Cancer and mTORi in KT: Case Sharing

NEPHROLOGY
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Disclosure Information

- **Asst. Prof. Naowanit Nata, MD**

- **Scientific Advisor/Honoraria:**
  - Novartis

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Outlines: Cancer and mTORi in KT

1. Epidemiology of post-KT cancer?
2. Risk factors and pathogenesis of post-KT cancer?
3. Post-KT cancer and outcomes?
4. How to detection and management post-KT cancer?
5. mTORi in post-KT malignancy?

❖Case sharing

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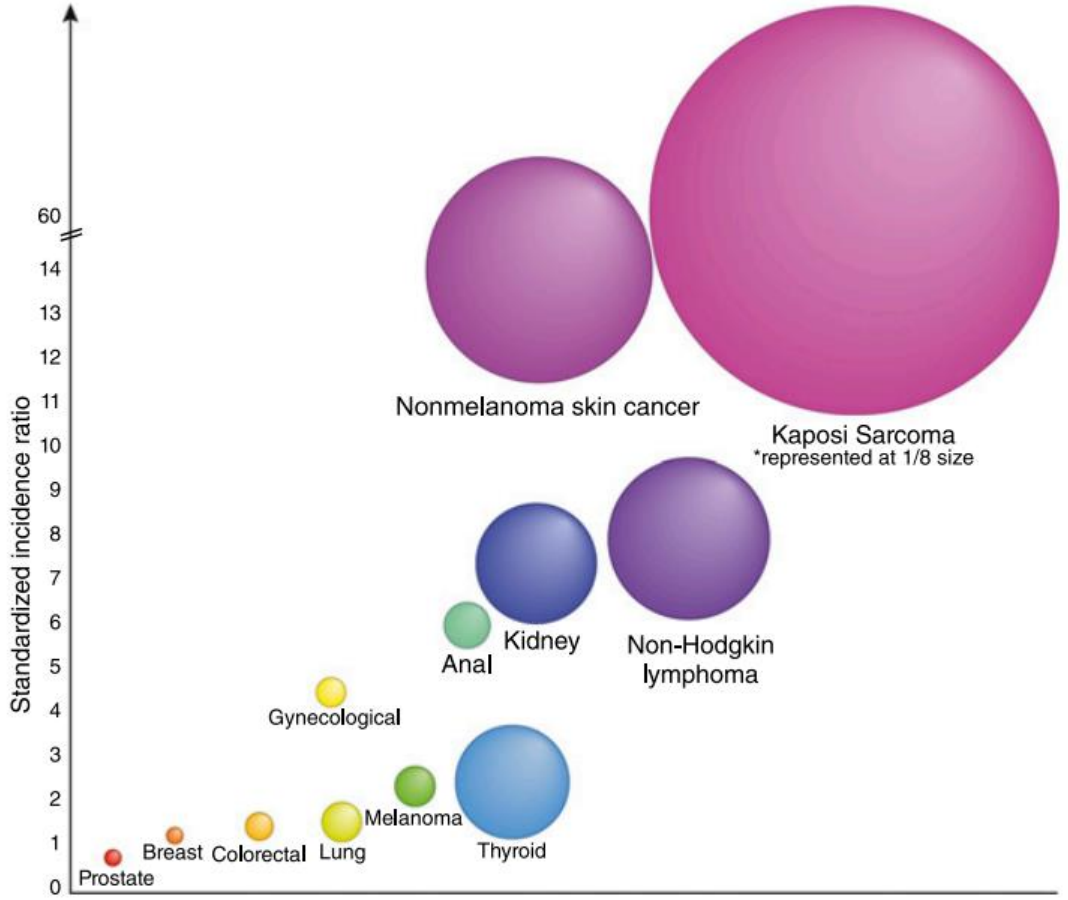
❖**Case sharing**

Incidence of Cancer after kidney transplants

- Cumulative incidence of solid organ CA ~ 10% and 15% at around 15 years after KT
- Caucasian: Skin CA incidence > 60%
- Higher risk magnitude depends on CA type
- Risk increases in viral/immune driven cancers



The standardized incidence ratios of different cancer types in recipients of kidney transplants

Al-Adra D, et al. Clin J Am Soc Nephrol. 2022 Mar;17(3):434-443.

Incidence of de novo post-transplant malignancy among Thai adult kidney transplant recipients: a single-centered, population-controlled, retrospective cohort study at the highest-volume kidney transplant center in Thailand

Method & Cohorts

2,024 adult kidney transplant recipients

Single center retrospective cohort study in Thailand

From 1986 to 2019
16,495 person-years at risk

Incidence of de novo malignancy compare with national cancer registry

3.85 times higher risk of all malignancy compared with general population, adjusting for age and sex

Standardize incidence ratio (SIR) of most common cancer

- **SIR 36** (95% CI (23.9-52)) — Urothelial malignancy ✓
- **SIR 20.3** (95% CI (13.6-29.1)) — Non-Hodgkin's lymphoma ✓
- **SIR 24.7** (95% CI (15.3-37.8)) — Non melanoma Skin cancer ✓

Conclusion

There are excessive risk for PTMs in KTRs compared to the Thai general population, especially for urothelial cancer. Future studies are needed to identify the risk factors and need for systematic screening among PTMs with excessive risk in KTRs.

SrisuwarnP, et al. *Transpl. Int.* 2024
doi: 10.3389/ti.2024.11614

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GRAPHICAL ABSTRACT |

Srisuwarn P, et al. Transpl Int. 2024 Feb 26;37:11614.

Distribution and clinical characteristics of malignancies following KT by sex

Solid

Hematologic

Skin

	Male patients	Female patients	All	Percentage	Age at transplantation, mean ± SD, y	Age at diagnosis of PTM, mean ± SD, y	Time from transplant to PTM, median (IQR), y
Solid							
Urothelial	11	17	28	35.0	49.7 ± 9.93	58.7 ± 12.7	6.63 (4.55, 10.4)
Prostate	9		9	11.3	56.3 ± 7.22	68.8 ± 7.32	11.8 (8.70, 13.0)
Liver and bile duct	5	4	9	11.3	46.0 ± 11.2	53.5 ± 14.1	4.96 (3.15, 9.34)
Breast		8	8	10.0	47.3 ± 7.31	53.0 ± 7.92	5.72 (2.64, 9.03)
Colorectal	2	4	6	7.5	47.8 ± 9.91	62.8 ± 7.80	13.0 (12.2, 14.4)
Trachea, lung, bronchus	5	1	6	7.5	57.0 ± 6.04	61.4 ± 6.73	4.67 (3.24, 6.23)
Other solid malignancies, unspecified	1	1	2	2.5	54.8 ± 5.59	58.7 ± 6.54	3.79 (3.12, 4.46)
Cervix		3	3	3.8	57.1 ± 2.77	61.5 ± 5.53	3.49 (1.89, 7.85)
Gallbladder	1	0	1	1.3	38.6	40.5	1.96
Kidney	3	0	3	3.8	55.0 ± 6.77	62.9 ± 4.29	9.36 (4.43, 9.94)
Thyroid	0	2	2	2.5	49.6 ± 23.8	53.1 ± 21.3	3.43 (1.64, 5.22)
Stomach	1	0	1	1.3	63.7	77.0	13.3
Ovary		1	1	1.3	60.9	63.3	2.43
Uterus, part unspecified		1	1	1.3	35.6	47.4	11.8
Total	38	42	80	100			
Hematologic							
NHL							
Monomorphic B cell	15	8	23	71.9	47.1 ± 10.2	57.2 ± 11.1	11.4 (4.11, 15.4)
Polymorphic	1	3	4	12.5	49.0 ± 12.7	54.6 ± 11.0	4.16 (4.11, 4.57)
Monomorphic T cell	2	0	2	6.3	37.3 ± 13.7	44.5 ± 19.6	4.84 (1.61, 12.7)
Leukemia, all types	1	1	2	6.3	54.1 ± 6.52	58.4 ± 6.23	4.36 (4.16, 4.57)
HL	1	0	1	3.1	52.3	60.1	7.78
Total	20	12	32	100			
Skin							
SCC	12	4	16	76.2	50.5 ± 7.31	63.0 ± 7.02	10.7 (7.10, 18.8)
BCC	4	1	5	23.8	52.4 ± 14.4	62.4 ± 8.73	7.62 (3.15, 15.3)
Total non-melanoma	16	5	21	100			

Abbreviations: BCC, basal cell carcinoma; HL, Hodgkin's lymphoma; IQR, interquartile range; NHL, non-Hodgkin's lymphoma; PTM, post-transplant malignancy; SCC, squamous cell carcinoma; SD, standard deviation.

Srisuwarn P, et al. Transpl Int. 2024 Feb 26;37:11614.

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Report on post-transplantation cancer in southeast Asia from the Thai kidney transplantation cohort

Suthanit Laowalert[1], Nattakan Naitook[1], Kesawan Boonnim[1], Uayporn Prungrit[1], Nidjaree Aekkachaipitak[1], Pornpawee Lamjantuek[1], Wisit Liwlompaisan[1], Rungrote Khunprakant[1], North Techawathanawanna[1], Viroon Mavichak[1] & Suwasin Udomkarnjananun[2]✉

1156 KTR with a post-transplant follow-up duration of 5.1 (2.7–9.4) years

Laowalert S, et al. Sci Rep. 2024 Aug 30;14(1):20154.

Post-kidney transplant cancer in the cohort

Cancer type	Primary cancer, n (%)	Second primary cancer, n (%)
Total	91 (100%)	8 (100%)
Urothelial cancer*	29 (31.9%)	2 (25.0%)
Hepatocellular cancer	13 (14.3%)	–
Skin cancer	9 (9.9%)	1 (12.5%)
Kidney cancer**	8 (8.8%)	1 (12.5%)
Colorectal cancer	6 (6.6%)	–
Prostate cancer	5 (5.5%)	1 (12.5%)
Other gastrointestinal tract cancers	5 (5.5%)	–
Post-transplant lymphoproliferative disease	4 (4.4%)	1 (12.5%)
Breast cancer	4 (4.4%)	–
Lung cancer	3 (3.3%)	1 (12.5%)
Thyroid cancer	3 (3.3%)	–
Parotid gland cancer	1 (1.1%)	1 (12.5%)
Uterine cancer	1 (1.1%)	–

1.
2.
3.
4.
5.

*All urothelial cancers occurred in the native urinary tract. **One case of kidney cancer was localized in the kidney allograft only, while another case of kidney allograft cancer occurred as a second primary cancer following native kidney cancer.

Laowalert S, et al. Sci Rep. 2024 Aug 30;14(1):20154.

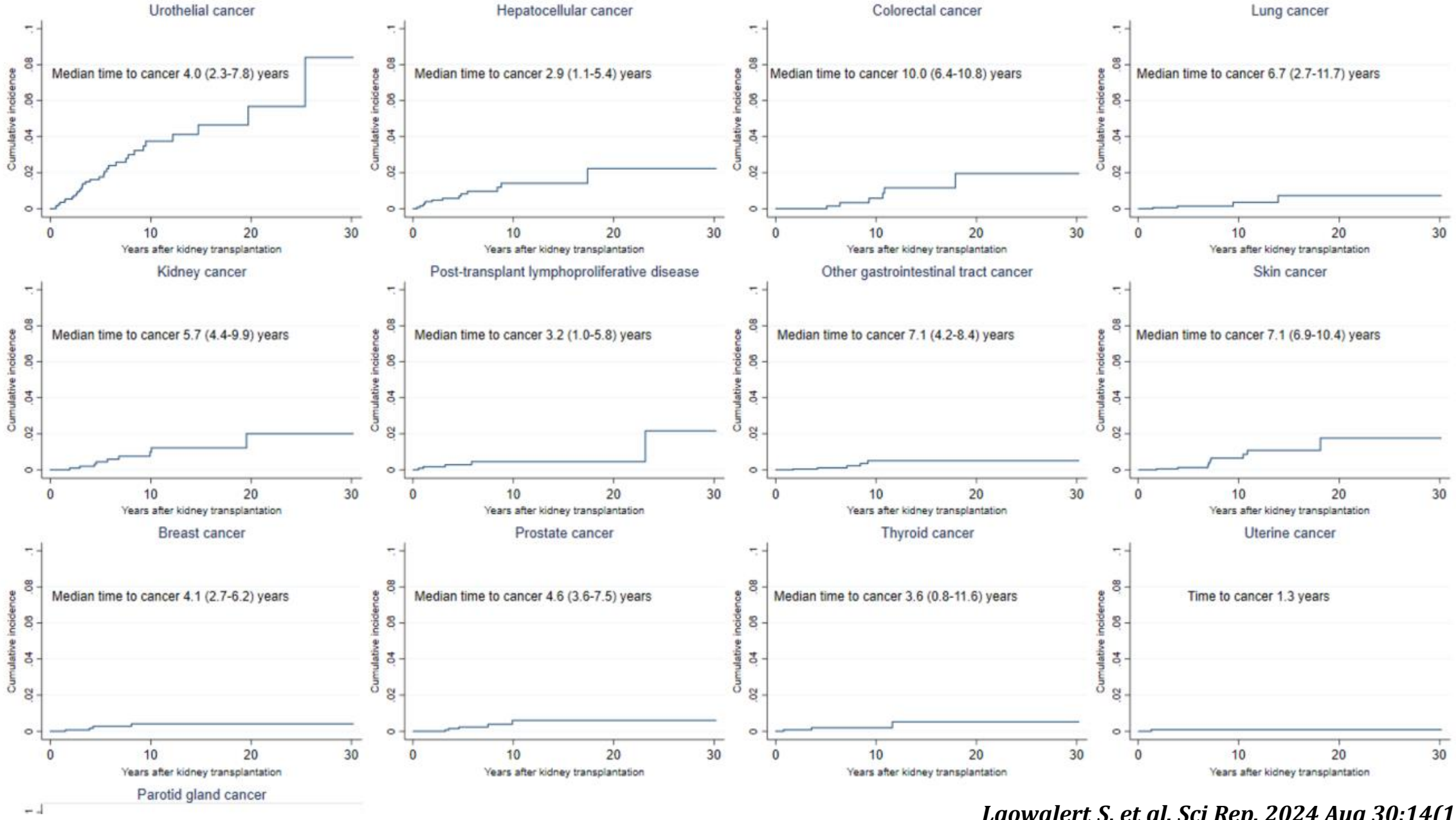
Incidence rate, age- and sex-adjusted incidence rate (per 1000 person-year), and SIR of post-kidney transplant cancer

Type of cancer	Incidence rate (per 1000 person-year) with 95% CI	95% CI	Adjusted-incidence rate (per 1000 person-year)	95% CI	SIR	95% CI	p-value
Total	12.1	9.9–14.8	18.9	16.5–21.4	2.7	2.4–3.1	<0.001
Urothelial cancer	3.8	2.7–5.4	6.9	5.4–8.4	42.5	32.9–54.9	<0.001
Hepatocellular cancer	1.6	0.9–2.7	2.4	1.5–3.3	2.1	1.4–3.0	<0.001
Skin cancer	1.1	0.6–2.1	1.8	1.1–2.6	7.7	5.0–11.9	<0.001
Kidney cancer	1.1	0.6–2.1	1.4	0.7–2.0	24.4	14.3–41.5	<0.001
Colorectal cancer	0.7	0.3–1.6	0.8	0.2–1.3	1.0	0.5–1.8	0.876
Other gastrointestinal tract cancers	0.6	0.2–1.4	2.2	1.4–3.0	6.7	4.5–9.9	<0.001
Prostate cancer	0.6	0.2–1.4	0.9	0.3–1.4	3.3	1.8–6.1	<0.001
Post-transplant lymphoproliferative disease	0.6	0.2–1.4	0.3	0.01–0.6	1.2	0.5–3.3	0.659
Lung cancer	0.5	0.2–1.3	0.6	0.2–1.0	0.6	0.3–1.3	0.218
Breast cancer	0.5	0.2–1.3	0.3	0.01–0.7	0.5	0.2–1.3	0.176
Thyroid cancer	0.4	0.1–1.1	0.6	0.1–1.0	3.8	1.7–8.1	0.001
Parotid gland cancer	0.2	0.1–1.0	0.1	0.01–0.3	3.2	0.5–21.9	0.244
Uterine cancer	0.1	0.01–0.9	0.2	0.01–0.5	7.7	0.9–59.7	0.051

SIR standardized incidence ratio

Laowalert S, et al. Sci Rep. 2024 Aug 30;14(1):20154.

Cumulative incidences of post-KT cancers and the median time from KT to cancer diagnosis



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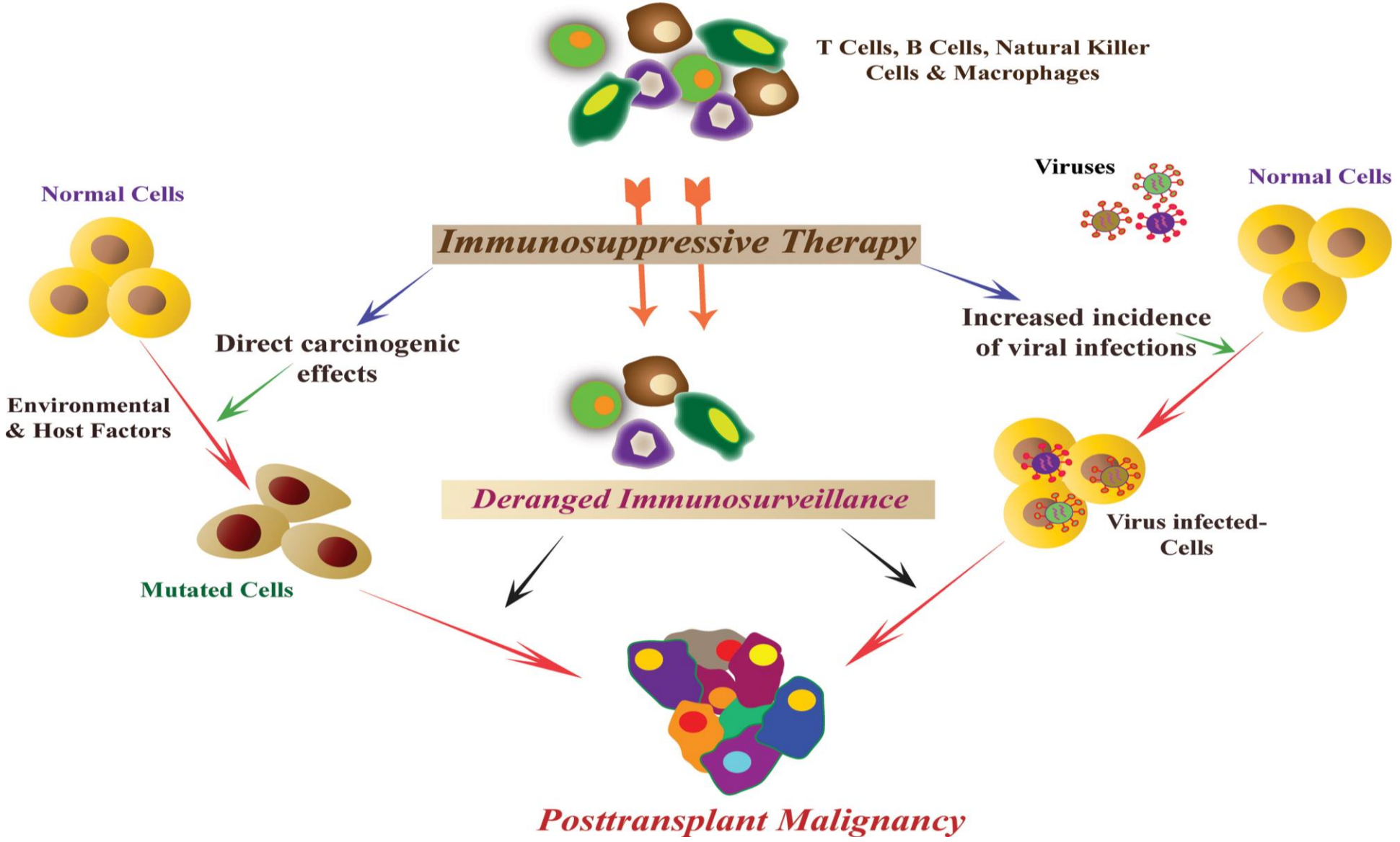
5. mTORi in post-KT malignancy?

❖Case sharing

Etiology and pathogenesis of malignancies after solid organ transplantation



Katabathina VS, et al. Radiographics. 2016 Sep-Oct;36(5):1390-407.

Classification of Cancers Post-Kidney transplant

Table 2. Classification of Cancers Post-KTx

Common Solid Organ Cancers in the General Population	Viral-Mediated Cancers	CKD/ESKD-Related Cancers	NMSC
Breast	Kaposi sarcoma (HHV-8)	Bladder	SCC
Prostate	Post-transplant lymphoproliferative disorder (EBV)	Kidney	BCC
Lung	Oral, genital, cervical, anal (HPV)	Thyroid	
Colorectal	Hepatocellular carcinoma (HBV, HCV)		
Melanoma			

NOTE. Melanoma is dependent on the geographic location (e.g., Australia, New Zealand). Thyroid is related to CKD/ESKD because the diagnosis may be related to incidental findings when evaluating parathyroid glands for CKD-related hyperparathyroidism.
Abbreviations: BCC, basal cell carcinoma; CKD, chronic kidney disease; EBV, Epstein-Barr virus; ESKD, end-stage kidney disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV-8, human herpesvirus 8; HPV, human papillomavirus; KTx, kidney transplantation; NMSC, nonmelanoma skin cancer; SCC, squamous cell carcinoma.

Massicotte-Azarniouch D, et al. Semin Nephrol. 2024 Jan;44(1):151494.

Risk Factors for Post-Kidney transplant Cancer

Risk Factor	Type of Cancer	Effect	Reference Group
Sex, male[7]	SCC	aOR 1.56	Female
	BCC	aOR 1.58	
	Melanoma	aOR 1.75	
Ethnicity, Caucasian[7]	SCC	aOR 9.95	African-American ethnicity
	BCC	aOR 38.78	
	Melanoma	aOR 2.04	
Multiple sexual partners[14]	High carcinogenic risk HPV infection	≥10 lifetime partners: aOR 13.78	1-2 lifetime partners
Pre-transplant dialysis duration, >4.5 years'[8]	Lung	aHR 3.32	<1.5 years' duration
	Urinary tract	aHR 2.57	
Pre-transplant cancer diagnosis[9]	Overall	Recurrence 1.6 per 100 p-y	
	Lung	Recurrence 5.4 per 100 p-y	
	Gastrointestinal	Recurrence 4.7 per 100 p-y	
	Cervical	Recurrence 3.9 per 100 p-y	
	Multiple myeloma[11]	75% recurrence	
	AL amyloidosis[12]	29% recurrence	
EBV mismatch donation, D+/R-[15]	PTLD	DD KTx: aHR 6.33 LD KTx: aHR 5.14	EBV R+ serostatus
Expanded criteria kidney donor[16]	Overall cancer	aHR 1.52	Living donor
	Urinary tract cancer	aHR 1.79	
	PTLD	aHR 2.72	
Pre-transplant immunosuppression for glomerular disease[17]	Overall solid or hematologic cancer	aHR 1.82	No pre-transplant immunosuppression
Lymphocyte-depleting induction[18]	PTLD	Monoclonal Ab: RR 1.72 Polyclonal Ab: RR 1.29 (p=0.27)	No induction therapy
Treatment of acute rejection with T-cell-depleting antibody[19]	Urinary tract cancer	aHR 2.20	No rejection

Abbreviations: Ab, antibody; aHR, adjusted hazard ratio; AL, amyloid light chain; aOR, adjusted odds ratio; BCC, basal cell carcinoma; D+, donor-positive serology; DD, deceased donor; EBV, Epstein-Barr virus; KTx, kidney transplantation; LD, living donor; PTLD, post-transplant lymphoproliferative disorder; P-Y, person-years; R-, recipient-negative serology; RR, relative risk; SCC, squamous cell carcinoma.

Massicotte-Azarniouch D, et al. Semin Nephrol. 2024 Jan;44(1):151494.

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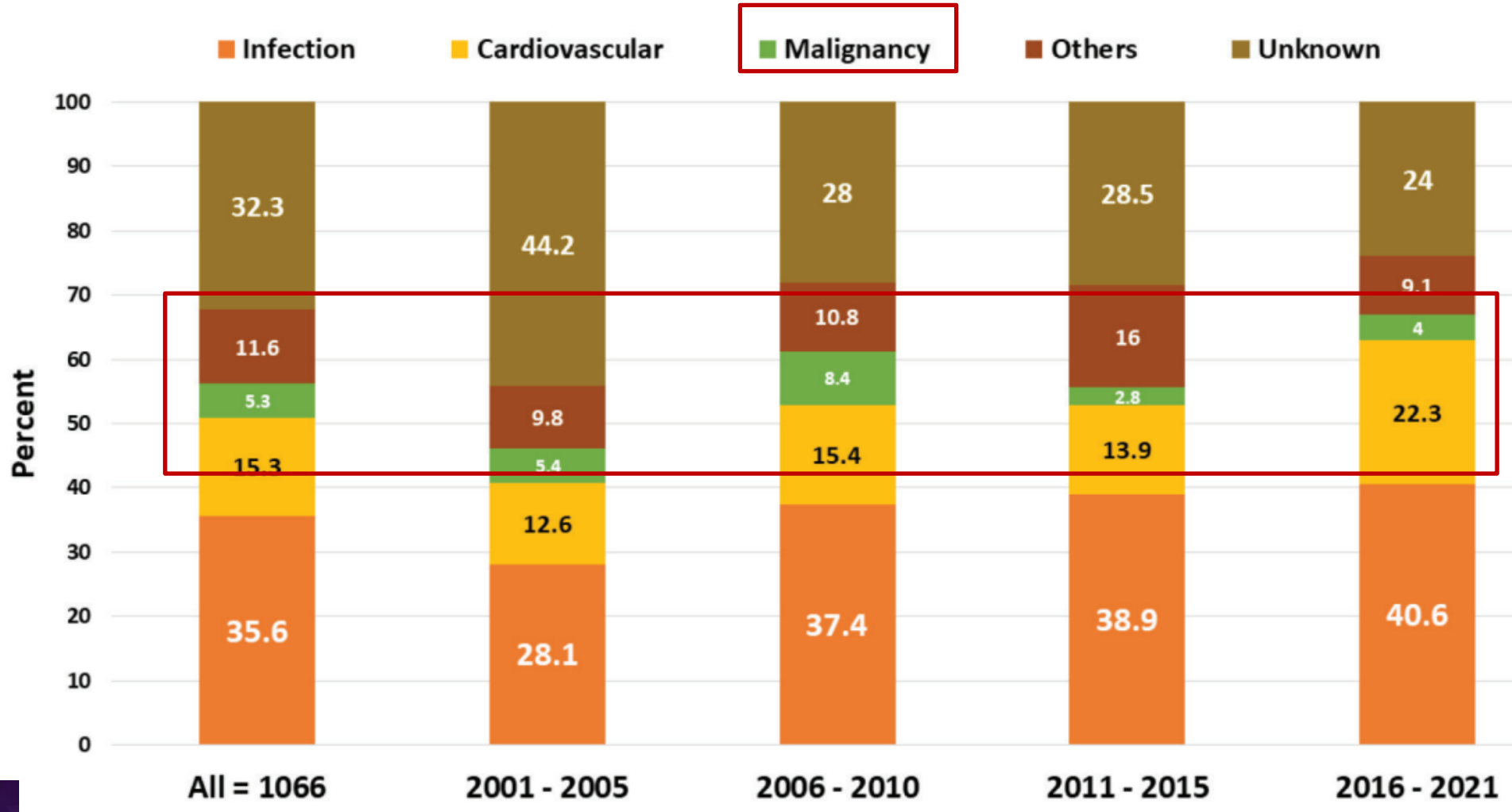
สาเหตุของการเสียชีวิตของผู้รับไตตามช่วงปีที่ได้รับการปลูกถ่ายไต



2.8 - 8.4%

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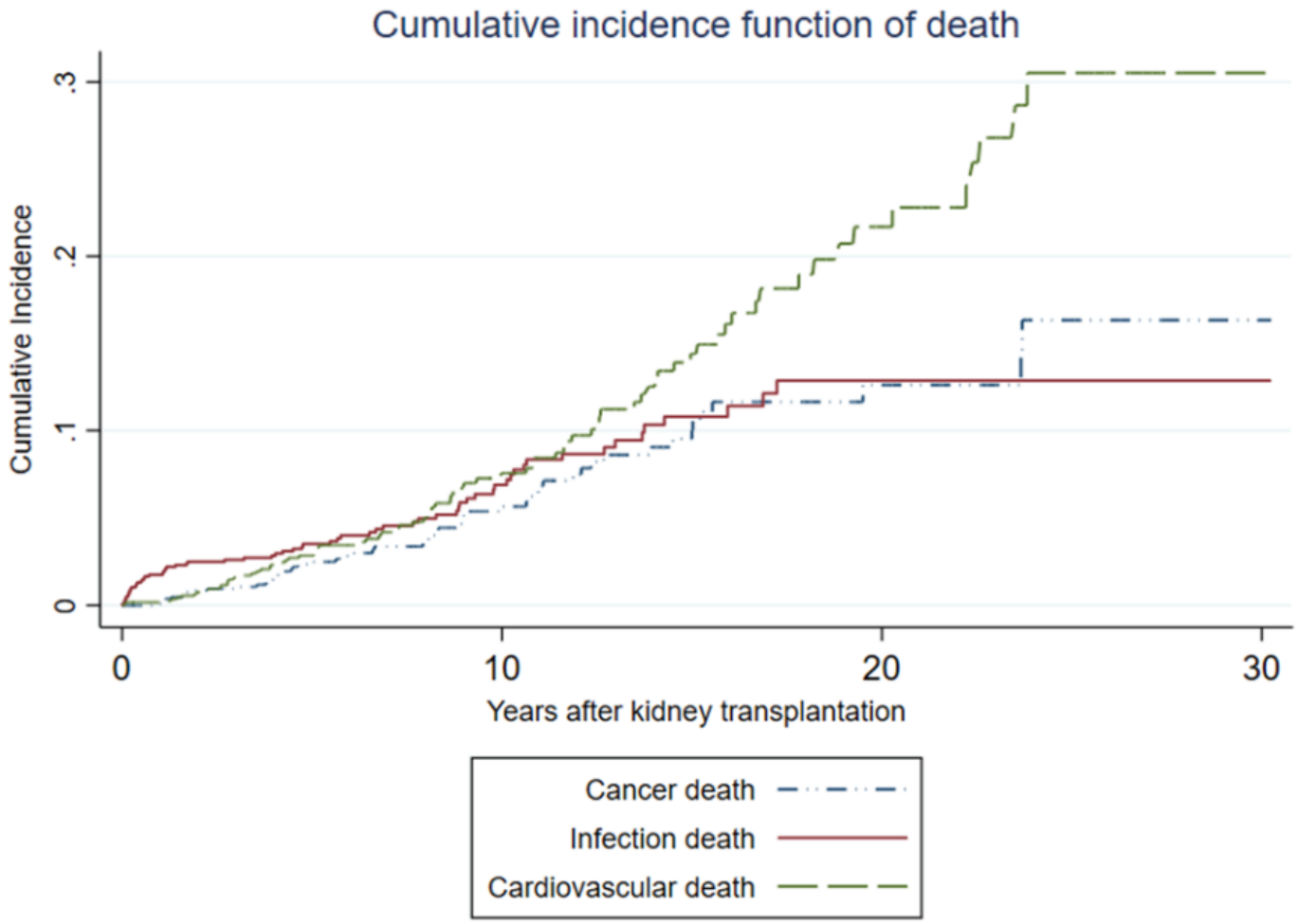
ข้อมูลการปลูกถ่ายอวัยวะ
ประจำปี พ.ศ. 2565

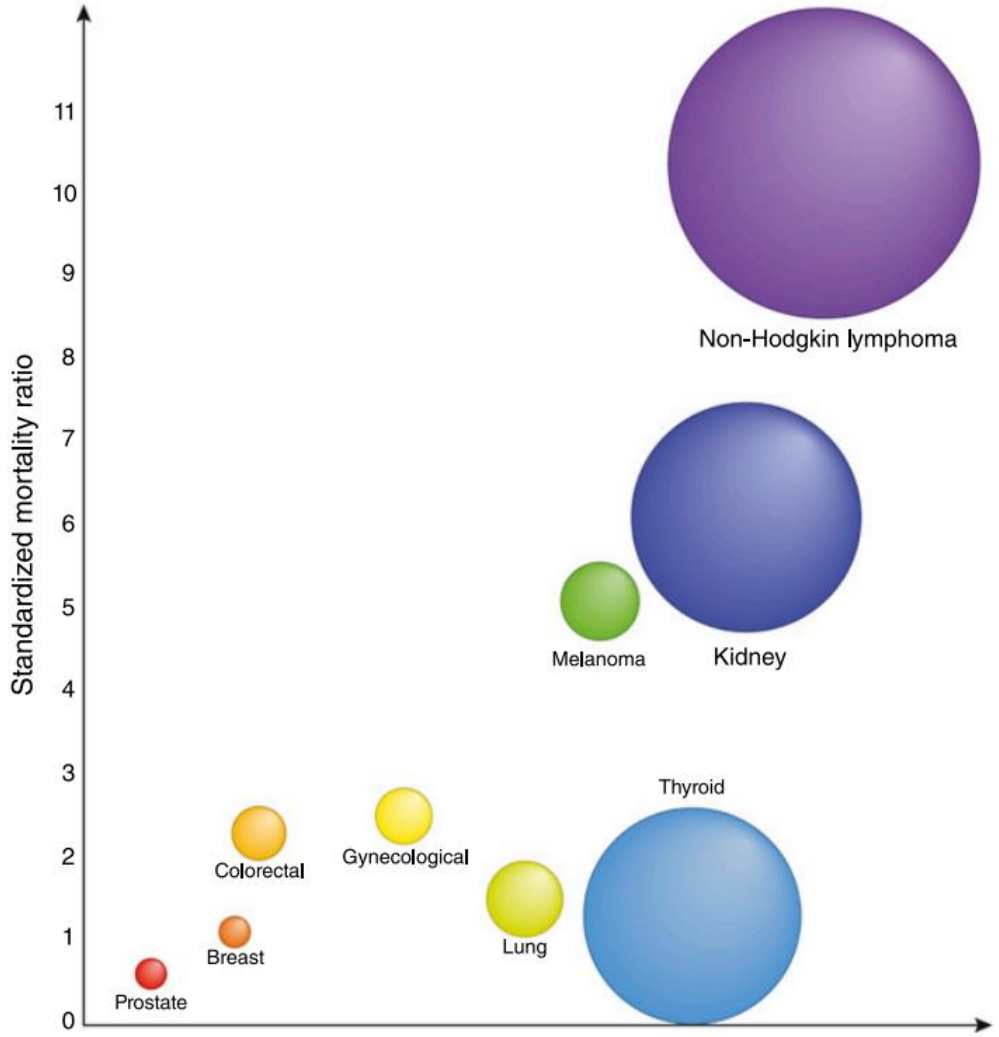
รายงานข้อมูลการปลูกถ่ายอวัยวะประจำปี พ.ศ. 2565

Cumulative incidence function of cancer death compared with infection and cardiovascular death



Laowalert S, et al. Sci Rep. 2024 Aug 30;14(1):20154.

The standardized mortality ratios of different cancer types in recipients of kidney transplants



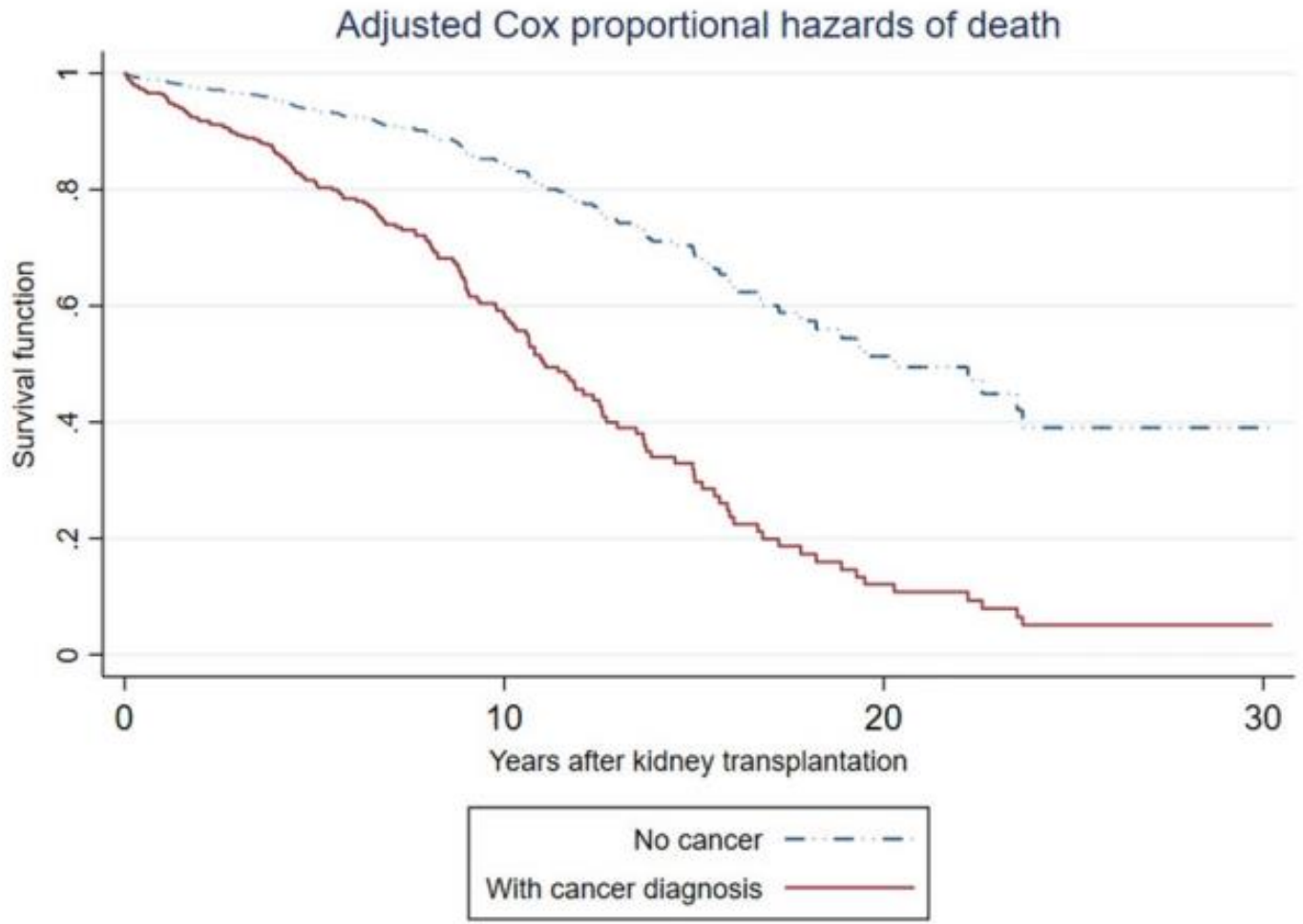
Al-Adra D, et al. Clin J Am Soc Nephrol. 2022 Mar;17(3):434-443.

Mortality rate of post-kidney transplant cancer (per 100 person-year) among recipients diagnosed with cancer

Type of cancer	Mortality rate among recipients with cancer (per 1000 person-year)	95% CI	Mortality risk ratio compared to recipients without cance	95% CI	p-value
Total	61.4	47.1–79.9	3.3	2.4–4.5	<0.001
Hepatocellular cancer	145.1	82.4–255.5	6.9	3.5–12.4	<0.001
Lung cancer	97.8	31.6–303.4	4.7	1.0–13.9	0.032
Other gastrointestinal tract cancers	83.7	31.4–223.1	5.8	1.5–15.0	0.007
Post-transplant lymphoproliferative disease	75.6	28.4–201.4	5.2	1.4–13.5	0.001
Skin cancer	68.6	28.5–164.7	3.3	1.0–7.8	0.026
Colorectal cancer	62.1	25.8–149.2	4.4	1.4–10.4	0.008
Breast cancer	59.4	14.8–237.4	2.8	0.3–10.4	0.195
Parotid gland cancer	59.3	8.4–421.0	5.5	0.1–30.9	0.183
Urothelial cancer	57.0	34.9–93.0	2.8	1.6–4.7	<0.001
Thyroid cancer	35.7	5.0–253.4	1.7	0.04–9.6	0.564
Prostate cancer	26.5	3.7–187.8	1.3	0.03–7.1	0.737
Kidney cancer	9.4	1.3–66.9	0.6	0.01–3.2	0.638
Uterine cancer	0	–	0	0–7.0	0.585
Patient without cancer	21.0	17.9–24.5	–	–	–

Laowalert S, et al. Sci Rep. 2024 Aug 30;14(1):20154.

Survivor function of kidney transplant recipients with and without post-transplantation cancer



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Recommendations identified in clinical practice guidelines by cancer site and transplant organ

	Kidney												
Screening	KDIGO (2009)	CST & CSN (2010)	NKF (2009)	KHA-CARI (2012)	AST-Kidney (2000)	EBPG (2002)	RA (2011)						
Skin/lip cancer													
Self-exam	R	R	–	R	Monthly	–	–						
Physician exam	–	–	Annually	–	Annually	–	R						
Specialist exam	Annually	Annually	–	Annually	–	–	–						
Anal/anogenital cancer													
Physician exam	–	–	–	–	Annually	–	–						
Testicular cancer													
Self-exam	–	–	–	–	–	–	R						
Cervical cancer													
Pelvic exam	G (every 3 years)	–	–	Annually	Annually	Annually	G (every 3 years)						
Pap cytology	G (every 3 years)	Annually	–	–	Annually	Annually	G (every 3 years)						
Breast cancer													
Mammography	G (annually)[2]	G (every 2 years)[1]	–	–	Every 1–2 years	R	G (every 3 years)						
Self-exam	–	–	–	–	–	–	R						
Prostate cancer													
PSA	–	–	–	–	Annually[1]	Annually[1]	–						
DRE	–	–	–	–	Annually[1]	Annually[1]	–						
Not recommended	G	G	–	–	–	–	G	–	–	–	G	–	
Lung cancer													
Not recommended	–	–	–	–	R	–	–	–	–	–		–	
Kidney cancer													
Ultrasound	–	–	–	–	–	R	–	–	–	–	–	–	
Not recommended	–	–	–	–	–	–	R	–	–	–	–	–	
Bladder/urothelial cancer													
Not recommended	–	–	–	–	R	–	–	–	–	–	–	–	

KDIGO:

- Skin – Specialist annually
- Cervical – Every 3 years
- Breast- Mamogram annually
- Prostate - General
- HCC – AFP/US annually
- CRC – Colonoscope every 10 years

Others Recommendation:

- Lung – AT-Kidney
- Kidney – EBPG
- Urothelial – AST-Kidney
- Lymphoma - AST-Kidney

Acuna SA, et al. HuA Systematic Review of Clinical Practice Guidelines. Am J Transplant. 2017 Jan;17(1):103-114.

Recommendations identified in clinical practice guidelines by cancer site and transplant organ

	Kidney							Liver				
Screening	KDIGO (2009)	CST & CSN (2010)	NKF (2009)	KHA-CARI (2012)	AST-Kidney (2000)	EBPG (2002)	RA (2011)	AST-Liver (2009)	AASLD-Adult (2013)	AASLD-Pediatric (2013)	Heart/lung ISHLT (2010)	All solid organs SCPG (2009)
Liver/HCC												
AFP level	Annually[3]	Annually[3]	–	–	Every 6–12 months[5]	–	Annually[3]	–	–	–	–	–
Ultrasound	Annually[3]	Annually[3]	–	–	Every 6–12 months[4]	–	Annually[3]	–	–	–	–	–
Abdominal imaging	–	–	–	–	–	–	–	–	–	–	–	–
Colorectal cancer												
FOBT	G (annually)	G (annually)	–	–	G (annually)[1]	R	G	–	–	NS	G	–
Sigmoidoscopy	or G (every 5 years) or	or G (every 5 years) or	–	–	G (every 5 years)[1]	–	G	–	–		G	–
Colonoscopy	G (every 10 years)	G (every 10 years)	–	–	–	–	G	–	Annually[4]		G	–
Lymphomas												
Physician exam	–	–	–	–	Every 3 months in first year, then annually	–	–	–	–	–	–	–

[1]Only for patients older than 50 years.
[2]Only for patients older than 40 years.
[3]Only for patients with cirrhosis.
[4]Only for patients at high risk.
[5]Only for patients with liver disease.
R = Screening recommended, but no frequency.
G = Same as the guidelines for the general population.

AASLD, American Association for the Study of Liver Disease; AFP, alpha-fetoprotein; AST, American Society of Transplantation; CRC, colorectal cancer; CST & CSN, Canadian Society of Transplantation and Canadian Society of Nephrology; DRE, digital rectal exam; EBPG, European Best Practice Guidelines; FOBT, fecal occult blood test; HCC, hepatocellular carcinoma; ISHLT, International Society of Heart and Lung Transplantation; KDIGO, Kidney Disease: Improving Global Outcomes; KHA-CARI, Kidney Health Australia—Caring for Australasians with Renal Impairment; NKF, National Kidney Foundation; NS, nonspecific modality; Pap, Papanicolaou; PSA, prostate-specific antigen; RA, Renal Association Clinical Practice Guidelines; SCPG, Swiss Clinical Practice Guidelines.

Acuna SA, et al. HuA Systematic Review of Clinical Practice Guidelines. Am J Transplant. 2017 Jan;17(1):103-114.

Recommendations for cancer screening in recipients of KT

Cancers	Recommendations	Evidence
Breast	For women aged 50–74 years, screening mammography once every 2 years. For women <50, the decision to start regular screening should be an individual one (77).	Extrapolation from general population
Prostate	For men aged 55–69 years, screening decisions should be individualized after a conversation with their clinician about the potential benefits and harms. For men ≥70 years, the potential benefits may not outweigh the expected harms, and these men should not be routinely screened for prostate cancer (78).	Extrapolation from general population
Cervical	Annual Pap testing or HPV testing every 3–5 years starting at the age of 25 years until 74 years (72).	In view of the higher risk of disease, some have suggested more frequent Pap testing. However, no evidence to suggest increased frequency of HPV testing.
Bowel	For adults aged 45–75 years, fecal immunochemical testing biennially, sigmoidoscopy every 5 years, or colonoscopy every 5–10 years (79).	Screening using fecal immunochemical testing is accurate in recipients of kidney transplants. However, it may be associated with higher risk of complications associated with diagnostic colonoscopies (80).
Lung	For adults aged 55–79 years, annual low-dose computed tomography scans for those who have smoked one pack per day for 30 years or equivalent (two packs per day for 15 years) (81).	Extrapolation from general population
Skin	Monthly self-skin examination and 6- to 12-monthly total body skin examination by expert physicians and dermatologists (82).	Expert opinions
Renal cell	Routine screening for renal cell carcinoma using US is not recommended for all recipients of transplants, except for high-risk individuals.	Population-based screening using US for all recipients of kidney transplants is not cost-effective (76).
Liver	Routine screening using US, with and without α-fetoprotein, every 6 months in patients with cirrhosis.	Extrapolation from general population
PTLD	Routine monitoring of patients at high risk (donor EBV seropositive/recipient seronegative) for EBV by NAT. Once in the first week after transplantation, monthly for the first 3–6 months, and every 3 months until the end of the first post-transplant year (82).	Expert opinions

Pap, Papanicolaou; HPV, human papillomavirus; US, ultrasonography; PTLD, post-transplant lymphoproliferative disease; EBV, Epstein–Barr virus; NAT, nucleic acid amplification techniques.

Al-Adra D, et al. Clin J Am Soc Nephrol. 2022 Mar;17(3):434-443.

Patients with a de novo cancer after transplant

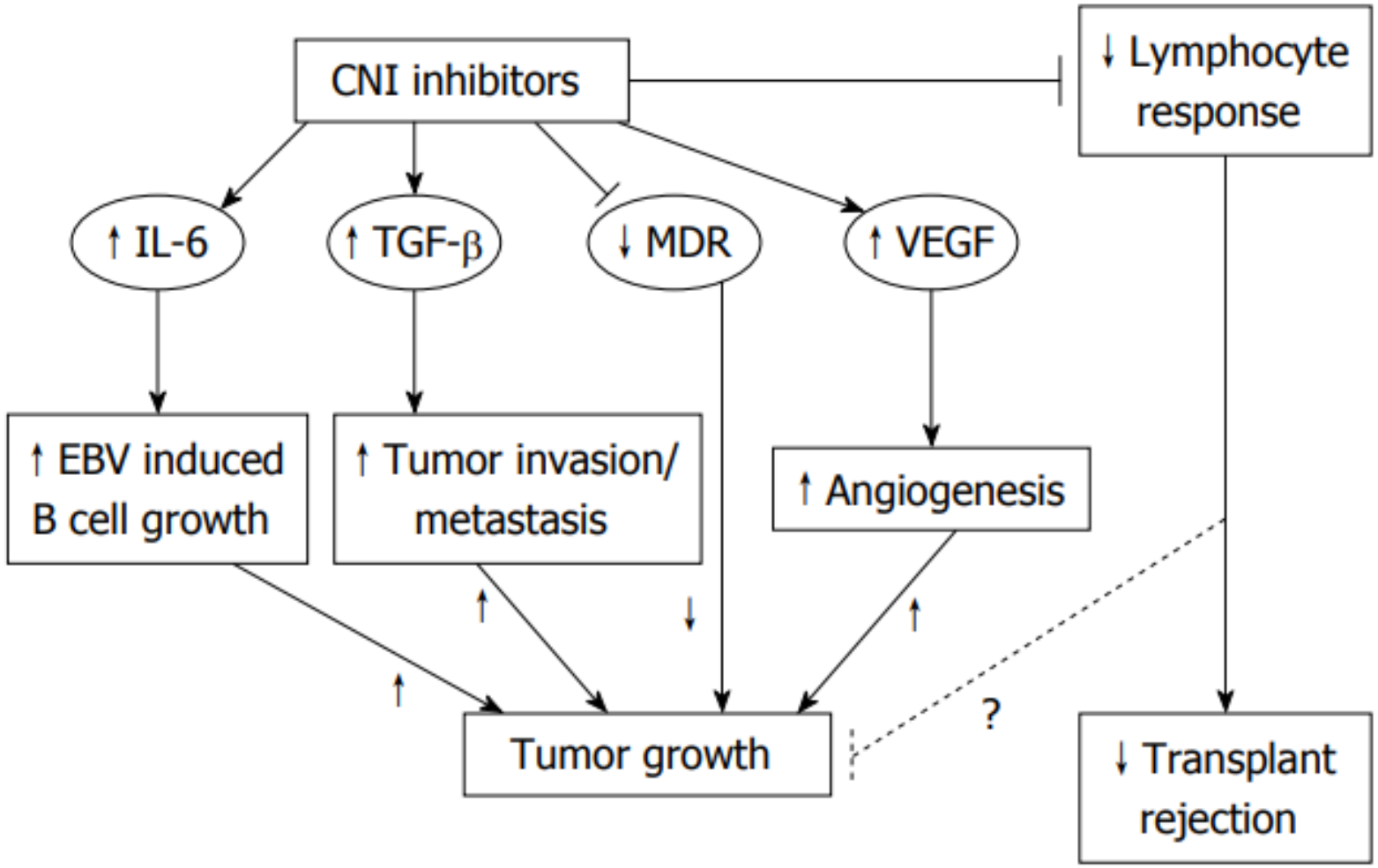
1. Correct cause and specific management
2. Reduction in immunosuppression
3. Avoidance of immune checkpoint inhibitors

Outlines: Cancer and mTORi in KT

1. Epidemiology of post-KT cancer?
2. Risk factors and pathogenesis of post-KT cancer?
3. Post-KT cancer and outcomes?
4. How to detection and management post-KT cancer?
5. **mTORi in post-KT malignancy?**

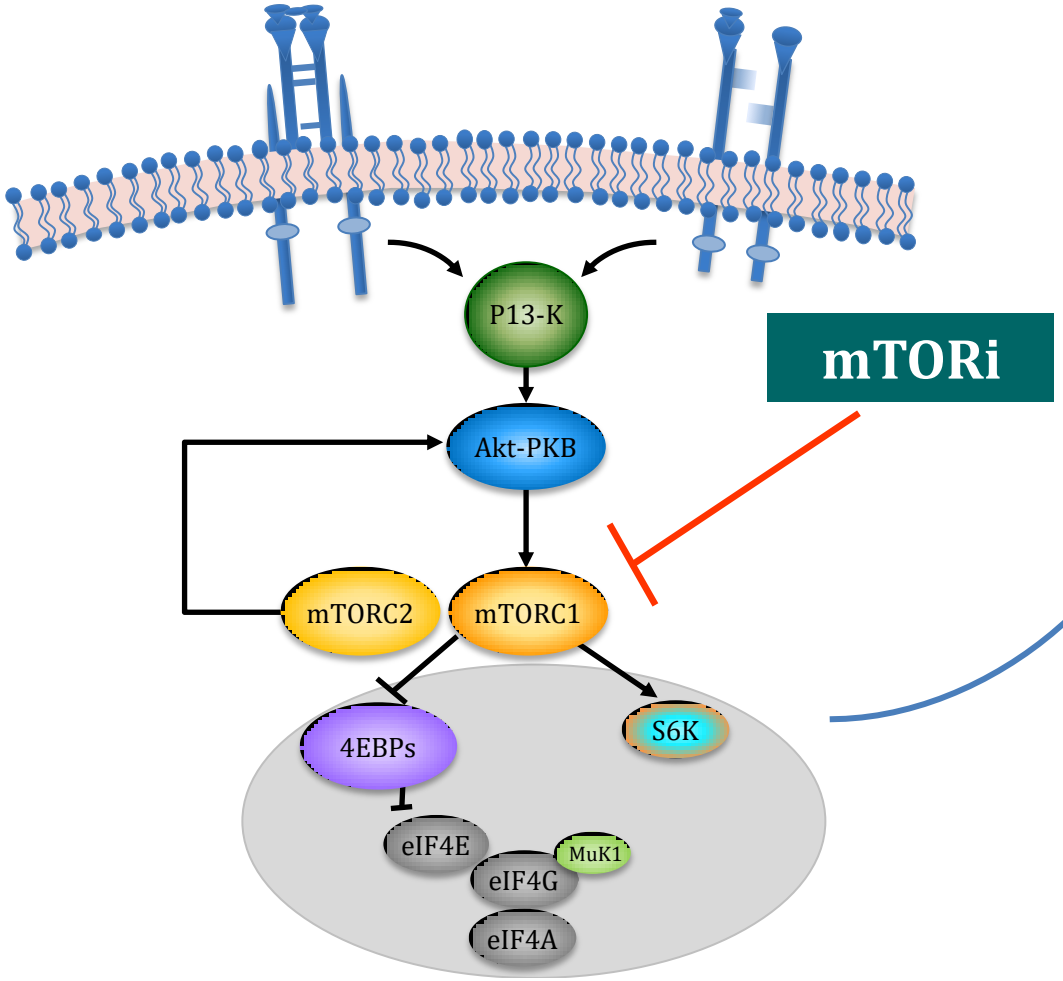
❖Case sharing

Calcineurin inhibitor and malignancies



Salvadori M. Antineoplastic effects of mammalian target of rapamycine inhibitors. World J Transplant. 2012 Oct 24;2(5):74-83.

mTOR plays a central role in cell growth, proliferation and survival[5,6]



mTORi

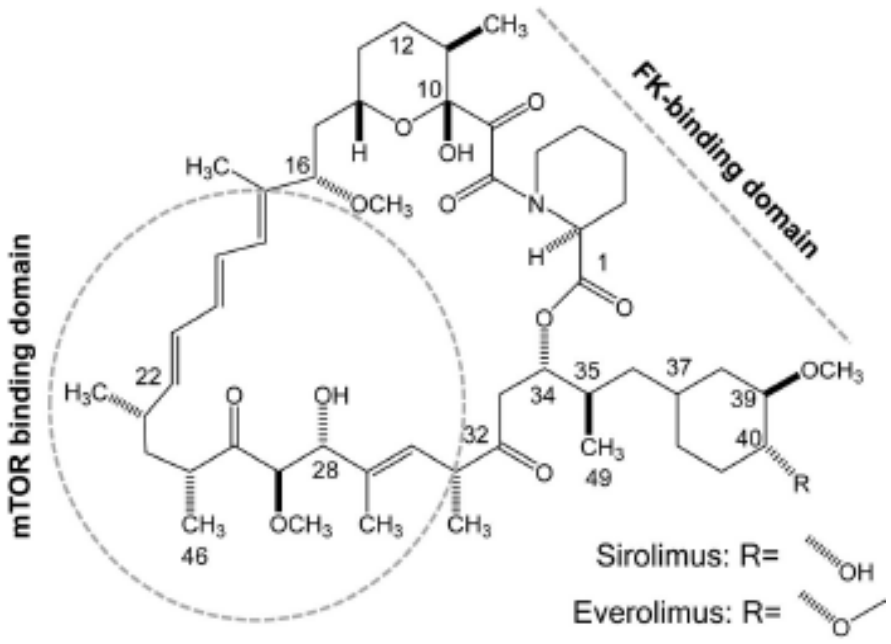
Control of gene expression

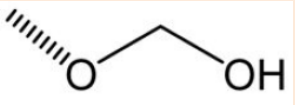
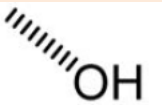
- Cell growth
- Proliferation
- Cell survival

Physiological processes mediated by mTOR activation	
Amino acid biosynthesis	Tumor cell proliferation
Glucose homeostasis	Angiogenesis
Adipogenesis	Viral replication

Pópulo, Helena, et al. Intl J of Molecular Sciences 2012;13(2):1886–1891.
Buchkovich NJ, et al. Nat Rev Microbiol. 2008 Apr;6(4):266-75.

Current mTOR inhibitors

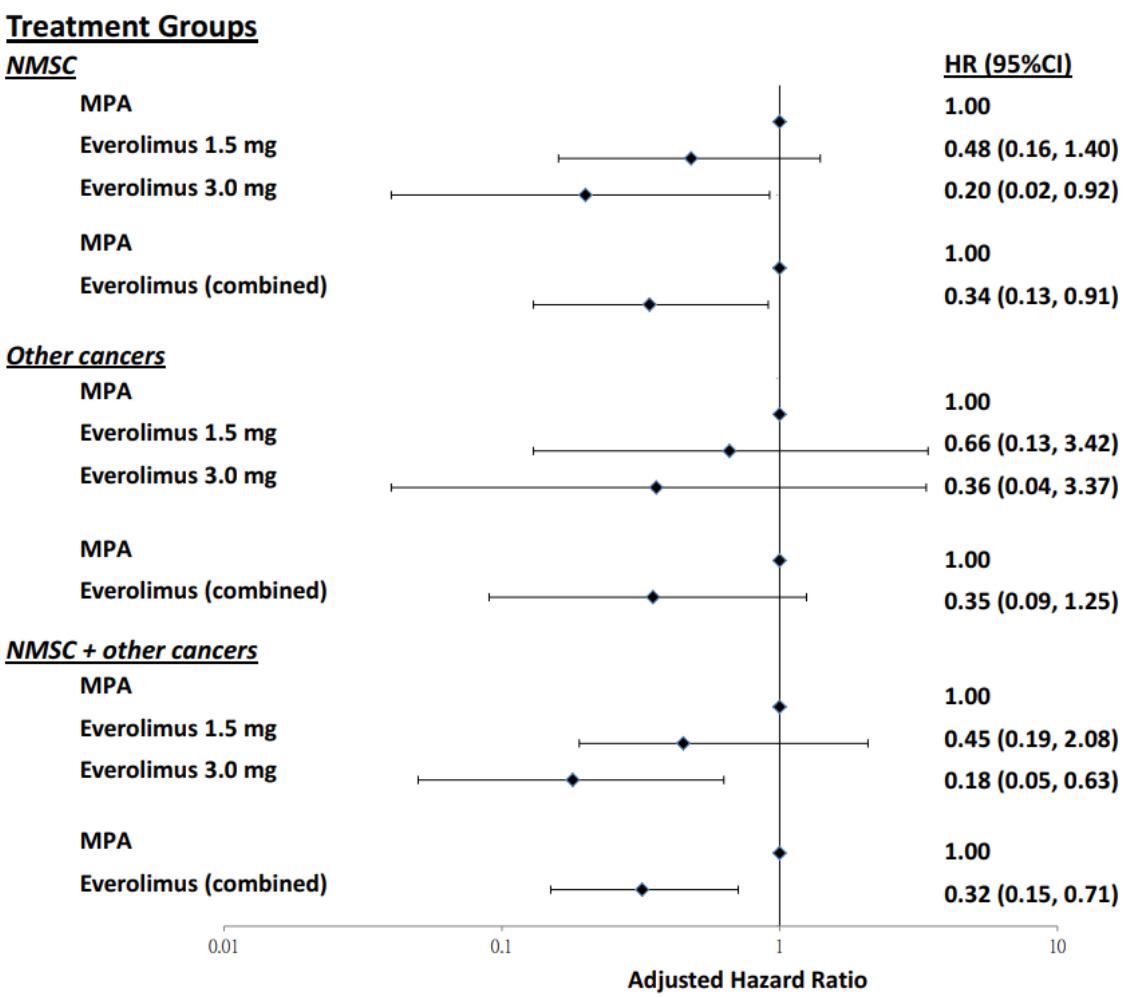


Pharmacokinetic property	Everolimus[1,3] R= 	Sirolimus[2,3] R= 
Oral bioavailability	20%	14%
Elimination $t_{1/2}$	28 hours	62 hours
Time to steady state	4 days	5–7 days
Plasma protein binding	74%	92%
Loading dose	No	Yes (6.0 mg)
Dosing interval	Twice daily	Once daily
Target trough levels	3–8 ng/mL	4–12 ng/mL
Concomitant dosing with CsA	Yes	4 hr post-CsA dose

The risk of cancer in kidney transplant recipients may be reduced in those maintained on everolimus and reduced cyclosporine

Wai H. Lim[1,2], Graeme R. Russ[3], Germaine Wong[4,5], Helen Pilmore[6,7], John Kanellis[8] and Steven J. Chadban[9,10]

2309 study (n= 95)
ANZDATA linkage
Cancer after
7 years follow-up



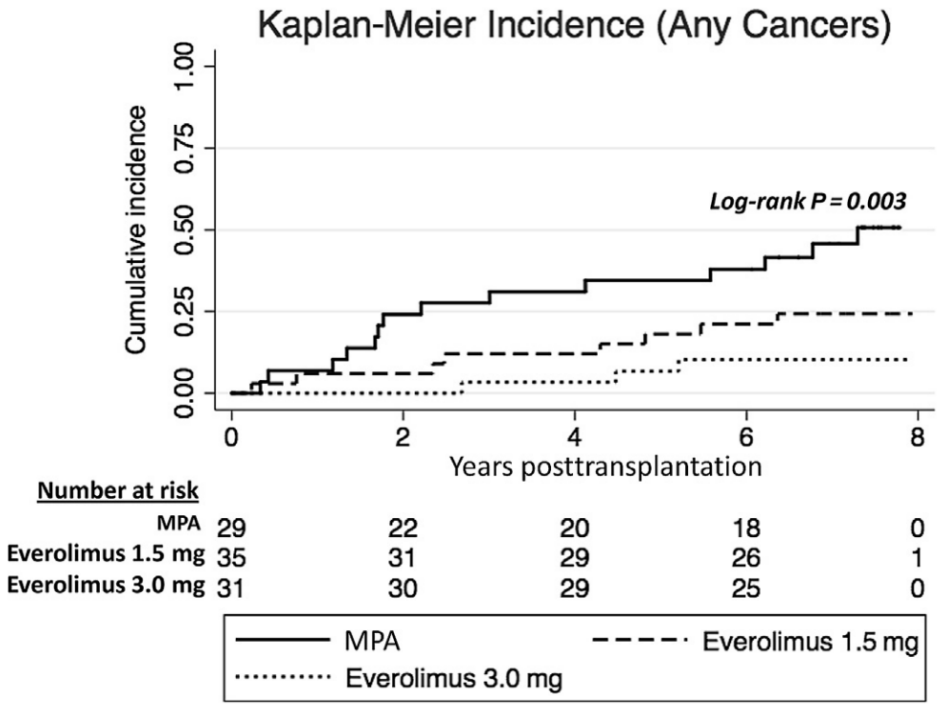


Figure 4 | Unadjusted Kaplan-Meier curves of any incident cancers, including nonmelanoma skin cancers (NMSC) by study group (standard exposure cyclosporine with mycophenolate sodium and corticosteroids [MPA] vs. everolimus 1.5 mg and everolimus 3.0 mg; log-rank P value 0.003).

Lim WH, et al. Kidney Int. 2017 Apr;91(4):954-963.

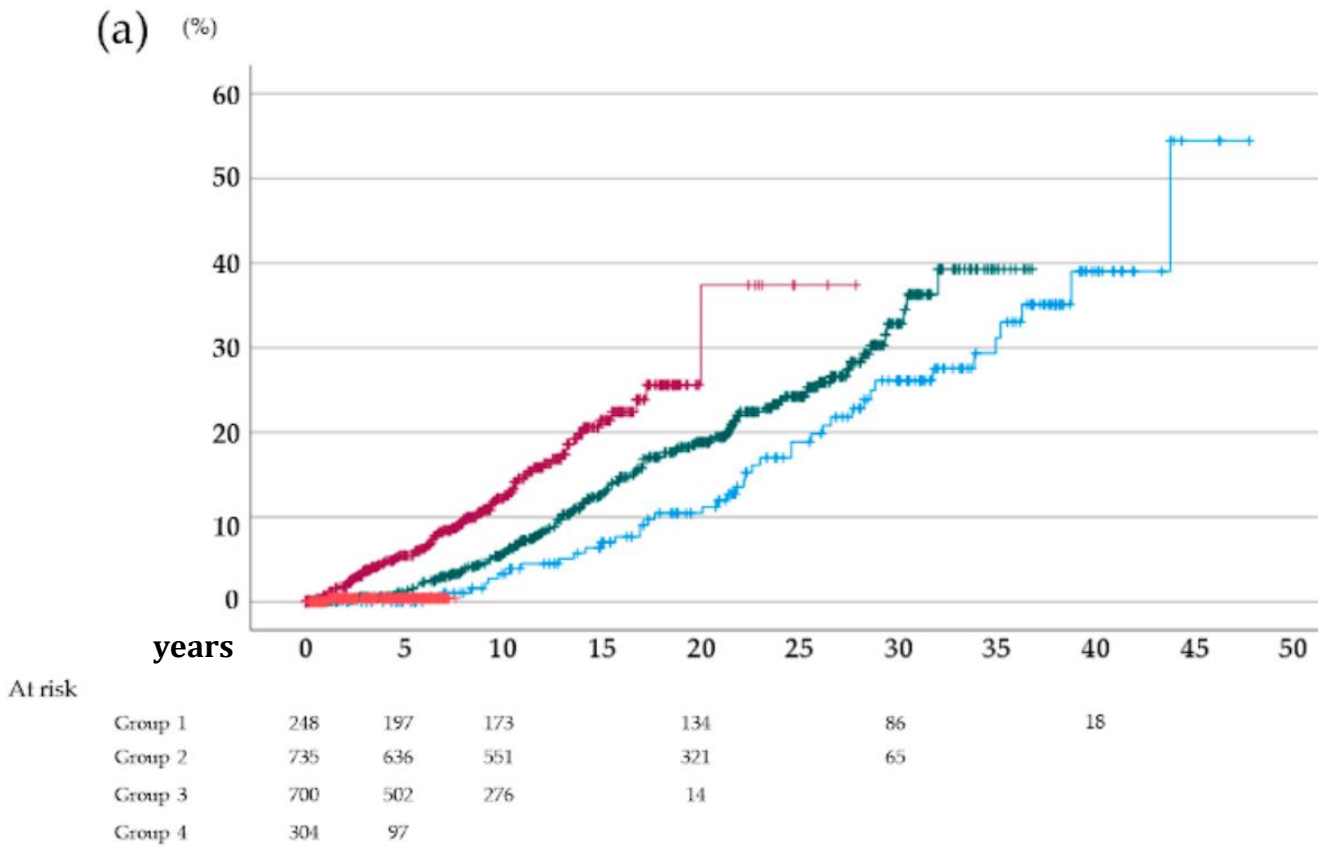
Everolimus Reduces Cancer Incidence and Improves Patient and Graft Survival Rates after Kidney Transplantation: A Multi-Center Study

Table 3. Distribution of cancer types.

	Group 1	Group 2	Group 3	Group 4
The number of recipients	248	735	700	304
Total cancer-positive recipients	42 (16.9)	119 (16.2)	80 (11.7)	1 (0.3)
Double cancer-positive recipients	6	12	9	0
Triple cancer-positive recipients	4	1	0	0
Type of cancer				
PTLD	3	21	13	1
renal cell carcinoma	2	12	13	0
breast cancer	4	13	13	0
skin cancer (melanoma)	0	0	1	0
skin cancer (non-melanoma)	10	12	9	0
prostate cancer	1	5	5	0
colorectal cancer	5	7	6	0
uterus cancer	2	10	5	0
gastric cancer	5	8	5	0
urothelial cancer	2	6	4	0
thyroid cancer	1	6	3	0
tongue cancer	3	7	2	0
pancreas cancer	0	2	2	0
hepatocellular carcinoma	5	7	1	0
lung cancer	2	1	0	0
ovarian cancer	1	1	0	0
vaginal cancer	0	1	0	0
anal cancer	0	1	0	0
others	10	13	7	0
Total	56	133	89	1

PTLD, post-transplant lymphoproliferative disorders.

group 1: Antiproliferative agents, steroids
group 2: CNIs, antiproliferative agents, steroids
group 3: CNIs, MMF, steroids
group 4: mTORi



Cumulative cancer incidence rates after kidney transplantation. (a) all cancers, (b) all cancers except non-melanoma skin cancer: Blue, group 1; green, group 2; dark red, group 3; vermilion, group 4.

Imamura R, et al. J Clin Med. 2022 Jan 4;11(1):249.

PLOS ONE

RESEARCH ARTICLE

Effects of mTOR-Is on malignancy and survival following renal transplantation: A systematic review and meta-analysis of randomized trials with a minimum follow-up of 24 months

Sebastian Wolf[1,2☯], Verena S. Hoffmann[3,4☯], Antje Habicht[5], Teresa Kauke[1], Julian Bucher[1], Markus Schoenberg[1], Jens Werner[1], Markus Guba[1], Joachim Andrassy[1]*

1 Department of General, Visceral and Transplant Surgery, Ludwig-Maximilian's University, Munich, Germany, **2** Department of Visceral and Transplant Surgery, Augsburg Hospital, Augsburg, Germany, **3** Institute of Medical Information Sciences, Biometry and Epidemiology (IBE), Ludwig-Maximilian's-University, Munich, Germany, **4** Helmholtz Center Munich, German Research Center for Environmental Health, Munich, Germany, **5** Transplant Center, University Hospital Grosshadern, Ludwig-Maximilian's University, Munich, Germany

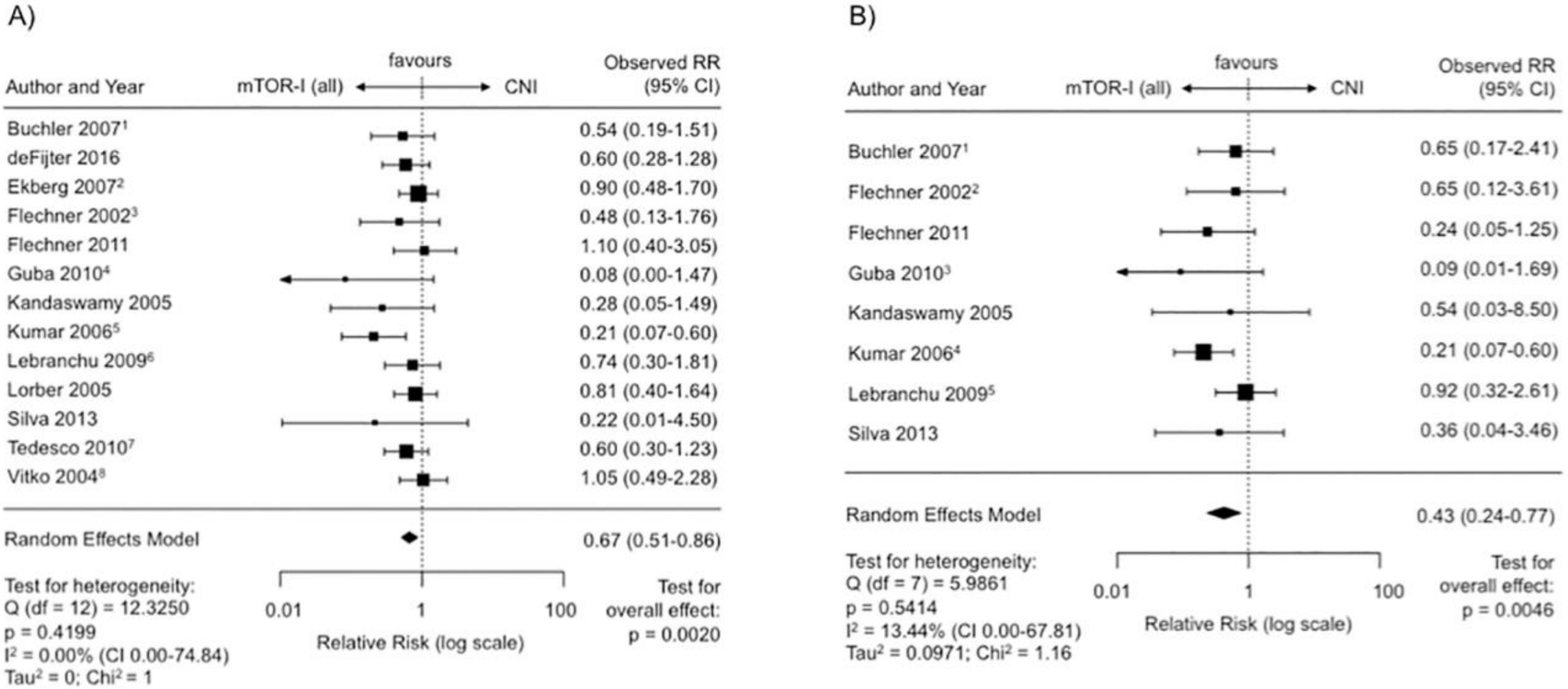
☯ These authors contributed equally to this work.
* joachim.andrassy@med.uni-muenchen.de

Check for updates

Include 14 RCT studies in KT recipients, mean F/U 40.6 months

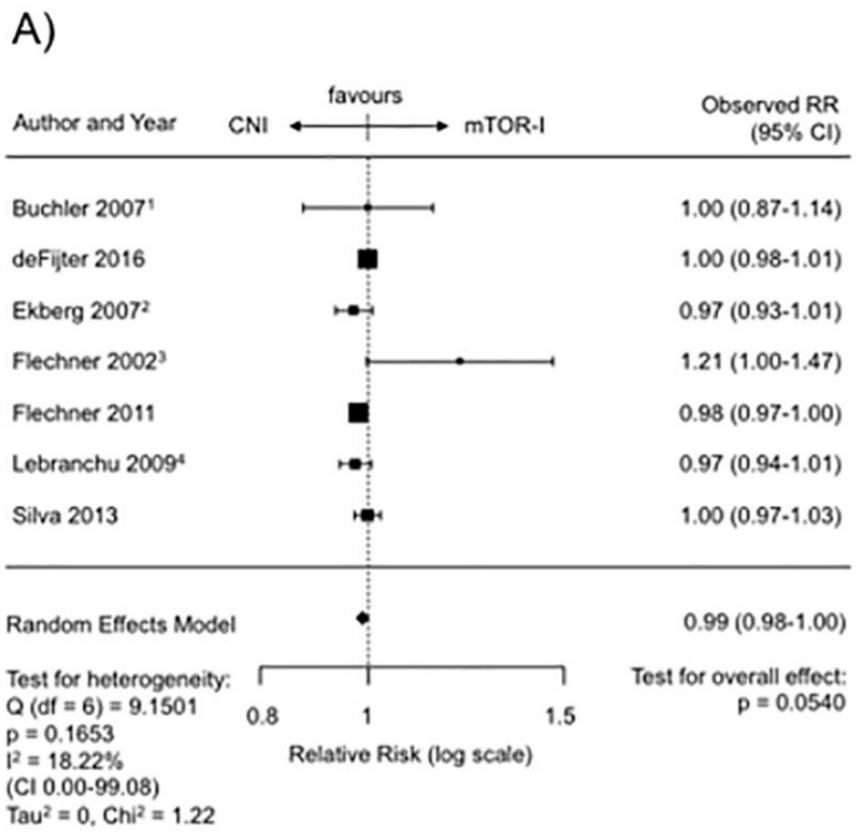
Wolf S, et al. PLoS One. 2018 Apr 16;13(4):e0194975.

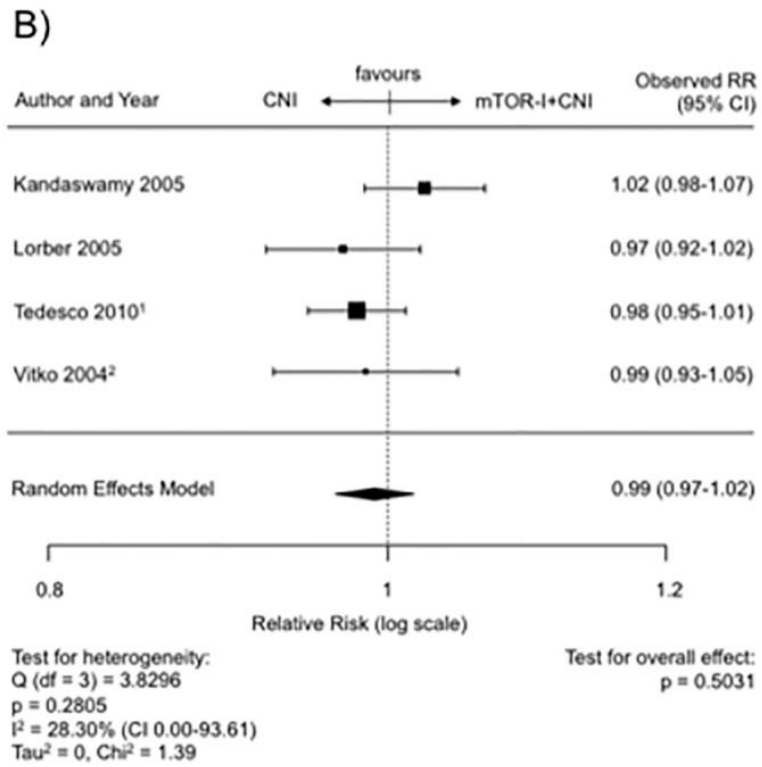
Malignancies on mTOR-I (monotherapy or combined with CNIs) versus CNI treatment post transplantation

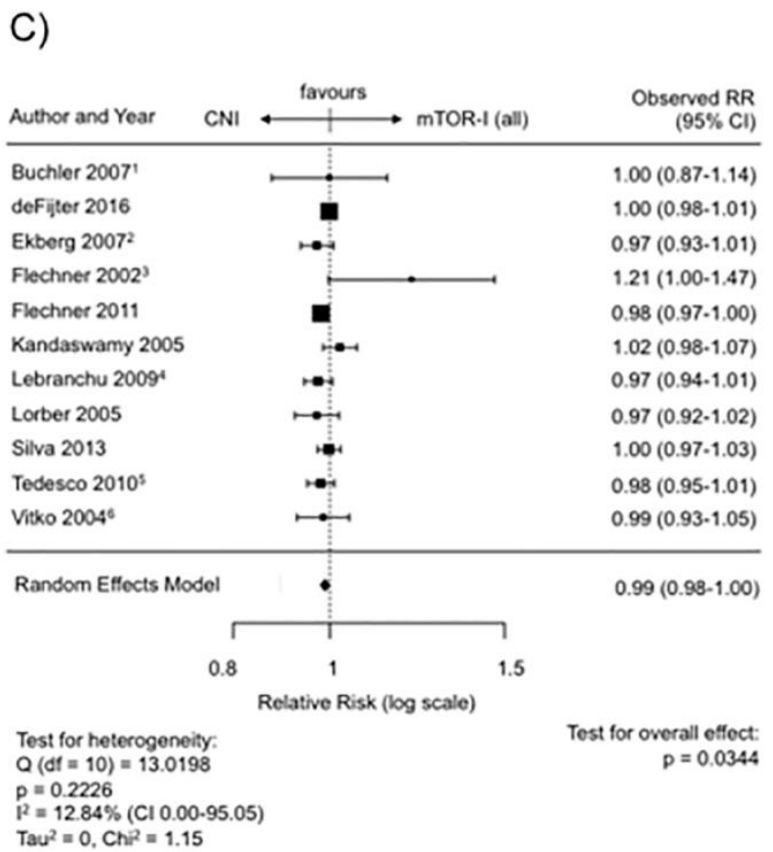


Wolf S, et al. PLoS One. 2018 Apr 16;13(4):e0194975.

Graft survival censored for death post transplantation

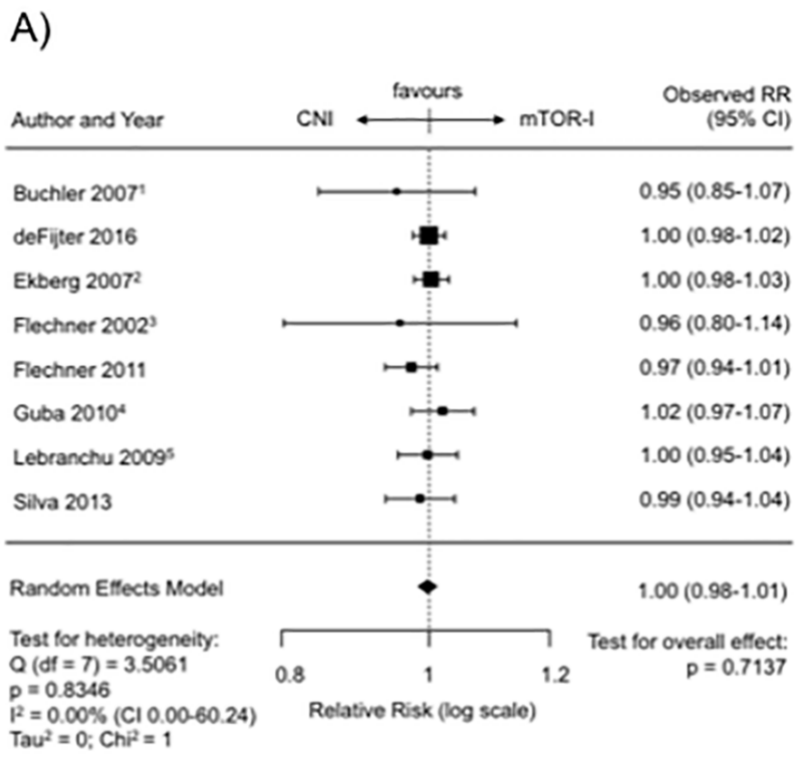


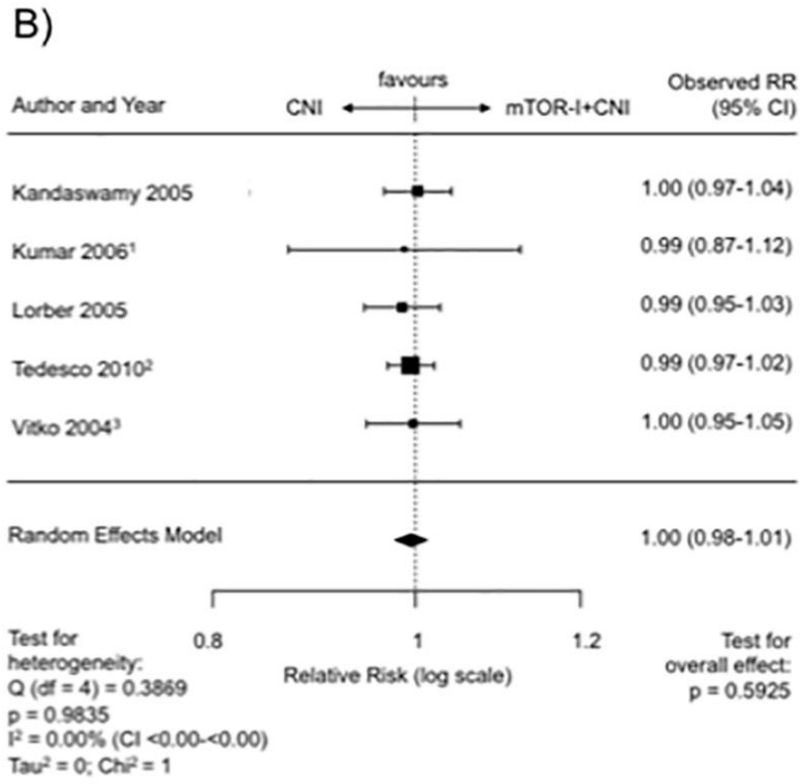


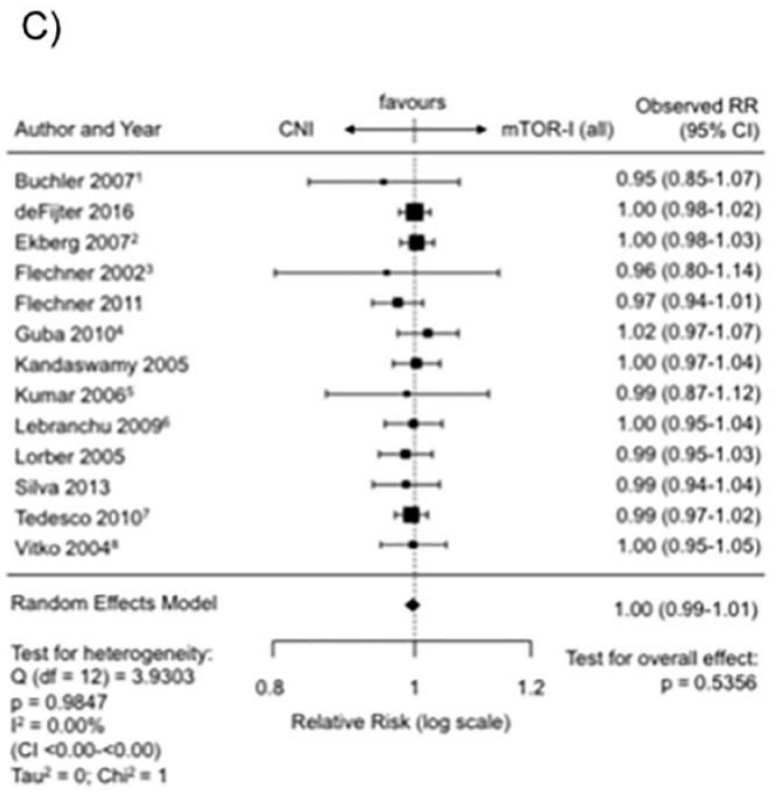


Wolf S, et al. PLoS One. 2018 Apr 16;13(4):e0194975.

Overall patient survival post transplantation







Wolf S, et al. PLoS One. 2018 Apr 16;13(4):e0194975.

CLINICAL KIDNEY JOURNAL

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Original Article

ORIGINAL ARTICLE

Sirolimus in renal transplant recipients with malignancies in Germany

Marcel G. Naik [1,2], Wolfgang Arns[3], Klemens Budde[1], Fritz Diekmann[4], Frank Eitner[5], Wilfried Gwinner[6], Nils Heyne[7], Jan Steffen Jürgensen[8], Christian Morath[9], Udo Riester[10], Katharina M. Heller[11,*] and Michael Fischereder[12,*]; for the German Sirolimus Study Group

[1]Division of Nephrology, Charité University-Mitte, Berlin, Germany, [2]Berliner Institut für Gesundheitsforschung/Berlin Institute of Health (BIH) Körperschaft des öffentlichen Rechts Anna-Louisa-Karsch-Str. 2 10178 Berlinn, Germany, [3]Transplant Centre Cologne, Cologne General Hospital, Cologne, Germany, [4]Department of Nephrology and Kidney Transplantation, Hospital Clinic, Barcelona, Spain, [5]Division of Nephrology and Immunology, Kidney Diseases Research, RWTH Aachen University Hospital, Bayer AG, Wuppertal, Germany, [6]Division of Nephrology, Hannover Medical School, Hannover, Germany, [7]Division of Nephrology, University of Tübingen, Tübingen, Germany, [8]Division of Nephrology, Charité University - Virchow, Berlin, Germany, [9]Division of Nephrology, University of Heidelberg, Heidelberg, Germany, [10]Pfizer Pharma GmbH, Berlin, Germany, [11]Department of Medicine, Division of Nephrology, University of Erlangen, Erlangen, Germany and [12]Department of Medicine IV, University Hospital of Munich, Munich, Germany

Correspondence to: Marcel G. Naik; E-mail: marcel.naik@charite.de

- Retrospectively analysed 726 renal allograft recipients converted to SRL from 10 German transplant centres. Patient and graft survival were analysed depending on malignancy status prior to conversion and tumour entity.
- Conversion to SRL in patients with a history of cancer is safe regarding renal function and graft survival, while patient survival is largely dependent on tumour entity.

Naik MG, et al. Clin Kidney J. 2020 Dec 14;14(9):2047-2058.

Effect of mechanistic target of rapamycin inhibitors on postrenal transplantation malignancy: A nationwide cohort study

	Noncancer		Cancer		
	N	%	N	%	*P* value
Total subjects	3879	87.40	559	12.60	
The age receiving transplantation (y)					
20-44	1747	45.04	163	29.16	<0.0001
45-64	1969	50.76	361	64.58	
65+	163	4.20	35	6.26	
Sex					
Female	1797	46.33	306	54.74	0.00
Male	2080	53.62	252	45.08	
Using mTORi duration					
Never used	2990	77.08	430	76.92	0.93
Within 1 y	238	6.14	38	6.80	
Within 1-5 y	390	10.05	55	9.84	
Over 5 y	261	6.73	36	6.44	

	mTORi nonusers[a]		mTORi users		
	N	%	N	%	*P* value
Overall cancer	469	12.69	90	12.13	0.67
Urothelial malignancy	219	5.93	40	5.39	0.57
Kidney malignancy	58	1.57	12	1.62	0.92
Liver malignancy	66	1.79	13	1.75	0.95
Digestive system malignancy	48	1.30	11	1.48	0.69

	mTORi nonusers[a]		mTORi users		
	N	%	N	%	*P* value
Immunosuppressive agents	3696		742		
Transplant rejection	376	10.17	119	16.04	<0.0001
Calcineurin inhibitor	3435	92.94	720	97.04	<0.0001
MMF	3151	85.25	696	93.80	<0.0001
Azathioprine	199	5.38	63	8.49	0.001
Steroid	3436	92.97	714	96.23	0.001

[a]Nonusers: Included subjects who never used or using <1 y.

Hou YC, et al. Cancer Med. 2018 Sep;7(9):4296-4307.

Effect of mechanistic target of rapamycin inhibitors on postrenal transplantation malignancy: A nationwide cohort study

Table 4. Propensity score matching of mTORi use for the occurrence of post-transplantation malignancy

	All cancer		Urothelial malignancy		Kidney malignancy		Liver malignancy		Digestive system malignancy	
mTORi	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI
Never used	1.00		1.00		1.00		1.00		1.00	
Users	0.67	0.44, 1.03	0.66	0.35, 1.26	0.49	0.16, 1.51	0.91	0.31, 2.67	0.88	0.25, 3.15
Never used	1.00		1.00		1.00		1.00		1.00	
Using 1-5 y	0.88	0.65, 1.19	0.80	0.51, 1.24	0.52	0.21, 1.31	1.58	0.78, 3.17	0.71	0.28, 1.81
Using more than 5 y	0.68	0.48, 0.95	0.60	0.36, 0.99	0.53	0.20, 1.42	0.51	0.18, 1.45	0.80	0.30, 2.11

Adjusted for age, gender, comorbidities, and modalities of renal replacement therapy before transplantation and immunosuppressive agent.

Table 5. Adjusted hazard ratio for the occurrence of overall malignancy and subgroups of malignancy based on the exposure of mTORi

	All cancer		Urothelial malignancy		Kidney malignancy		Liver malignancy		Digestive system malignancy	
mTORi	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI	Hazard ratio	95% CI
Never used	1.00		1.00		1.00		1.00		1.00	
Users	0.67	0.44, 1.03	0.66	0.35, 1.26	0.49	0.16, 1.51	0.91	0.31, 2.67	0.88	0.25, 3.15
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Hou YC, et al. Cancer Med. 2018 Sep;7(9):4296-4307.

Case sharing

Outlines

1. Epidemiology of post-KT cancer
2. Risk factors and pathogenesis of post-KT cancer
3. Post-KT cancer and outcomes?
4. How to detection and management post-KT cancer
5. mTORi in post-KT malignancy

❖Case sharing

Thank You for Your Attention

NEPHROLOGY
PHRAMONGKUTKLAO HOSPITAL

Lt. Col. Naowanit Nata, MD
Nephrology Division, Department of Medicine
Phramongkutklao Hospital & College of Medicine