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REVIEW

Post-transplant *de novo* malignancies in renal transplant recipients: the past and present

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Summary

Post-transplant *de novo* malignancies are reviewed in three time periods: (i) the azathioprine (AZA) era from 1962 to 1980–1981, (ii) the cyclosporine (CYA) era (1980 to present) in which the calcineurin inhibitors, CYA and tacrolimus (TAC), were the mainstay of recipient immunosuppression, and (iii) the TOR inhibitor era starting in the year 2000. Both transplant registry and transplant center reports on malignancies occurring in the AZA era are reviewed. Reports from transplant centers and from the Cincinnati Transplant Tumor Registry (CTTR) in both the early CYA era (1980s) and the 1900–2000 CYA era are reported. Cancer incidence associated with AZA versus CYA, CYA versus TAC, and AZA versus mycophenolate mofetil (MMF) is compared in both transplant center and registry reports including new, unreported Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) data from 1998 to 2003. The malignancy incidence associated with lymphocyte-depleting antibody and corticosteroid immunosuppression is discussed. Reduced malignancy incidence recently reported with TOR inhibitors is compared with that of conventional immunosuppression. Important nondrug factors influencing the incidence of post-transplant malignancies from seven single and three registry reports are detailed. The substantial role that *de novo* malignancies play in post-transplant mortality is discussed. Finally, management recommendations for recipients who develop *de novo* post-transplant malignancies are briefly presented.

Introduction

Post-transplant *de novo* malignancies are reviewed in three time periods: (i) the azathioprine (AZA) era from 1962 to 1980–1981, (ii) the cyclosporine (CYA) era in which the calcineurin inhibitors, CYA and tacrolimus (TAC), were the mainstay of recipient immunosuppression, and (iii) the TOR (target of rapamycin) inhibitor era starting in the year 2000 when sirolimus (SRL) was used either as a stand alone immunosuppressant, or in conjunction with one of the calcineurin inhibitors. Post-transplant lymphoproliferative disorder (PTLD) was not reviewed in detail but when lymphomas are a component of post-transplant *de novo* malignancy reports, they are included. When either two immunosuppressive drugs, or two immunosuppressive drug regimens were compared and follow-up times were grossly unequal, the reports were not usually included because duration of immunosuppression is an important independent variable in malignancy incidence.

Early transplant registry reports

Dr Joseph Murray and co-workers performed his landmark successful identical twin transplant in 1954 [1]. Five years later, Murray and co-workers performed a successful

nonidentical twin transplant with the recipient receiving pretransplant total body radiation (TBR) as immunosuppression [2]. Although TBR was used as immunosuppression in 11 other patients that were all failures [3], there were isolated reports in 1962 and 1963 of prolonged patient survival following TBR [4–6].

The almost simultaneous reports by Calne [7] and Zukoski *et al.* [8] in 1960 of prolongation of canine kidney homograft survival by 6-mercaptopurine ushered in the immunosuppression era in which drugs alone, or in combination with radiation therapy, were used for human transplantation immunosuppression.

In September 1963, Dr Murray chaired a *Conference on Human Kidney Transplants*, which summarized all human kidney transplants ($N = 244$) performed in Europe, England, and the United States [9]. The Second Human Kidney Transplant Registry (HKTR) Report in 1964 detailed 374 kidney transplants from 30 worldwide transplant centers [10]. The Fourth Report of the HKTR in 1965 ($N = 672$), detailed the first two malignancies, both of which were fatal donor-transmitted tumors [11].

In 1969, 13 post-transplant primary malignancies from seven different transplant programs (five from the USA, one from Scotland, and one from New Zealand) were reported to the HKTR [12]. Seven of the 13 tumors were lymphomas and all 13 were fatal. Each patient had received AZA and steroids and three lymphoma patients also received antilymphocyte serum. These patients were young (age: 14–48 years) and the calculated tumor incidence was 4.6–8 times that of the general population [12].

In 1969, Penn *et al.* reported on five lymphomas in living donor recipients [13]. All patients had been treated with AZA and prednisone with three patients receiving antilymphocyte globulin (ALG) and four patients having undergone splenectomy. Survival time ranged from 6 to 30 months in four patients while the fifth patient who underwent radiation of her brain lymphoma was alive at the time of the report [13].

Two years later (1971), Penn *et al.* had collected 40 tumors: 17 of the malignancies were mesenchymal tumors (14 lymphomas, two leiomyosarcomas, one visceral Kaposi's), nine were skin cancers, five were squamous cell carcinoma *in situ* (CIS) of the uterine cervix, and nine were solid nonlymphoid tumors [14]. Sixteen of 17 patients with mesenchymal tumors died as a consequence of their malignancy. Nine patients with skin cancers and five with CIS of the cervix were alive. The nine recipients who developed solid, nonlymphoid malignancies died as a result of their malignancy [14].

An update of malignancy cases ($N = 75$) reported to Penn and Starzl's registry through 1971 [15] is shown in Table 1. Thirty-one patients had mesenchymal tumors of which 20 were reticulum cell sarcomas (RCS), three unclassified lymphomas, three Kaposi's sarcoma, and five miscellaneous sarcomas. Twenty-eight of these 31 patients were dead at the time of the report. In the 44 recorded

Table 1. Comparison of malignancies reported by the HKTR with malignancies reported by Penn and Starzl [15].

	Report (Ref. number), year*					
	HKTR [16], 1971	Penn and Starzl [15], 1971	HKTR [17], 1973	Penn [18], 1974	HKTR [19], 1976	Penn [20], 1976
Number of transplants†	6297	~7581	14 479	~15 000	19 631	
Number of malignancies in kidney recipients	65	75	192	231	290	425
Number and percentage with specific malignancies						
Skin	21 (32)	21 (28)	83 (43)	95 (41)	122 (42)	182 (43)
Lymphomas‡	25 (38)	26 (35)	33 (17)	60 (26)	46 (16)	90 (21)
Cervix	N/A	8 (11)	18 (9)	18 (8)	23 (8)	32 (8)
Lung	3 (5)	4 (5)	10 (5)	12 (5)	15 (5)	17 (4)
Brain	1 (2)	N/A	12 (6)	N/A	14 (5)	3 (0.7)
Kaposi's sarcoma	N/A	3 (4)	N/A	6 (3)	1 (0.3)	13 (3)
Breast	2 (3)	1 (1)	5 (3)	N/A	8 (3)	11 (3)
Colon/rectum	3 (5)	2 (3)	6 (3)	N/A	9 (3)	11 (3)
Leukemias	1 (2)	N/A	2 (1)	N/A	5 (2)	10 (2)

*HKTR, Human Kidney Transplant Registry – last year included in report; Penn and Starzl, CTTR – last year included in report.

†Number of transplants, Penn's numbers are approximate for first two studies; no numbers were available for third study.

‡Lymphomas, reticulum cell sarcoma counted as lymphoma; Penn counted Kaposi's sarcoma as a lymphoma; Kaposi's not counted as lymphoma in this table.

Cervix, HKTR reported as cancer of 'female reproductive'; Brain, lymphomas of the brain excluded in table; Colon/rectum, HKTR reported as 'GI tract'; N/A, no numbers given in report.

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epithelial tumors, eight were CIS of the uterine cervix, 21 were skin carcinomas, and 15 were solid nonlymphoid tumors. Thirteen of these 15 patients were dead with one survivor having thyroid carcinoma and a second having breast carcinoma [15].

The HKTR report on 6297 transplants recorded through 1971 showed a total of 65 malignancies including 25 lymphomas, 21 skin tumors, and 19 solid nonlymphoid tumors (Table 1) [16]. Lymphoma incidence was estimated to be 30–40 times greater than expected for transplant patients relative to nontransplant patients. Further, 13 of the 25 lymphomas involved the brain when compared with a <1% incidence in nontransplant patients. Skin cancers were calculated to be 4.2 times higher and solid nonlymphoid cancer 2.5 times higher than expected [16].

The 12th HKTR Report on 14 479 patients recorded a total of 192 tumors of which 43% were skin malignancies (Table 1) [17]. It was noted that SCC not only constituted 50% of the skin cancers, but also outnumbered basal cell carcinomas (BCC) by a ratio of roughly 8:5. In non-immunosuppressed patients, the generally accepted ratio is 1:5.

Penn's data through June 1974 included 234 recipients (231 kidney, two heart, one liver) who developed a total of 241 malignancies [18]. Data on the kidney patients is included in Table 1. Lymphomas occurred earlier after transplantation than other malignancies (20.6 vs. 31.6 months), and lymphoma recipients more frequently received ALG (40% vs. 25.4%). Lymphoma patients had the worst survival rate (11%), followed by solid nonlymphoma tumors (25%), and patients with cancer of skin, lip, and uterine cervix (82%). These survivals are the actual survivals at the time of the report.

The 13th and final report of the HKTR included 19 631 patients through 1976 of whom 13 384 (68.2%) were alive at the time of the report (Table 1) [19]. There were 290 total malignancies reported of which 122 (42%) were skin, 46 (16%) were lymphomas, and 122 were solid nonlymphoma tumors. The malignancy incidence was a significantly increased ($P < 0.05$) in patients with polycystic kidney disease when compared with other primary kidney diagnoses. The mortality rate in patients with malignancies was high (46.9%) and 60% of the 136 deaths were directly due to the malignancy.

Penn's report through August 1976 included 425 kidney recipients with malignancies (Table 1) [20]. Remarkably, the report contains 135 more kidney recipients with cancer than were recorded by the HKTR during the same time period [19] even though the HKTR was thought to have data on the majority of kidney transplants performed in the entire world [21,22]. The percentages of certain tumors reported by the two registries were strikingly similar for skin, carcinoma of the cervix, lung, breast, colon/rectum, and for leukemia (Table 1). However, Penn [20] reported almost twice as many lymphomas and substantially more Kaposi's sarcomas than the HKTR. Penn [20] noted that eight of the skin cancers were fatal: four melanomas and four SCC.

The 1977 Australia/New Zealand Transplant Registry (ANZTR) Report on 1884 kidney transplants detailed a total of 126 recipients (7%) with a malignancy of which 97 (74%) were skin tumors [23]. The ratio of SCC to BCC was 3.1:1 with eight of 71 patients with SCC developing metastases and three resulting in deaths. One of three melanomas also metastasized and resulted in death. Lymphomas, in the form of RCS, occurred in 15 patients and were the cause of death in seven patients. Adenocarcinoma occurred in eight patients, metastasized in seven patients, and was the cause of death in five patients. Although the number of living donor transplants was small ($N = 41$), the incidence of malignancy was less (2%), presumably due to less immunosuppression. Overall, after 4 years, malignancy caused 17% of deaths [23].

A 1979 ANZTR follow-up report indicated that the incidence of cancer in patients surviving with a functioning graft beyond 1, 5 and 10 years was 26%, 43% and 47%, respectively [24]. Of 35 patients who died more than 5 years after transplantation, 57% had cancer and cancer was the primary cause of death in 29% of the patients.

A 1981 European Dialysis and Transplant Association report included 138 post-transplant malignancies [25]. Only 18.8% of reported cancers were skin cancer and BCC outnumbered SCC by a ratio of 7:6. Only three lymphomas (2%) were reported which is different from the reports of other registries. Of note, 8.7% of the 138 malignancies were breast cancer that is higher than that of other registries.

A report from Scandia-Transplant on 3956 patients (4820 transplants) from 1969 to 1979 compared cancer incidence in recipients of living-related kidneys ($N = 753$), first cadaver kidneys ($N = 2339$), and re-transplant cadaver kidneys ($N = 864$) [26]. The incidence rates were 2.4%, 3.3% and 1.9%, respectively.

Early transplant center reports

Doak *et al.*, in 1968, reported two patients who developed lymphomas shortly after transplantation (7 and 9 months) [27]. One patient had a RCS of the brain and the second a disseminated RCS and these tumors were major factors in both patients' deaths.

In 1970, Montreal physicians reported on 54 recipients surviving for 1 year [28]. Two patients developed malignant tumors; one a CIS of the cervix and the second, a

leiomyosarcoma of the bowel that, at autopsy, involved the jejunum, ileum, pancreas, and liver.

UCLA physicians reported on 66 recipients with graft function over 1 year in whom four malignancies developed [29]. Two of these tumors were SCC of the lip in young patients (ages: 17 and 27 years), one was a lymphoma of the brain, and the fourth a CIS of the cervix.

Medical College of Virginia surgeons reported three RCS in 151 renal transplant recipients [30]. In two recipients, the tumors were discovered 5 years post-transplantation in patients with excellent renal function and minimal difficulty with rejection.

University of Minnesota surgeons in 1975 described an increased incidence of malignancies (1.4%) in patients with progressive uremia before transplantation or before the initiation of chronic dialysis [31]. In comparison, 11 of 530 (2.1%) renal transplant recipients developed post-transplant malignancies with nine of the 11 tumors being either SCC or a lymphoma.

Peter Bent Brigham Hospital Surgeons reported on 584 kidney transplants through January 1976 [32]. Post-transplant malignancies developed in 23 patients (3.9%) with 10 being skin cancers and four additional tumors occurring in the uterine cervix. Additionally, there were three lymphomas, one leukemia, three solid carcinomas, one sarcoma, and a glioblastoma multiforme. Recipients developing cancer were older, more likely males, and a higher percentage had received cadaver donor transplants. The authors noted a statistically better graft survival in cancer patients when compared to patients without cancer [32].

A report from Sweden on 934 patients transplanted between 1965 and 1981 recorded 32 malignancies with skin and renal cancers excluded [33]. The overall incidence was 3.4% but in 5-year survivors the incidence had risen to 6.1%. Compared with nontransplant patients in the Swedish Tumor Registry, there was a significantly increased risk ratio for lymphomas, lip cancer, vulva/anus cancer, and colorectal cancer for transplant recipients.

Calcineurin inhibitor era – early (1980s) reports

Calne *et al.*, in 1978, reported the first seven cadaveric donor kidney recipients treated with cyclosporin A (CYA) utilizing high starting doses of 25 mg/kg/day [34]. A later report on 45 CYA-treated cadaveric donor kidney recipients detailed nine deaths, three failed grafts, and 33 functioning transplants [35]. Two of the patients who died were found to have a lymphoma; one in the jejunum and the other a disseminated malignancy [35,36]. A third patient developed a gastroduodenal lymphoma and underwent a partial gastrectomy plus reduction of immunosuppression with no evidence of lymphoma after 13 months [36].

Following these initial reports on CYA, two national trials [37,38], and a European multicenter trial [39,40] compared CYA with AZA. No tumors were reported from either the Canadian or Australian/New Zealand trials [37,38]. At 5 years in the European trial, the CYA group had one skin cancer and three solid tumors and the AZA group had two skin cancers and one urothelial carcinoma [40]. An additional ANZTR trial of 417 patients had four recurrent and four *de novo* skin cancers in 137 patients in the AZA arm. In the long-term CYA arm of 140 patients, there were nine recurrent and five *de novo* skin cancers, one melanoma, and two nonskin solid tumors. In the short-term CYA arm (3 months and switched to AZA) there were five recurrent and four *de novo* skin cancers [41].

Three single center reports deserve mention. A report from Minnesota detailed no significant differences in graft or patient survival with a CYA/prednisone protocol versus an ALG/AZA/prednisone protocol [42] and reported a single CYA-associated case of PTLD that completely regressed following reduction in immunosuppression but at the cost of irreversible graft rejection [43]. Pittsburgh surgeons detailed improvement in graft and patient survival with a CYA regimen [44] but six of 310 recipients developed a lymphoma [45]. Five of the six cases involved lymphoma of the bowel, which in each instance was resected while the sixth case involved the neck that was treated with radiation. All patients had reduction of the CYA dosage with all six patients being alive at the time of the report although two lost their graft from rejection [45]. The third report, from Iowa, compared CYA, AZA, and prednisone (triple therapy; $N = 129$) with CYA and prednisone ($N = 189$) and with AZA and prednisone ($N = 669$) [46]. The incidences of lymphoma were 3.9%, 0% and 0.3%, respectively ($P < 0.0001$).

Cincinnati Transplant Tumor Registry – 1980s reports

In 1988, the Cincinnati Transplant Tumor Registry (CTTR) reported on 3551 *de novo* malignancies in 3320 patients of which 412 tumors occurred in 405 patients treated with CYA [47]. Ninety-one of these 405 patients (22%) received extrarenal organs with 60 (66%) developing lymphomas. The incidence rates of the more frequently occurring post-transplant malignancies reported to the CTTR under AZA-based versus CYA-based immunosuppression are shown in Table 2. Because the overall patient denominator is unknown, the incidence rates and percentages are those of patients reported to the CTTR rather than true incidence rates. Skin cancers were more frequent with AZA while lymphomas, Kaposi's sarcoma, and renal tumors were more common with CYA-based immunosuppression.

Table 2. Comparison of tumor incidence rates between azathioprine and cyclosporine. Based immunosuppression as reported to the Cincinnati Transplant Tumor Registry (CTTR; adapted from Penn and Brunson [47]).

	Azathioprine based ($N = 3139$)		Cyclosporine based ($N = 412$)	
Tumor type	*N*	%	*N*	%
Skin cancers	1255	40	90	22
Lymphomas	362	12	119	29
Kaposi's sarcoma	106	3	44	11
Renal tumors	89	3	23	6

Calcineurin inhibitor era – 1990s and 2000s reports

From the plethora of reports on post-transplant malignancies in the 1900s and early 2000s, we have selected single center and registry reports that included analyses of substantially large patient cohorts for this portion of the review. Table 3A,B shows the percentages of each type of tumor from five single center and five registry reports. The last row of Table 3A,B shows data, not previously reported, from the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) database for cancers reported during 1998–2003.

The percentage of skin malignancies varied between 37.4% and 63% with the exceptions of Ref. [48] and [49] which both had extraordinary low percentages. SCC was the most frequent skin cancer in studies that reported both SCC and BCC [50–54]. Melanoma frequency was lowest in the Denmark report [55] and highest in the report from Milan, Italy [51] that may reflect differences in sunlight exposure. The percentages of Kaposi's sarcoma were highest in reports from Italy [49,51] while no Kaposi's were reported from England, northern USA, or Northern Ireland [48,50,53]. Not shown in the table, Kaposi's sarcoma is most often seen in transplant recipients of the Mediterranean, Jewish, Arabic, Caribbean, or African descent [56]. Lymphoma frequency varied between 3.9% [51] and 21.7% [49] that, in part, may reflect differences in post-transplant immunosuppressive therapy [57] as well as length of follow up.

Table 3B shows that percentages of solid nonlymphoma cancer varied between 32.8% and 80% in nine of the 10 reports depicted. In the solid tumor categories listed in Table 3B, the highest percentages are seen with genitourinary and the lowest with primary hepatic and endocrine malignancies.

Nondrug factors influencing post-transplant cancer incidence

Table 4 lists seven single center and three registry reports that identified nondrug factors that are associated with either increased, or decreased risks of post-transplant malignancy. All 10 reports indicated that increasing age was associated with an increased risk of any *de novo* cancer [48–52,58–62]. A report from the OPTN/UNOS

Table 3A. Tumor percentages from five single center and five transplant registry programs.

Reference, country	Number of patients with tumors/number of tumors	Total skin	SCC	BCC	Kaposi	Melanoma	Lymphoma
[50] (1995), England	70/80	42 (52.5)	30 (37.5)	12 (15)			7 (8.8)
[51] (1996), Italy	76/76	48 (63)	26 (26.3)	11 (14.5)	13 (17)	4 (5.3)	3 (3.9)
[58] (1997), France	133/139	52 (37.4)			9 (6.5)	4 (2.9)	20 (14.4)
[52] (2003), Spain	95/102	49 (48)	23 (22.5)	23 (22.5)	8 (7.8)	3 (2.9)	8 (7.8)
[48] (1999), the USA	87/88	2 (2.3)	1 (1.2)				16 (18)
[53] (2000), Northern Ireland	86/103	48 (47)	32 (31)	16 (15.5)			11 (10.7)
[55] (2000), Denmark	175/209	118 (56.5)				3 (1.4)	11 (5.3)
[49] (2003), Italy	172/175		12 (6.8)	Not counted	39 (22.3)		38 (21.7)
[59] (2004), ANZTR	1412/1545	Not counted	Not counted	Not counted	28	183	231
[54] (2000), CTTR	10 955/11 663	4406 (37.8)	2855 (24.5)	1240 (10.6)	467 (4.0)	227 (1.9)	1953 (16.7)
OPTN/UNOS	2505	1030 (41.1)	694 (27.7)	317 (12.7)	28 (1.1)	65 (2.6)	429 (17.1)

Values are given as *N* (%).

SCC, squamous cell carcinoma; BCC, basal cell carcinoma; ANZTR, nonmelanoma skin cancers not included in report, therefore percentages were not calculated; CTTR SCC, 683 patients had both SCC and BCC, listed in Table 3A as SCC only; CTTR lymphoma, CTTR reported PTLD and did not report lymphomas separately; OPTN SCC, 115 patients had SCC and BCC, listed as SCC only; OPTN lymphoma, reported as PTLD; CTTR, Cincinnati Transplant Tumor Registry; ANZTR, Australia/New Zealand Transplant Registry; OPTN/UNOS, Organ Procurement and Transplantation Network/United Network for Organ Sharing; PTLD, post-transplant lymphoproliferative disorder.

Table 3B. Solid tumor percentages from five single center and five transplant registry programs.

Reference	Total number of solid tumors	GU	GI	Respiratory	Liver	Breast	Endocrine	Other
[50]	38 (47.5)	12 (15)	6 (7.5)	6 (7.5)	1 (1.3)	1 (1.3)		12 (15)
[51]	25 (32.8)	13 (17)	3 (3.9)	2 (2.6)	2 (2.6)	2 (2.6)	1 (1.3)	3 (3.9)
[58]	49 (35.3)							
[52]	38 (37.3)	11 (10.8)	5 (4.9)	6 (5.9)				16 (15.6)
[48]	70 (80)	15 (17)	12 (13.6)	15 (17)		5 (5.7)	1 (1.2)	22 (25)
[53]	44 (43)	10 (9.7)	9 (8.7)	4 (3.9)		5 (4.9)	1 (1.0)	15 (14.5)
[55]	81 (38.8)	29 (13.9)	15 (7.2)	15 (7.2)		11 (5.3)	2 (1.0)	9 (4.3)
[49]	86 (49)	24 (13.7)	17 (9.7)	7 (4)		8 (4.6)		30 (17)
[59]	1103	388	188	119	27	87	31	263
[54]	4610 (39.5)	1325 (11.4)	530 (4.5)	652 (5.6)	187 (1.6)	363 (3.1)	139 (1.2)	1414 (12.1)
OPTN/UNOS	1056 (42.2)	310 (12.4)	114 (4.6)	150 (6.0)	20 (0.8)	96 (3.8)	32 (1.3)	334 (13.3)

Total solid tumors = All tumors – Skin cancers (including Kaposi's and melanoma) – Lymphomas.
Values are given as *N* (%).
Percentage was calculated out of number of tumors in Table 3A.
GU, genitourinary – includes kidney, bladder, prostate, uterus, and uterine cervix; GI, gastrointestinal – includes esophagus, stomach, small intestine, colo-rectum; Respiratory, includes larynx, bronchi, lungs; Liver, primary hepatic tumors; Endocrine, includes thyroid, adrenal, does not include testes or ovary; OPTN/UNOS, Organ Procurement and Transplantation Network/United Network for Organ Sharing.

Table 4. Risk factors other than immunosuppressive drugs for development of post-transplant *de novo* malignancy*.

Author	Reference	Year	Cohort size	Risk factors†
Gruber *et al.*	[62]	1994	1165	+ Age >50 years, nondiabetic
London *et al.*	[50]	1995	918	+ Age >38 years, length of dialysis
Hiesse *et al.*	[58]	1997	1710	+ Older age, dialysis <30 months, cerebrovascular accident (CVA)
Danpanich and Kasiske	[48]	1999	1500	+ Age >45 years, splenectomy, history of cancer, cigarette smoking – Type 1 diabetes
Montagnino *et al.*	[51]	1996	854	+ Age >40 years, male gender
Pedotti *et al.*	[49]	2003	3521	+ Older age, male gender
Marcen *et al.*	[52]	2003	793	+ Older age, male gender
Kasiske *et al.*‡	[60]	2004	35 765	+ Older age, male gender, duration of dialysis ≥3 years – Race, diabetes
Kasiske *et al.*§	[60]	2004	35 765	+ Older age, male gender, cystic kidney disease – Race, diabetes, duration of dialysis ≥1 year, increased body mass index
Chapman and Webster	[59]	2004	14 354	+ Older age, male gender, nondiabetic
Kauffman *et al.*¶	[61]	2005	33 249	+ Older age, male gender, race, history of cancer – Diabetes
Kauffman *et al.***	[61]	2005	33 249	+ Male gender, race, history of cancer

*Reports with drug factors alone were excluded, and reports with both nondrug factors and drug factors were included.
†Risk factors: + = increased relative risk; – = decreased relative risk.
‡Kasiske *et al.*– risk factors for the development of any cancer.
§Kasiske *et al.* – risk factors for the development of nonmelanoma skin cancer.
¶Kauffman *et al.* – risk factors for the development of any cancer.
**Kauffman *et al.* – risk factors for the development of nonskin solid cancer.

database indicated recipients age 18 years or greater had a 133% increased risk of developing nonskin solid cancer that approached statistical significance ($P = 0.063$) [61]. Male gender was a significant risk factor for an increased incidence of any malignancy in six studies [49,51,52,59–61] as well as for nonmelanoma skin cancer [60] and

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nonskin solid cancer specifically [61]. The duration of pretransplant dialysis was significant in three reports; however, the effects differed [50,58,60]. London *et al.* reported a reduced risk of cancer with dialysis duration greater than, or less than, the mean duration of 20 months [50]. Heisse *et al.* reported that patients with cancer had a shorter dialysis time than those patients without cancer [58]. Kasiske *et al.* indicated that dialysis duration of 3 or more years was associated with a significant increased risk of any cancer but that duration of 1 or more years was associated with a significantly reduced risk of developing skin cancer [60].

Four studies identified diabetes mellitus as a risk factor [48,60–62]. The University of Minnesota indicated that nondiabetics, when compared with diabetics, had a significantly increased risk of developing any cancer, skin cancer, and lymphomas [62]. A second study showed type 1 diabetes was associated with an 81% reduced RR of developing any post-transplant malignancy [48]. The USRDS study indicated a significantly reduced risk of both nonskin malignancies and nonmelanoma skin malignancies observed with diabetes [60]. The OPTN/UNOS report also indicated a reduced risk of developing any post-transplant malignancy with diabetes [61]. The USRDS report further identified patients with cystic kidney disease as being associated with an increased risk of nonmelanoma skin malignancy [60]. Previous reports have identified an increased incidence of renal cell carcinoma in patients with cystic kidney disease [63,64].

Both the University of Minnesota study and the OPTN/UNOS data indicated that a past history of cancer was a risk factor for a post-transplant *de novo* malignancy [48,61] with the latter showing an increased risk for nonskin solid tumors [61]. An earlier UNOS study of both kidney and heart recipients indicated that patients with a past history of cancer not only had an increased risk of malignancy recurrence, but also had a significant increased risk of developing an independent *de novo* post-transplant cancer [65].

Other positive, nondrug risk factors cited in the literature include a previous splenectomy and a history of cigarette smoking [48]. Kasiske *et al.* reported an increased body mass index was a negative risk factor for development of nonmelanoma skin cancer [60]. The USRDS, ANZTR, and OPTN/UNOS registry reports all indicated that older age was a positive risk factor for malignancy [59–61].

Role of immunosuppressive drugs in development of post-transplant *de novo* malignancies

The early demonstration of immunologic rejection of donor-transmitted malignancies after discontinuation of immunosuppressive therapy was the first indication of the role of immunosuppression in transplant-related malignancies [66,67]. The tumor-enhancing role of drugs was further supported by Starzl *et al.*'s report of regression of lymphomas and lymphoproliferative lesions after the reduction or discontinuation of immunosuppressive drug therapy [68]. Reduction/discontinuation of immunosuppression has also been shown to be associated with regression of Kaposi's sarcoma [69,70] and Merkel cell carcinoma [71] as well as decreasing skin squamous cell carcinogenesis [72]. There is one case report of a kidney recipient who developed multiple hepatocellular carcinomas in both lobes of her liver [73]; however, 14 months after converting her CYA immunosuppression to low-dose AZA there was evidence of complete regression of her lesions [73]. To our knowledge, there are no other reports of regression of *de novo* solid tumors.

The role of immunosuppression was further amplified by the seminal work of Dantal *et al.* that prospectively compared the cancer incidence with a low-dose CYA regimen with that of a standard dose CYA regimen [74]. At 66 months follow up, although there were more acute rejections in the low-dose group, there were no differences in graft or patient survival. The normal dose group had a significantly higher incidence of any cancer ($P < 0.034$) and of skin cancer ($P < 0.05$). This observation was supported by the retrospective review from Northern Ireland, which found that the total CYA dose of patients developing cancer (5764 mg/kg; 4.47 mg/kg/day) was significantly higher ($P = 0.026$; $P = 0.014$) than the total dose of patients not developing cancer (3887 mg/kg; 3.42 mg/kg/day) [53].

Cancer incidence: azathioprine versus cyclosporine

We found only four reports that compared AZA with CYA immunosuppression in which the duration of follow up was equal between the two regimens (Table 5). Montreal surgeons performed a univariate comparison of all patients, and patients age 45 years or greater, who received either an AZA-based ($N = 260$) or a CYA-based regimen ($N = 421$) [75]. In both comparisons, the cancer incidence was significantly greater in patients receiving the CYA regimen (Table 5). The study from Belfast, Northern Ireland was a univariate analysis to compare the cumulative number of tumors that developed by 5 years in AZA-treated patients ($N = 335$) versus CYA-treated patients ($N = 268$) [53]. The incidence of total malignancies, skin cancers, PTLD, and nonskin solid tumors was higher in the CYA group (Table 5). The report from Paris used both univariate and multivariate analyses on 597 AZA-treated, and 1113 CYA-treated patients for 4 years post-transplant [58]. The incidence in the CYA group

Table 5. Malignancy incidence with azathioprine (AZA) versus cyclosporine (CYA) immunosuppression.

Reference	Cohort	Length of follow up	AZA (*N*)	Cancer incidence, *N* (%)	CYA (*N*)	Cancer incidence, *N* (%)	Type of analysis	*P*-value
[75]	All patients	14	260	15 (5.8)	421	43 (10.2)	Univariate	<0.04
[75]	Age >45 years	14	75	4 (5.3)	223	32 (14.3)	Univariate	0.03
[53]	All patients	5	335	15 (4.5)	268	34 (12.7)	Univariate	<0.001
[58]	All patients	4	597	1.5	1113	4.1	Multivariate	<0.0001
[52]	All patients	5	203	4.0	510	8.0	Multivariate	<0.05

was significantly greater than that of the AZA group ($P < 0.0001$). The Spanish report of 203 AZA-treated and 510 CYA-treated patients followed for 5 years found a significantly higher cancer incidence with CYA with both univariate and multivariate analyses (Table 5) [52].

Cancer incidence: lymphocyte-depleting antibodies

Swinnen *et al.* first reported the strong association of monoclonal antibody induction (OKT3) with PTLD (lymphoma) in cardiac recipients [76]. Among 75 patients not receiving OKT3, there was one lymphoma (1.3%) while nine of 79 patients (11.4%) who received OKT3 developed a lymphoma ($P = 0.018$). Further, there was a dose phenomena with four lymphomas in 65 patients (6.2%) who received 75 mg or less of OKT3 and five lymphomas in 14 patients (35.7%) in patients who received more than 75 mg of OKT3 ($P < 0.01$). Of note, seven of the 10 patients who developed a lymphoma died from the malignancy [76]. Opelz and Henderson and the Collaborative Transplant Study on 45 141 kidney recipients, of whom 11 967 received either monoclonal or polyclonal antilymphocyte antibody induction, reported a significantly higher incidence of lymphoma in patients receiving induction (0.43%) when compared with recipients receiving no induction (0.15%) [77]. A more recent Collaborative Transplant Study report also showed increased lymphoma incidence with ATG/OKT3 induction as well as an increased lymphoma incidence associated with rejection treatment with either ATG or OKT3 [78]. That study also indicated that maintenance immunosuppression with TAC is associated with a significantly increased incidence of lymphoma ($P = 0.037$).

A multivariate analysis from ANZTR indicated that either polyclonal (ATG) or monoclonal (OKT3) antibody induction was associated with a significantly increased incidence of both non-Hodgkin's lymphoma and carcinoma of the cervix, vulva, and vagina [79].

A published analysis of OPTN/UNOS data indicated a PTLD incidence of 0.51% in 23 663 primary kidney recipients with no induction, 0.50% in 7800 patients with interleukin-2 receptor antibody, 0.81% in 4343 with polyclonal antilymphocyte antibody, and 0.85% in 2713 with monoclonal antibody ($P = 0.02$) [80]. This study failed to shows any increased risk of PTLD with rejection treatment with either monoclonal or polyclonal antibody but did shows a significant reduction in the adjusted risk of PTLD with mycophenolate mofetil (MMF) maintenance immunosuppression when compared with AZA maintenance ($P = 0.005$). The study did not confirm Opelz's observation of a higher lymphoma incidence with TAC maintenance immunosuppression on either univariate or multivariate analysis [80].

The North Italian Transplant Program multivariate analysis on 3521 kidney recipients indicated that polyclonal induction therapy was an independent risk factor (RR = 1.6; CI: 1.0–2.6) for the development of any malignancy [49]. In contrast, Kasiske *et al.* reported that any antibody induction and TAC maintenance immunosuppression were independently associated with significant reduced risk of developing nonmelanoma skin cancer [60].

A report comparing thymoglobulin induction ($N = 48$) with ATGAM induction ($N = 24$) through 5 years post-transplant indicated a significantly higher incidence of malignancy in the ATGAM group but included recurrent malignancy with the *de novo* tumors [81]. If only *de novo* tumors are compared (ATGAM = 4; thymoglobulin = 3) the difference was not statistically significant ($\chi^2 = 1.98$; $P > 0.20$). A comparison of ATG Fresenius ($N = 129$) with thymoglobulin (Sangstat; $N = 65$) reported the incidence of nonskin malignancy was 3.9% with ATG-F and 12.3% with thymoglobulin ($P = 0.01$) [82]. Multivariate analysis revealed a relative risk of 2.16 (CI: 1.04–4.48) with thymoglobulin for the development of malignancy. Furthermore, thymoglobulin was a significant risk factor for post-transplant death (RR = 4.14; CI: 1.36–12.6).

A comparison of patients requiring OKT3 + steroid treatment for rejection with patients with no rejection treatment and patients treated with steroids only, revealed a significantly increased incidence of nonskin *de novo* cancer associated with OKT3 (10.6%) compared with a 4.5% incidence in patients not receiving OKT3 ($P < 0.025$) [83].

Cancer incidence – cyclosporine versus tacrolimus

The European and the US Multicenter Trial reports comparing maintenance immunosuppression with TAC versus CYA in kidney transplantation indicated no significant difference in cancer incidence [84,85]. The 5-year follow-up report of the US Multicenter Trial comparing maintenance immunosuppression with CYA versus TAC in liver transplantation also revealed no statistically significant difference in cancer incidence [86].

An OPTN/UNOS study of 18 404 recipients of deceased donor liver grafts showed a significantly reduced risk of any cancer and of skin cancer with TAC alone and also showed a significantly reduced risk of any cancer and of nonskin solid cancer with TAC + MMF immunosuppression [87].

The OPTN/UNOS post-transplant *de novo* malignancy incidence, in a cohort 62 896 primary kidney transplants performed during 1/1/1998–12/31/2003 by maintenance immunosuppressive drugs, is shown in Table 6. The unadjusted incidence rates of any cancer, nonskin, nonlymphoid solid cancer, and nonmelanoma skin cancer were significantly less in recipients discharged on TAC regimens when compared with CYA regimens. The incidence of PTLD was 0.07% with both TAC and CYA regimens. While it may not be appropriate to compare PTLD incidence with non-Hodgkin lymphoma incidence, the OPTN/UNOS data does not corroborate the Opelz and Dohler report showing a higher incidence of non-Hodgkin's lymphoma with TAC [78].

Cancer incidence – azathioprine versus mycophenolate mofetil

The US Randomized and the Tricontinental Multicenter study comparing MMF with AZA in cadaveric renal recipients showed no difference in the incidence of any malignancy between the two drugs [88,89]. An independent report using data from the SRTR database (which is essentially the OPTN database) on 17 145 adult patients with pre-existing diabetes mellitus indicated a significantly higher ($P < 0.001$) incidence of malignancy in AZA-treated patients (3.7%) than in MMF-treated patients (2.2%) [90]. This report also indicated a significant difference in lymphoproliferative malignancies (0.6% vs. 0.3%, $P = 0.013$) and *de novo* solid tumors (2.5% vs. 1.6%; $P < 0.001$). Earlier, a different multivariate analysis of OPTN/UNOS data indicated that MMF were an independent variable associated with a significantly reduced risk of PTLD [80].

Table 6 shows a univariate comparison of OPTN/UNOS data of AZA with MMF for post-transplant malignancies. The incidence for any malignancy, solid tumors, skin cancer, and PTLD was significantly less with MMF than AZA.

Cancer incidence – corticosteroids

There are two reports of an association of nonmelanoma skin cancer with glucocorticoid therapy in nontransplant patients [91,92] and the second report also indicated an association of glucocorticoid therapy with an increased incidence of non-Hodgkin lymphoma [92].

TOR inhibitor era

Shortly after SRL was approved for maintenance immunosuppression by the FDA in 1999, published studies indicated that SRL prevented tumor progression in mice [93,94]. These studies indicated that SRL had both a direct effect on malignant cells and also exhibited an anti-angiogenesis effect by decreasing production of vascular endothelial growth factor (VEGF) while at the same time-protecting allografts from rejection [94].

Recently, there have been three reports of successful treatment of Kaposi's sarcoma by discontinuing calcineurin immunosuppression and replacing it with SRL [95–97]. It is unresolved whether the Kaposi's lesions

Table 6. Incidence of post-transplant *de novo* malignancy by immunosuppressive drug kidney transplants from OPTN/UNOS database during 1998–2003.

	Cyclosporine ($N = 26\,250$)		Tacrolimus ($N = 30\,942$)			Azathioprine ($N = 3399$)		MMF ($N = 7366$)		
	N	%	*N*	%	*P*-value	*N*	%	*N*	%	*P*-value
Any cancer	1275	4.9	1046	3.4	<0.001	211	6.2	1904	4.0	<0.001
Solid	537	2.0	432	1.4	<0.001	85	2.5	801	1.7	<0.001
Skin	576	2.2	382	1.2	<0.001	93	2.7	804	1.7	<0.001
PTLD	174	0.7	224	0.7	NS	37	1.1	302	0.6	<0.01

OPTN/UNOS, Organ Procurement and Transplantation Network/United Network for Organ Sharing; PTLD, post-transplant lymphoproliferative disorder; MMF, mycophenolate mofetil.

regressed because of stopping the calcineurin inhibitor, or because of adding SRL, or both. This conundrum exists because of a separate report in which eight of 24 patients with Kaposi's sarcoma had a complete tumor response to reduction/cessation of immunosuppressive drug therapy [98]. A more convincing report involved a hepatic recipient who experienced complete regression of three pulmonary metastases of hepatocellular carcinoma after conversion of maintenance drugs from CYA and AZA to SRL and MMF [99]. The patient was tumor free at 18 months.

The 2-year incidence of malignancies from five multicenter studies on the immunosuppressive efficacy of SRL in renal recipients, was recently reported [100]. The two studies that compared CYA-based with SRL-based maintenance immunosuppression revealed four malignancies (5%) in the CYA group and none in the SRL group. The second two studies used CYA maintenance and compared two separate dosages of SRL with either AZA or placebo. There were no differences in the incidences of any malignancy among the four arms of the study [100]. Patients in the fifth study received both CYA and SRL for the first 3 months. At 3 months, patients were randomized to remain on CYA and SRL or to have the CYA withdrawn. The incidence of any malignancy at 24 months in the CYA withdrawal group was 4.2% when compared with 9.8% in the CYA + SRL group ($P = 0.036$).

A retrospective study of the OPTN/UNOS database on 33 249 deceased donor kidney transplants revealed that 504 patients received either SRL or everolimus (EVL) without a calcineurin inhibitor, 2321 received either SRL or EVL in combination with a calcineurin inhibitor, and 30 424 received a calcineurin inhibitor without a TOR inhibitor [61]. Data were censored at 963 days to allow comparable follow up among the treatment groups. The incidence of any malignancy was 0.60% for both SRL/EVL alone and for SRL/EVL plus a calcineurin inhibitor and was 1.81% for calcineurin inhibitors ($P < 0.0001$). The incidence rates for *de novo* solid malignancies were 0% for SRL/EVL, 0.47% for SRL/EVL + calcineurin inhibitors, and 1.0% for calcineurin inhibitors. Multivariate analysis indicated that TOR inhibitor maintenance immunosuppression was associated with a 60% reduced risk of any post-transplant malignancy and a 55% reduced risk of solid malignancy [61].

Post-transplant *de novo* cancer mortality

The overall mortality associated with post-transplant *de novo* malignancies is high and progressively increases with time. ANZTR data on 6596 cadaveric donor kidney recipients of whom 420 developed post-transplant cancer other than skin, revealed a 26% mortality from cancer at 10 years [101]. Data from the North Italian Transplant Program indicates that the 10-year survival in kidney recipients with no cancer is 92.8%, with any cancer is 56.6%, with skin cancer or Kaposi's sarcoma is 82.2%, with nonskin solid cancer is 54.4%, and with PTLD is 46.4% [49]. Data from Canada on 760 renal recipients followed for a mean of 13.4 years revealed an overall mortality of 54% with the majority of deaths resulting from the malignancy [75]. In 35 patients who developed skin cancer there was a 26% mortality rate from malignancies and an additional 14% from other causes. In the 58 patients who developed a nonskin malignancy, there was a 50% mortality rate from cancer and an additional 12% died from other/unknown causes [75].

Table 7. Causes of death for kidney transplants performed during 1970–1999 by transplant era (adapted from Howard *et al*. [102]).

Cause of death	Transplant era		
	1970–1979	1980–1989	1990–1999
Infection	42.0	42.0	28
Cardiac	9.6	23.8	30.2
Neurologic	2.4	5.2	8.5
Cancer	1.2	5.2	13.2

Surgeons from the University of Florida reported on causes of deaths by different transplant eras (Table 7) [102]. Cancer increased as a cause of death from 1.2% for patients transplanted during 1970–1979, to 5.2% during 1980–1989, and to 13.3% during 1990–1999. This statistically significant increase in cancer deaths was due to a combination of older patients, better survival, and newer immunosuppressive drugs.

The OPTN/UNOS data on deaths occurring between 5 and 10 years post-transplantation indicate that malignancy was the cause in 14.5% of kidney recipients, 18.7% of liver recipients, and 21.5% of heart recipients. Data on heart recipients from Italy was similar with malignancies reported as the cause of death in 23.5% of patients surviving over 2 years [103].

In liver recipients, it has been shown that the type of post-transplant cancer profoundly affects mortality rates [104]. At a median time of 36 months, the mortality rate was 15% for nonmelanoma skin cancer; 40% for genitourinary cancers, 60% for gastrointestinal malignancies, 62.5% for respiratory tumors, and 71.4% for oropharyngeal cancers.

Patient management recommendations

Positive nondrug risk factors for the development of post-transplant malignancies have been detailed in Table 4. For recipients with these risk factors, maintenance

immunosuppression with drugs that have been shown to be associated with a reduced incidence of malignancy (TAC, MMF – Table 6) should be considered. Additionally TOR inhibitors, alone or in combination with calcineurin inhibitors, should be considered for maintenance immunosuppression as the TOR inhibitors have been shown to be associated with a reduced incidence of post-transplant malignancy in renal recipients [61,105]. These short term reports showing a reduced incidence of malignancies associated with TAC, mycophenolate, and TOR inhibitor maintenance immunosuppression need to be confirmed by additional long-term studies.

When post-transplant patients develop a malignancy, standard cancer treatment options including surgery, radiotherapy, and chemotherapy must be individualized to the patient and should be coordinated by the oncologist and transplant surgeon/physician. A thorough consideration of the patient's tumor risk, treatment risk, and risk of graft loss must be made. For renal recipients immunosuppression may be reduced/stopped even to the point of graft loss and return to hemodialysis. For liver recipients, re-transplantation is an option. Our personal bias is to reduce immunosuppression to the point of precipitating graft (and hopefully malignancy) rejection before re-transplantation is performed.

Switching immunosuppression to a TOR inhibitor should be seriously considered for patients with malignancies who have received life-saving grafts (heart, lung, liver). Dosage regimens for SRL in renal recipients have been well described before patients develop a post-transplant malignancy and these dosages may be used while other immunosuppressive drugs are reduced or stopped [105].

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Conflicts of interest

This authors have no conflicts of interest.

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