

Malignancies in a renal transplant population: The St. Michael's Hospital experience

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Abstract

Introduction: Previous publications have shown an increased incidence of various malignancies amongst renal transplant populations. The objective of this study was to analyze the rate and types of malignancies occurring in the St. Michael's Hospital renal transplant population and to determine whether our results were comparable to those previously published.

Methods: After approval by the hospital's research ethic board, review of the records and pathology of the 1584 patients in the renal transplant clinic database patients was performed. The reports dated back to the year 1970.

Results: Amongst the 1584 renal transplant patients, 106 patients with 132 dysplastic and malignant posttransplant lesions were identified. The highest incidence amid the malignancies was in nonmelanoma skin malignancies squamous cell carcinoma (SCC), basal cell carcinoma, and Kaposi sarcoma, with a total of 32 patients having 54 separate tumors (2.02% of all patients, 43.2% of tumors). Following skin tumors in incidence were genitourinary (28 tumors), gastrointestinal tract (GIT) lesions (8 adenocarcinomas, 14 dysplastic lesions, 1 low grade neuroendocrine tumor/carcinoid), posttransplant lymphoproliferative disorders (PTLDs) (10 cases), gynecologic (6 carcinomas), cervical/anal/vulvar dysplasia and invasive (SCCs) (4), and thyroid (3 papillary tumors). Nine patients had tumors of multiple sites/types. With respect to outcome, 14 patients died of malignancy, with the highest mortality being in the GIT malignancies (six patients). Second in mortality were the PTLT and skin tumor groups.

Discussion: Information on the incidence and outcome of various malignancies in renal transplant patients is important in designing guidelines for the follow-up of these patients regarding tumor screening and prevention. The rate of malignancies in our group is comparable to that reported in other centers.

Key Words: Kidney, malignancy, transplantation

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INTRODUCTION

A kidney transplant is the preferred treatment for patients with end-stage renal disease. It improves overall survival and

demonstrates considerable improvements in quality of life. Immunosuppressive regimens are a necessary component of solid organ transplantation, to reduce the risk of rejection.^[1]

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Other than infections, this chronic immunosuppression is a significant risk factor for the development of a variety of malignancies due to reduced immune surveillance which normally prevents the development of malignancies and increased incidence of cancers related to viral infections, such as Kaposi's sarcoma (KS) and posttransplant lymphoproliferative disorders (PTLDs).^[2-4] In addition to the potential for chronic immunosuppression itself to increase the risk of malignancy, some of the drugs utilized for control of the recipient immune system have significant risks for the development of neoplasia. Treatment with calcineurin inhibitors as cyclosporine and tacrolimus may be directly related to carcinogenesis through activation of different proto-oncogenes, due to impairment of DNA repair mechanisms leading to permanent DNA damage, in addition to their role in diminishing immune surveillance.^[5,6] Rapamycin has been suggested as an alternative immunosuppressant drug as it actually has an anti-tumor effect.^[7,8]

Cancer in the posttransplant population has been a rising concern due to cancers arising *de novo* postrenal transplant, recurrence of a preexisting cancer in the recipient, or donor-related cancers due to risk of transmission from donors with known or unknown cancer diagnosis.^[2,9-12] Several publications have debated the need for increased posttransplant surveillance for the types of cancer for which there is increased risk.^[12,13] Nonmelanoma skin cancers have been an area of concern, particularly in Australia where skin cancer prevalence is high. However, there is great variability in the populations of these patients in the published literature.^[14,15] The purpose of

this study was to evaluate the rate and types of dysplastic and malignant lesions arising in the renal transplant population of St. Michael's Hospital.

METHODS

Approval for review of the renal transplant database was received from the Research Ethics Board at St. Michael's Hospital. The clinical and pathologic history of all of the patients in the St. Michael's Hospital renal transplant clinic database was retrospectively reviewed from approximately 1970 to the present. The hospital clinical database and the pathology laboratory information system were utilized to search for all pathology reports for any of these patients where malignancies were diagnosed in the posttransplant period, and for any available follow-up information.

RESULTS

Of the 1584 patients in the renal transplant database, 125 dysplastic or malignant lesions were identified in 106 patients (6.7% of patients), 79 males and 27 females. The average age at diagnosis was 61.8 years. Table 1 shows the details of the identified tumors. The majority of the tumors were skin cancers, both nonmelanoma basal cell carcinoma, squamous cell carcinoma (SCC) and KS and melanoma with a total of 32 patients having 54 separate tumors (2.02% of patients, 43.2% of tumors) [Figure 1]. Following skin tumors in incidence were urological tumors (28 tumors: 5 urothelial lesions of the bladder (4

Table 1: Sites and types of malignancies in the St. Michael's Hospital renal transplant cohort

Site	Total number of cases/ number of patients	Types of tumors (number of tumors)	Seer database tumor incidence converted to expected cases per our cohort
Skin	57/36	Squamous and basal cell carcinoma (53)	9/1584
		Kaposi's sarcoma (1)	0.33/1584
		Melanoma (3)	
Genitourinary	28/25	Bladder urothelial carcinomas, I PUNLMP (5)	0.33/1584
		Prostate adenocarcinomas (11)	1.22/792
		Native kidney - RCC (8, 1 patient has 3 RCC)	0.24/1584
		Allograft kidney - RCC (3), urothelial carcinoma (1)	
Gastrointestinal tract	22/22	Stomach adenocarcinomas (3), low grade dysplasia (1)	0.12/1584 0.73/1584
		Colon adenocarcinomas (4), adenomas (13), appendiceal carcinoid tumor (1)	
		CML, CLL, T-cell lymphoma (3)	0.02-0.07/1584
Posttransplant lymphoproliferative disorders	10/10	B-cell lymphomas (7)	0.26/1584
Gynecologic tract	10/10	Ovary - (2)	0.1/792
		Endometrium - 4	0.19/792
		Cervix/vulva/anus SCC/dysplasia (4)	0.03-0.06/1584
Thyroid	3/3	Papillary carcinoma of thyroid (3)	0.18/1584
Various sites	3/3	Lung adenocarcinoma (1)	0.99/1584
		Epithelioid sarcoma (1)	0.05/1584
		Liver metastatic carcinoma of unknown primary (1)	

RCC: Renal cell carcinomas, SCC: Squamous cell carcinoma, PUNLMP: Papillary urothelial neoplasm of low malignant potential, CML: Chronic myelogenous leukemia, CLL: Chronic lymphocytic leukemia

urothelial carcinomas and one papillary urothelial neoplasia of unknown malignant potential, PUNLMP), 11 prostatic adenocarcinomas, 8 renal cell carcinomas (RCC) arising in the native kidney, 3 RCCs arising in the allograft kidney and one urothelial carcinoma arising in the renal pelvis of the allograft kidney [Figure 2]. Of the three patients who developed RCC in the renal allograft, the histological type of the tumors were papillary RCC, clear cell renal cell carcinoma and mixed papillary and clear RCC. Tumours and dysplastic lesions also arose in the gastrointestinal tract (GIT), with 8 adenocarcinomas, 14 dysplastic lesions, and 1 low-grade neuroendocrine tumour/carcinoid tumor arising in the appendix. There were 10 cases of PTLDs, with one case each of chronic myelogenous leukemia, chronic lymphocytic leukemia, and T-cell lymphoma. There were 5 low-grade B-cell lymphomas, 2 arising in the allograft kidney, and 2 high-grade diffuse large B-cell lymphomas [Figure 3]. In the as gynecologic tract, 2 ovarian tumors were detected; one endometrioid adenocarcinoma and one poorly differentiated adenocarcinoma, high-grade. The female patients developed 4 endometrial carcinomas; 3 low grade (FIGO 1/3) endometrioid adenocarcinomas and one mixed serous/endometrioid adenocarcinoma. There were 4 cases of SCC arising in a background of dysplasia/intraepithelial neoplasia in the cervix, anal, and vulvar mucosal tissues. There were 3 papillary carcinomas of the thyroid, 1 lung adenocarcinoma, one sarcoma of the shoulder and one tumor of unknown primary with metastasis to the liver. Nine patients had tumors of multiple sites/types.

The Surveillance, Epidemiology and End Results (SEER) online database (SEER, <http://seer.cancer.gov/>) was utilized to determine the tumor incidence for many of these tumor types; this incidence rate was converted from their standard number/100,000 to a comparable number in 1584 persons; this number is given in the final column of Table I. The rate for nonmelanoma skin cancer is estimated from the United States National Cancer Institute (NCI) website data. A significantly increased incidence of tumors in the transplant population is noted in this comparison to the cohort in the SEER database and the NCI information. For skin cancers, there is a 5–10 fold increased incidence over the average population. Genitourinary (GU) tumors show variably increased risk; bladder urothelial lesions have a 15-fold increased risk, while prostate adenocarcinoma has nine-fold risk, and RCC (both native and allograft) is increased $\times 45$ over the SEER population risk. In the GIT, the risk of gastric cancer is $\times 33$ the average risk, and colon adenocarcinoma has a $\times 5.5$ risk. The various lymphoproliferative disorders show a 25–35-fold increase in incidence. In the gynecologic tract, the incidence of ovarian and endometrial adenocarcinomas is approximately $\times 20$ normal. The risk of development of cervical/vulvar/anal squamous

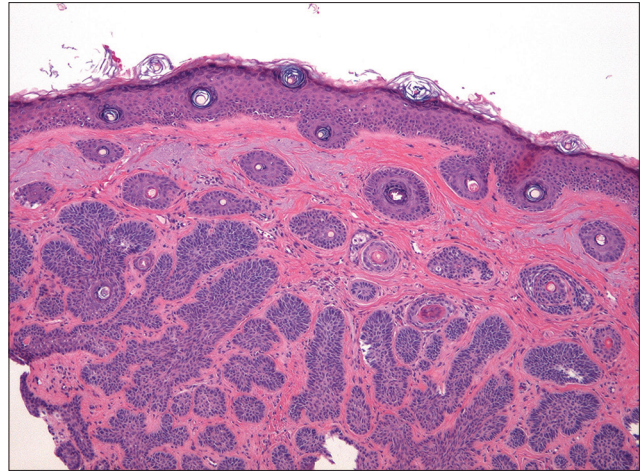


Figure 1: Skin, basal cell carcinoma, forearm (H and E, $\times 50$)

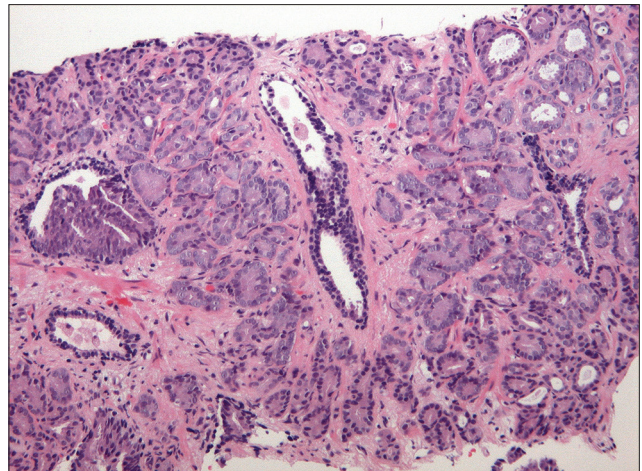


Figure 2: Prostate, adenocarcinoma (H and E, $\times 100$)

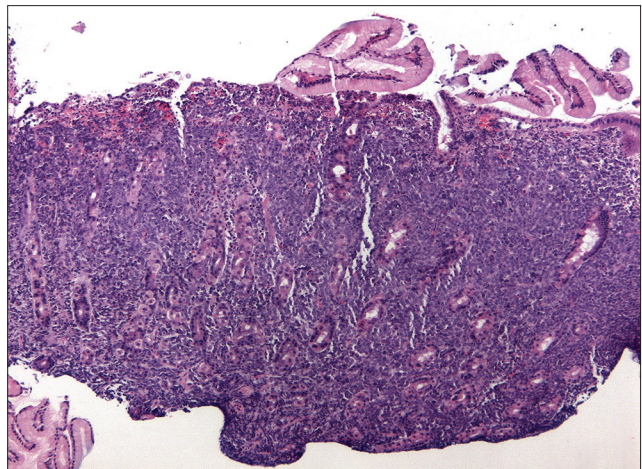


Figure 3: High Grade B cell lymphoma arising in the stomach (H and E, $\times 50$)

dysplastic lesions and SCC is considerably elevated, at $\times 80$ the incidence in the average population. While the risk of papillary thyroid carcinoma appears mildly elevated ($\times 17$), the numbers of tumors in the respiratory tract does not suggest increased

risk. One sarcoma was reported, while this is only one case in this time period, again this suggests increased risk ($\times 20$).

In patients where information about outcome was available, 14 patients died of disease; 6 with GIT malignancies (stomach and colon adenocarcinoma), 3 of PTLDs and 3 from skin malignancies (melanoma and metastatic SCC). The SEER database gives mortality data for gastric cancer, converted to our sample size, as 0.06/1584 persons, and for colorectal carcinoma as 0.26/1584 persons; this suggests that outcome in transplant patients is poor compared to the general population.

DISCUSSION

Transplantation of solid organs or bone marrow has long been recognized to increase the risk of development of a number of malignancies in the transplant recipients, most often linked to immunosuppression. Consistent with the pattern seen in HIV infection, a number of studies have shown that the incidence of a variety of cancers is increased by least 3–5 times that of the general population.^[3,4,12] Survival in many cases is also poor, possibly due to the limitations in treating patients who already have significant immunosuppression with chemotherapeutic agents,^[12] but the absence of tumor surveillance by a normal, intact immune system may also contribute to this poor outcome. In a review of transplant patients in Italy, it was found that cancer was the second most common cause of death posttransplant, 27% versus 30% of deaths due to cardiovascular events at 15 years.^[16]

Tumors in transplant populations can also be sub-grouped, according to the association of some malignancies with specific infections or with end-stage kidney disease.^[2] Cancers associated with infections included KS (human herpes virus type 8), non-Hodgkin's lymphoma and Hodgkin's lymphoma (Epstein–Barr virus), anogenital, oropharyngeal, and oral cavity cancers (human papillomavirus); hepatocellular carcinoma (hepatitis B and C viruses); and gastric adenocarcinoma (*Helicobacter pylori*). The risk of developing some of these malignancies, particularly KS, has been linked to the intensity of immunosuppression.^[17] In one study,^[4] cancer occurred at significantly increased incidence at 25 sites, and risk exceeded three-fold at 18 of these sites. Most of these cancers were of known or suspected viral etiology. Tumors particularly associated with end-stage kidney disease include RCC, urothelial carcinomas of the bladder, ureters, and renal pelvis, and parathyroid gland adenomas.

However, patient age may also be a factor in the development of some tumors: In a study of *de novo* urological tumors arising in renal transplant recipients, it was found that prostate cancer was the most common malignancy arising in male transplant patients. The authors noted that these findings may not be

solely related to immunosuppressant medications but also due to the natural patterns of occurrence of this tumor, as the transplant population was relatively elderly in their study.^[18] In our cohort, all patients over the age of 50, or patients over the age of 40 if of African descent, were seen by a urologist and had prostate-specific antigen testing as well as a digital rectal examination to screen for preexisting prostate cancer; this may have contributed to the relatively lower incidence of prostate carcinoma in our cohort. Reducing immunosuppression can have a direct effect on reducing the risk of developing certain tumors, particularly oral (lip), non-Hodgkin's lymphomas and melanomas, though it may not affect incidence of other tumors such as leukemia, kidney, bladder, lung, and thyroid.^[2]

The risk of development of malignancy occurs rapidly after the transplantation in several studies: In an American cohort, it was found that for the most common tumors (colon, lung, prostate, stomach, esophagus, pancreas, ovary and breast), cancer rates were roughly two-fold higher within in the first 3 years after renal transplant compared to the general population.^[13] Renal transplant patients developing bladder cancer appear to present with the advanced disease within the first 5 years after transplantation despite screening protocols.^[19]

In our cohort, we demonstrated a significantly increased risk of development of a variety of different tumors in different organ systems, particularly nonmelanoma skin cancers but also GU, gynecologic and gastrointestinal tumors. In tumors where comparable mortality statistics is available from the SEER database, there is also an increased risk of mortality from these tumors in our cohort.

Our results are comparable to other studies in transplant populations in Canada, the United States and Australia^[13-15] and to a previous Canadian study conducted on 11,155 patients who underwent renal transplant, where the percentage of patients with dysplasia/malignancies was 6.97%.^[20] The risk of cancer among this cohort was two and a half times higher than the rates observed in the Canadian population. However, they excluded nonmelanoma skin cancers which are often the most frequent tumors in this population in other studies.^[20,21]

Overall, these results demonstrate that renal transplant patients continue to have a significant risk for development of and mortality from malignancies in a variety of organs, despite advances in detection and treatment. Careful surveillance for skin lesions is appropriate. Considering the rate of dysplasia and malignancy in the GIT, GU and gynecologic tracts, the possibility of early and repeated screening for these patients (i.e., gastroscopy, colonoscopy, urine cytology, Pap smears, and endometrial biopsies) should be considered by the clinical groups following these patients. Early intervention in these malignancies, possibly

coupled with decreased immunosuppression, may aid in increasing survival for these at-risk patients.

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Conflicts of interest

There are no conflicts of interest.

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