-transplantation as the seroprevalence in the country is high, and this will allow for early antiretroviral therapy before the host immunity is compromised.

There is a need for increased awareness and education among the people of South Africa on the need to be organ donors as the numbers of transplants are decreasing, but the need for transplantation is growing.

A prospective multicentre study needs to be done in SA to assess the impact of the newer drug classes as more recipients are initiated on these drugs and a cost benefit analysis done as the older cheaper drugs may still offer adequate immunosuppression with no increased risk of malignancy.

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PROJECT	Malignancy in Renal Transplant Recipients at Charlotte Maxeke Johannesburg Academic Hospital: 1990-2010
INVESTIGATORS	Dr Joyce Tukayi Ziki.
DEPARTMENT	Department of Internal Medicine
DATE CONSIDERED	29/06/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

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*Guidelines for written 'informed consent' attached where applicable
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Data

Collection Sheet

DATA COLLECTION SHEET

Study No

Date of data collection

Demographic Data

Age at time of transplant

Gender (male=1; female=2; missing=3)

Self-identified ethnic group
(African=1; Indian=2; white=3; Coloured=4; missing=9)

Dialysis Data

Duration on dialysis before transplant (months)

Mode of dialysis (Haemodialysis=1; Peritoneal dialysis=2; both=3)

Immunosuppressant Regimens and Duration of use

Drug	Duration in Months	Drug	Duration in Months
Prednisone		MMF	
Azathioprine		Tacrolimus	
Cyclosporine		Sirolimus	

Renal Graft

Source of graft (cadaver=1; Related Living Donor=2; non-related living donor=3)

Was an oncogenic virus diagnosed? (Yes=1; No=2)

Type of virus diagnosed
(Human Papilloma Virus=1; Epstein-Barr Virus=2;
Hepatitis B=3; Hepatitis C=4; Human Herpes Virus=5; HIV= 6; CMV=7)

Malignancy Data

Duration from transplant to diagnosis of cancer (months)

Did the recipient develop cancer (Yes=1; No =2)

Histological Diagnosis

Approval of Study Title by the University

Faculty of Health Sciences
Medical School, 7 York Road, Parktown, 2193
Fax: (011) 717-2119
Tel: (011) 717-2076

Reference: Ms Salamina Segole
E-mail: salamina.segole@wits.ac.za
01 August 2012
Person No: 325542
PAG

Dr J Ziki
Unit 12 Oxford Mews
63 Oxford Road
Saxonwold
Johannesburg
2196
South Africa

Dear Dr Ziki

Master of Medicine (in the specialty of Internal Medicine): Approval of Title

We have pleasure in advising that your proposal entitled "*Malignancy in renal transplant recipients at Charlotte Maxeke Johannesburg Academic Hospital: 1990-2010*" has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
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