Malignancy after transplantation

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Spectrum of Cancer Risk among U.S. Solid Organ Transplant Recipients: The Transplant Cancer Match Study

Analyzed the frequency of malignancy in over 175,000 solid organ transplant recipients during the period 1987 to 2008

↑ risk of malignancy in 30 different primary sites.

Cancer risk in U.S. transplant recipients

Cancer site*	Observed cases	Expected cases	SIR†	95% lower CI	95% upper CI	P-value
Infection-related malignancies						
NHL	1504	199.4	7.54	7.17	7.93	<0.0001
Nodal NHL	831	136.6	6.08	5.68	6.51	<0.0001
Extranodal NHL	673	62.8	10.72	9.93	11.56	<0.0001
Liver	930	80.5	11.56	10.83	12.33	<0.0001
Stomach	152	90.9	1.67	1.42	1.96	<0.0001
Kaposi sarcoma	120	2.0	61.46	50.95	73.49	<0.0001

Engels EA et al: Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011, 306(17):1891-1901.

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Spectrum of Cancer Risk among U.S. Solid Organ Transplant Recipients: The Transplant Cancer Match Study

Lung	1344	682.8	1.97	1.86	2.08	<0.0001
Prostate	1039	1126.9	0.92	0.87	0.98	0.009
Kidney	752	161.8	4.65	4.32	4.99	<0.0001
Colorectum	627	504.9	1.24	1.15	1.34	<0.0001
Breast	481	567.9	0.85	0.77	0.93	0.0002
Melanoma	381	160.3	2.38	2.14	2.63	<0.0001
Thyroid	238	80.8	2.95	2.58	3.34	<0.0001
Urinary bladder	225	148.1	1.52	1.33	1.73	<0.0001
Skin (non-melanoma, non-epithelial)	184	13.3	13.85	11.92	16.00	<0.0001
Pancreas	157	107.3	1.46	1.24	1.71	<0.0001

Engels EA et al: Spectrum of cancer risk among US solid organ transplant recipients. JAMA 2011, 306(17):1891-1901.

Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis

Andrew E Grulich, Marina T van Leeuwen, Michael O Falster, Claire M Vajdic

Findings Seven studies of people with HIV/AIDS (n=444 172) and five of transplant recipients (n=31 977) were included. For 20 of the 28 types of cancer examined, there was a significantly increased incidence in both populations. Most of these were cancers with a known infectious cause, including all three types of AIDS-defining cancer, all HPV-related cancers, as well as Hodgkin's lymphoma (HIV/AIDS meta-analysis SIR 11·03, 95% CI 8·43–14·4; transplant 3·89, 2·42–6·26), liver cancer (HIV/AIDS 5·22, 3·32–8·20; transplant 2·13, 1·16–3·91), and stomach cancer (HIV/AIDS 1·90, 1·53–2·36; transplant 2·04, 1·49–2·79). Most common epithelial cancers did not occur at increased rates.

Interpretation The similarity of the pattern of increased risk of cancer in the two populations suggests that it is immune deficiency, rather than other risk factors for cancer, that is responsible for the increased risk. Infection-related cancer will probably become an increasingly important complication of long-term HIV infection.

Grulich AE: Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 2007, 370(9581):59-67.

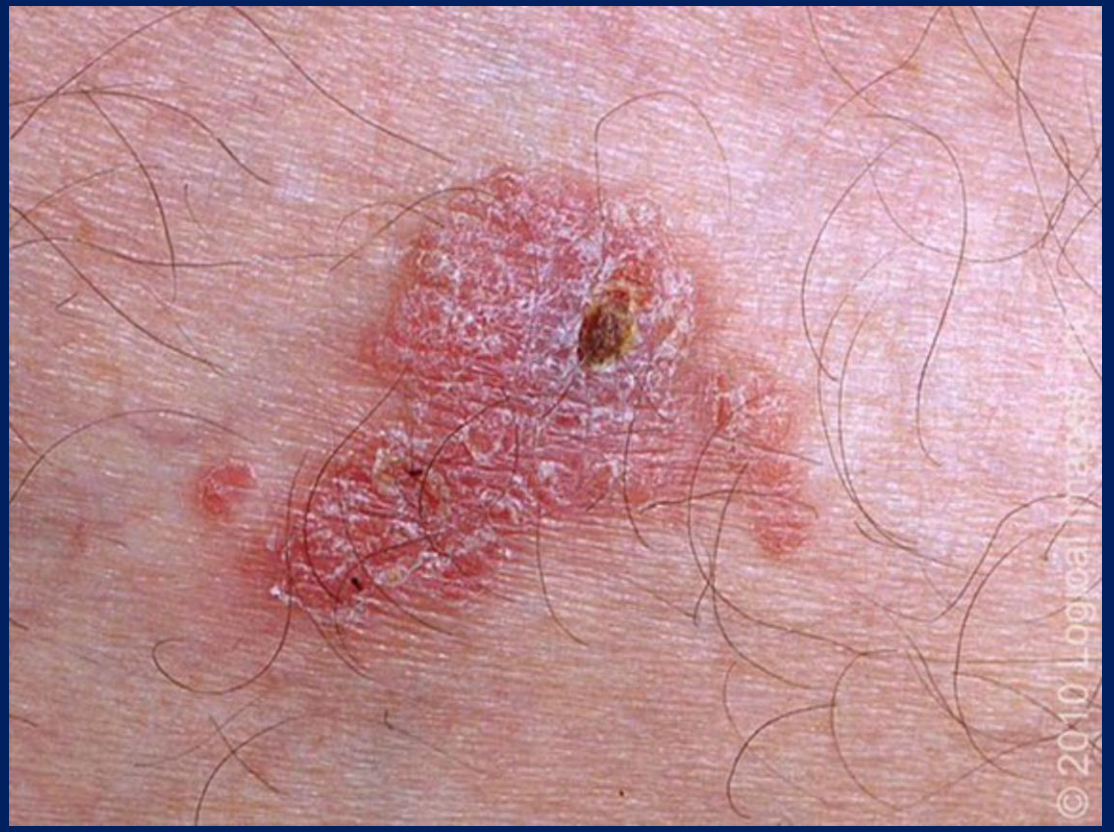
www.thelancet.com Vol 370 July 7, 2007

Skin cancer in solid organ transplant recipients

Skin cancers

Account for almost 40 % of malignancies in organ transplant recipients.

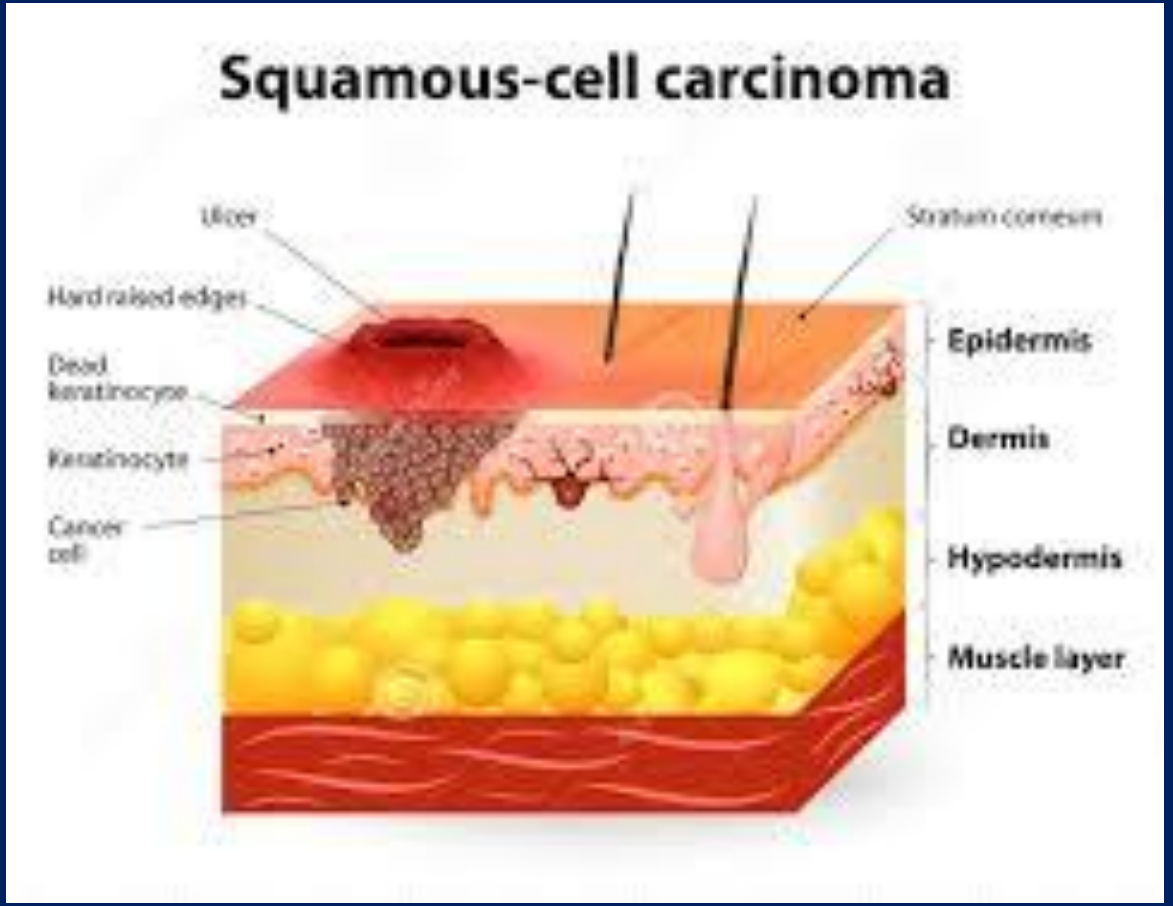
- The most commonly reported skin cancers in this population include:
  - Squamous cell carcinoma (SCC)
  - Basal cell carcinoma (BCC)
  - Melanoma
  - Kaposi sarcoma



Bowen's disease (cutaneous squamous cell carcinoma situ)

PREVENTION

- Organ transplant recipients are approximately 65 to 250 times more likely to develop SCC.
- **Sun protection:** sun-protective measures, including the use of daily sunscreen.

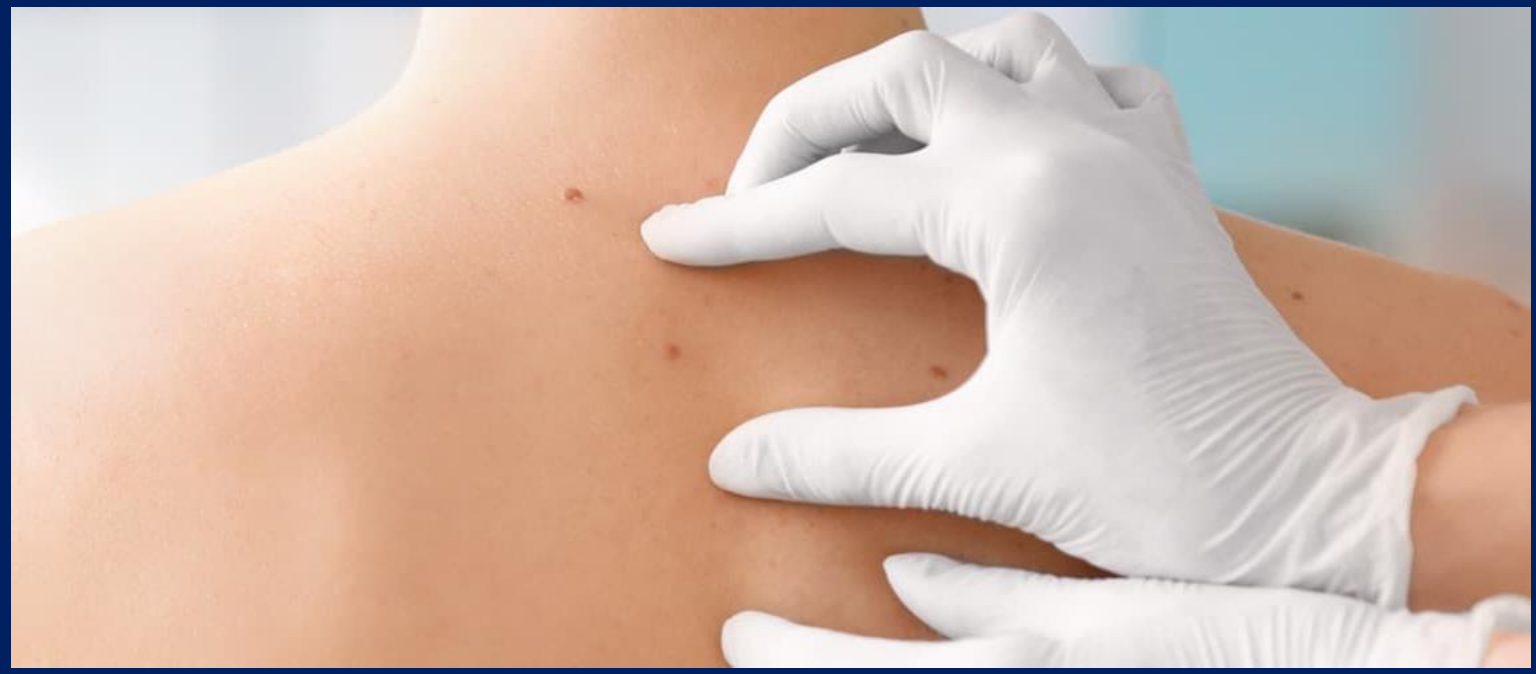


Pretransplantation Screening

- A dermatologic consultation is recommended before transplantation for the screening and treatment of skin cancer and precursor lesions.
- All suspicious lesions should be excised and sent for pathologic examination.
- Actinic keratoses, porokeratoses, and viral warts should be treated.

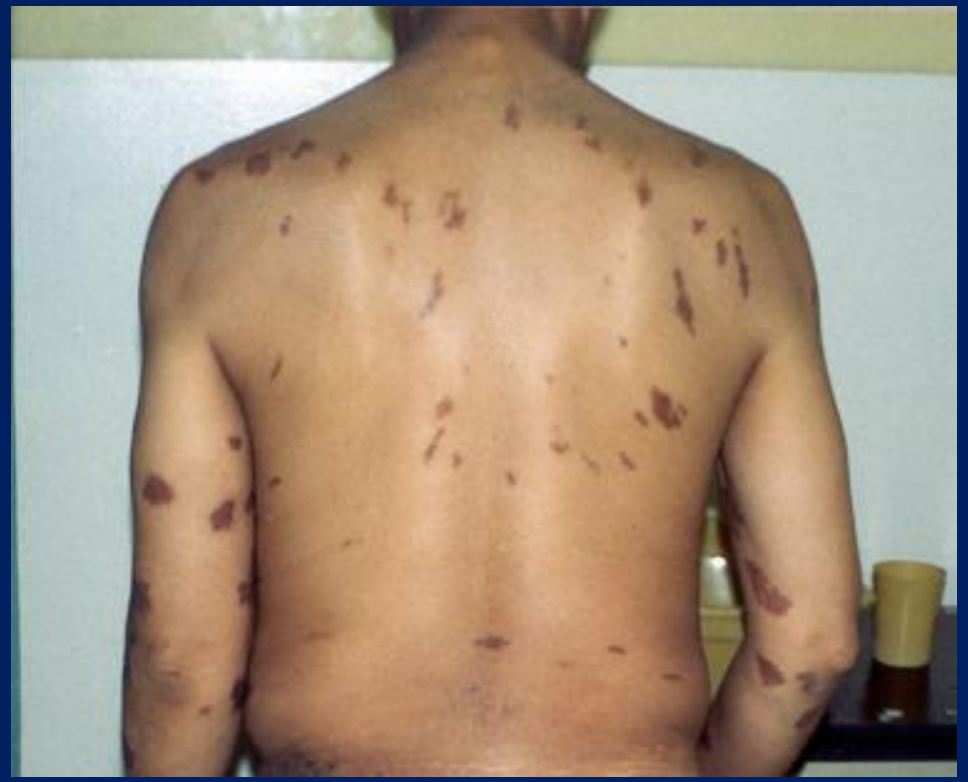
Post-transplantation surveillance

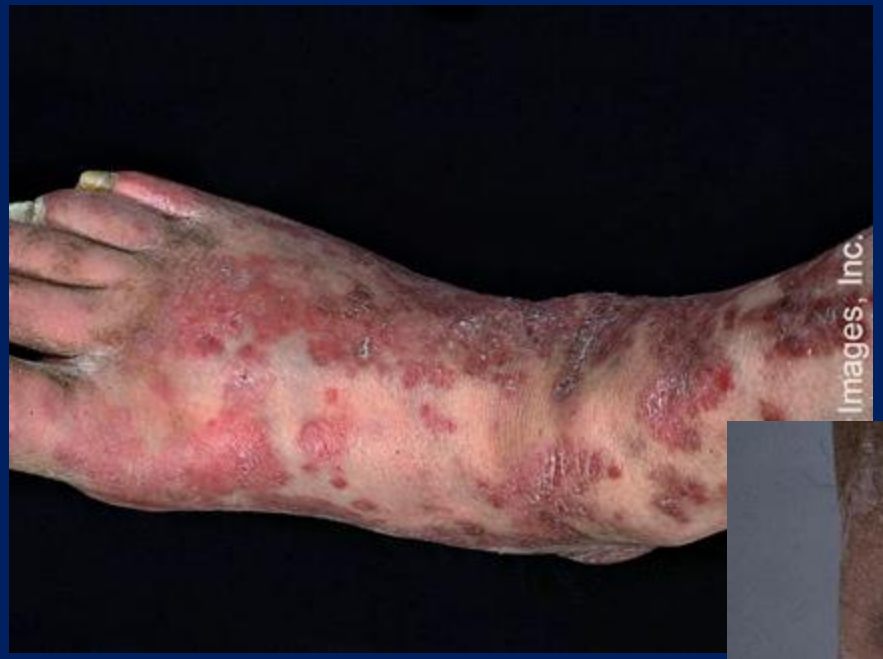
- Complete skin examinations at least once yearly
- Skin self-examination on a monthly basis.



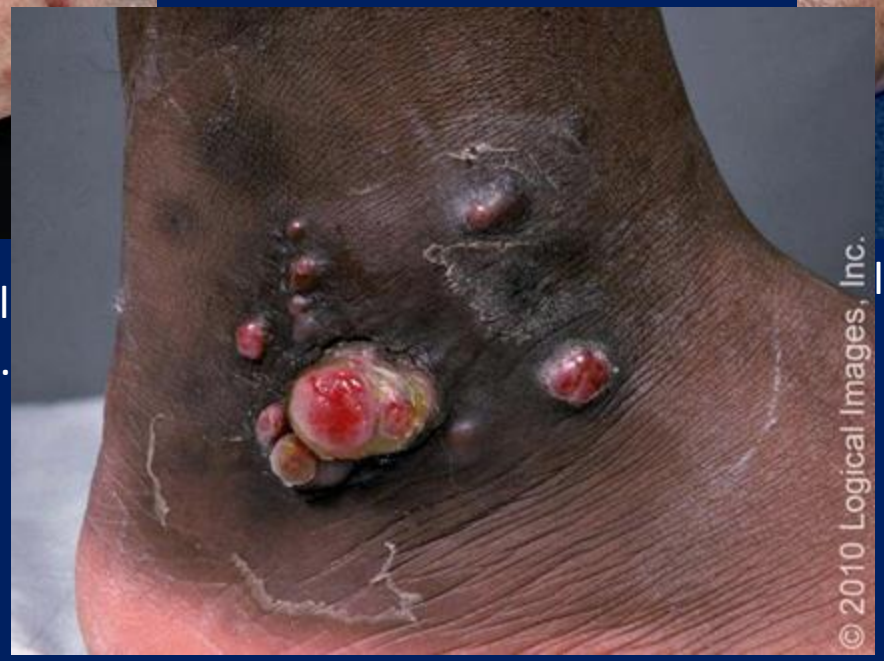
Kaposi sarcoma

- Angiomatous lesions predominantly affecting the legs and causing lymphedema.

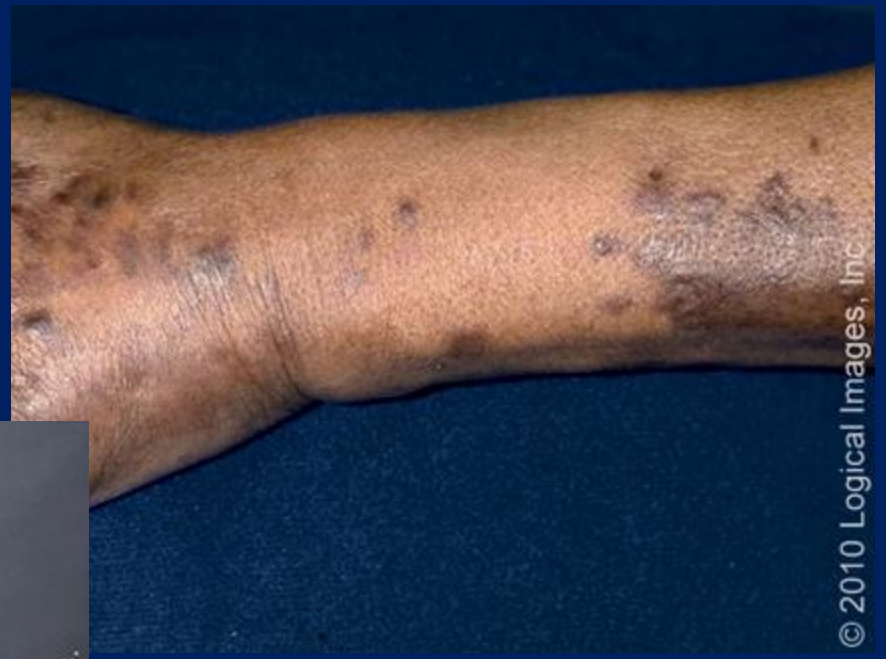




Multiple red-brown patches and pl
are present on the lower leg.



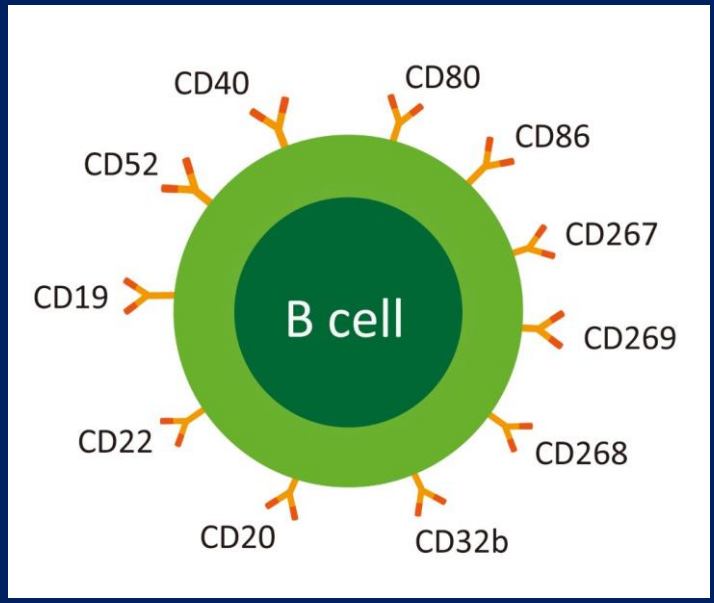
Multiple papules and nodules are present on the lower leg



ltiple violaceous papules and plaques present on the distal upper extremity

Lymphoproliferative disorders

The majority are of B-cell origin, most commonly non-Hodgkin lymphoma.



T-cell lymphoproliferative disorders are rare.

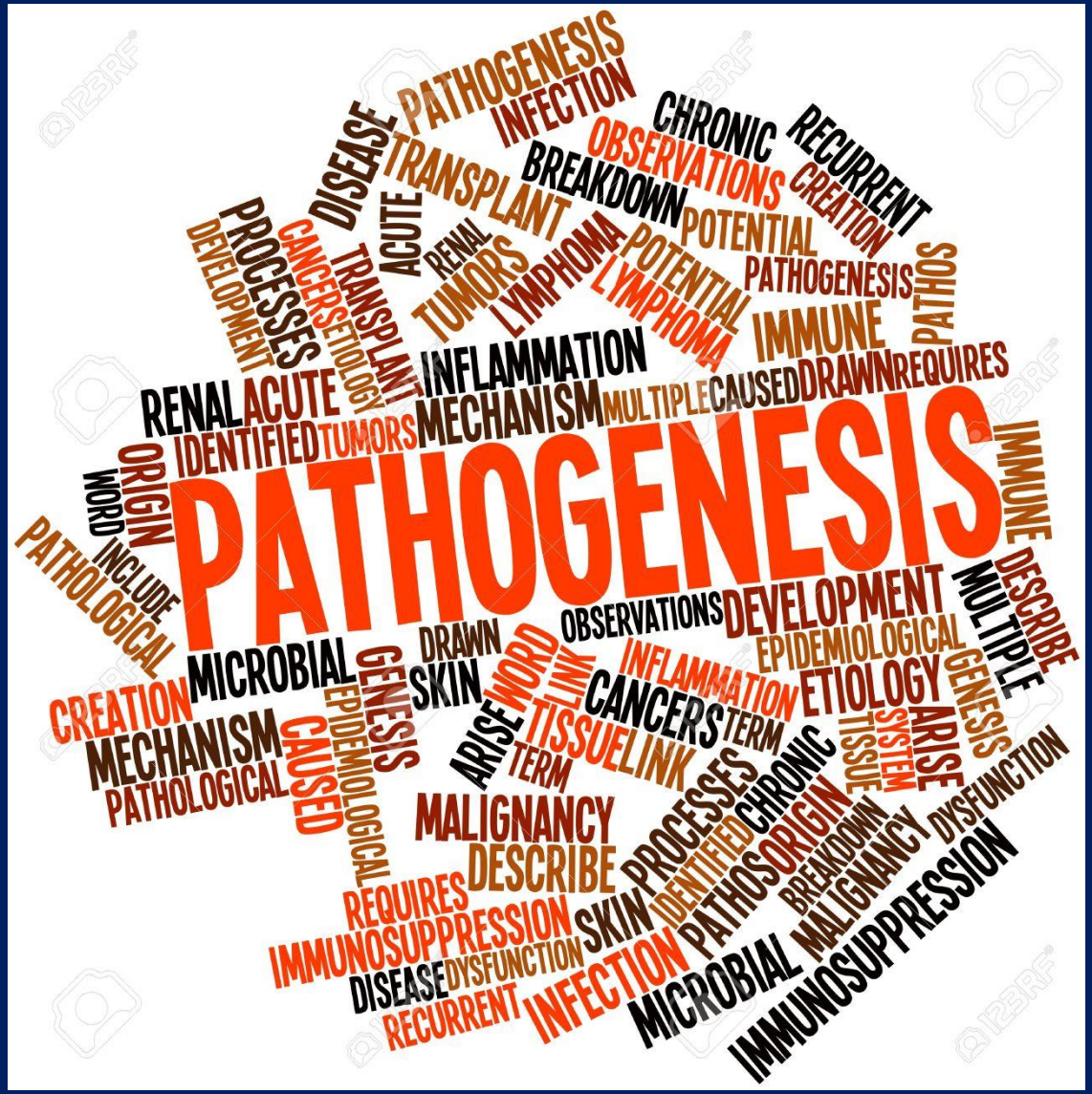
Myeloma, Hodgkin Disease, and Lymphoid Leukemia after Renal Transplantation: Characteristics, Risk Factors and Prognosis

Sophie Caillard,[1] Lawrence Y. Agodoa,[2] Erin M. Bohen,[1] and Kevin C. Abbott[1,3]

TABLE 1. Characteristics of patients with non Hodgkin lymphoma, myeloma, Hodgkin disease and lymphoid leukemia occurring after renal transplantation among 66,159 kidney recipients between 1991 and 2000 in the United States

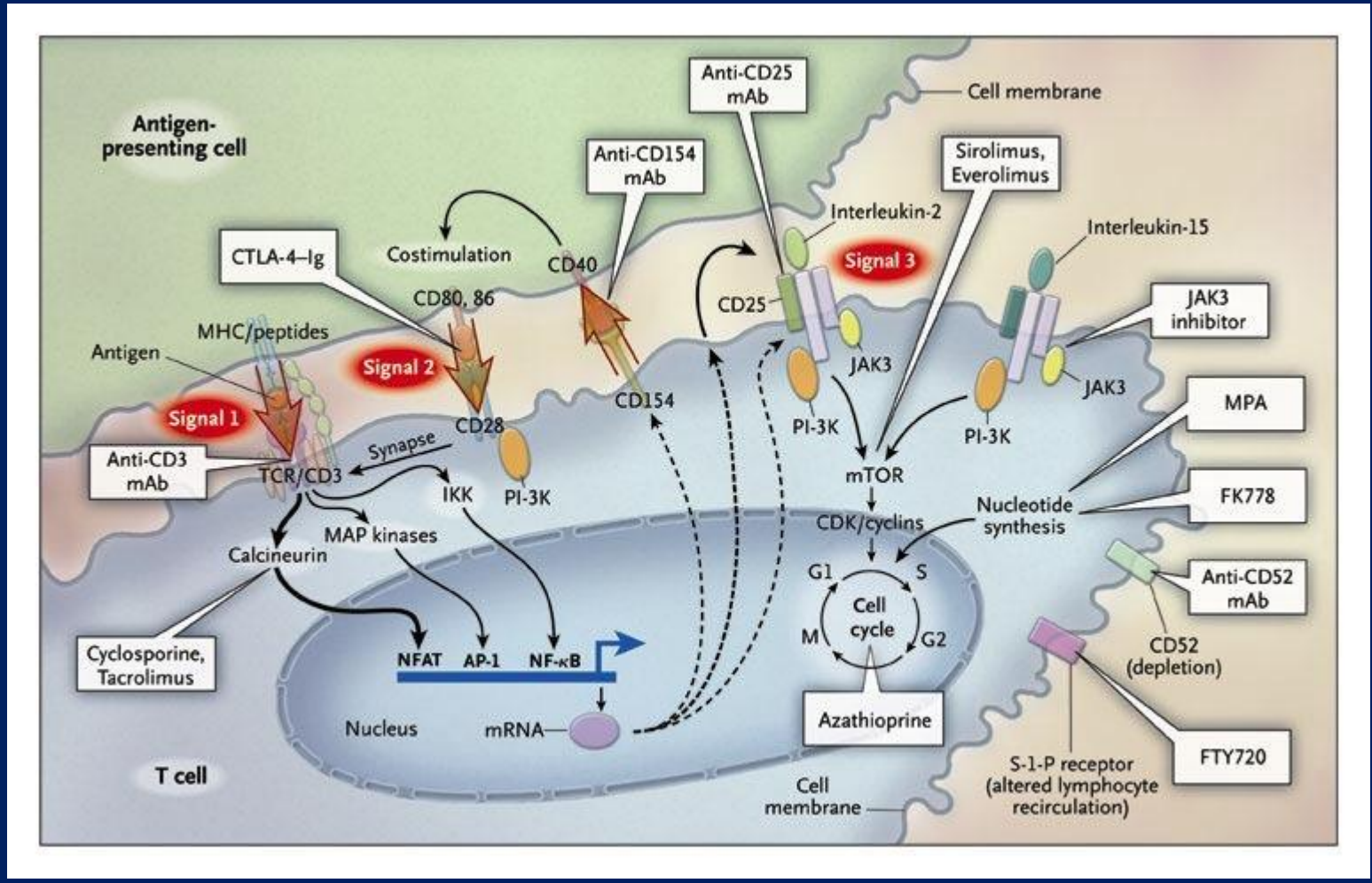
	No PTLD	NHL	MM	HD	LL
N	64990	823	160	60	126
Incidence (%)	/	1.2	0.24	0.1	0.19
Recipient					
Age at transplantation*	45.4±13	46.2±13	52.4±11.9[a,b]	47.3±12	48.3±13.3
20–40 years (%)	23422 (36)	277 (33.7)	27 (16.9)	17 (28.3)	37 (29.4)
40–60 years (%)	31734 (49)	399 (48.5)	89 (55.6)	34 (56.7)	65 (51.6)
>60 years (%)	9823 (15.1)	147 (17.9)	44 (27.5)	9 (15)	24 (19)

Myeloma, Hodgkin disease, and lymphoid leukemia after renal transplantation: characteristics, risk factors and prognosis. Transplantation 2006, 81(6):888-895.


PATHOGENESIS
PATHOGENESIS
INFECTION
DISEASE
CHRONIC
RECURRENT
OBSERVATIONS
CREATION
TRANSPLANT
BREAKDOWN
POTENTIAL
ACUTE
RENAL
TUMORS
LYMPHOMA
PROCESSES
DEVELOPMENT
CANCERS
ETIOLOGY
TRANSPLANT
PATHOS
IMMUNE
INFLAMMATION
RENAL
ACUTE
MECHANISM
MULTIPLE
CAUSED
DRAWN
REQUIRES
IDENTIFIED
TUMORS
ORIGIN
WORD
INCLUDE
PATHOLOGICAL
IMMUNE
DESCRIBE
MULTIPLE
OBSERVATIONS
DEVELOPMENT
EPIDEMIOLOGICAL
GENESIS
DRAWN
MICROBIAL
SKIN
INFLAMMATION
ETIOLOGY
CREATION
CANCERS
TERM
SYSTEM
TISSUE
ARISE
MECHANISM
CAUSED
EPIDEMIOLOGICAL
PATHOLOGICAL
TERM
LINK
MALIGNANCY
DESCRIBE
REQUIRES
IMMUNOSUPPRESSION
SKIN
DISEASE
DYSFUNCTION
RECURRENT
INFECTION
PROCESSES
IDENTIFIED
CHRONIC
PATHOS
ORIGIN
BREAKDOWN
MALIGNANCY
DYSFUNCTION
MICROBIAL
IMMUNOSUPPRESSION

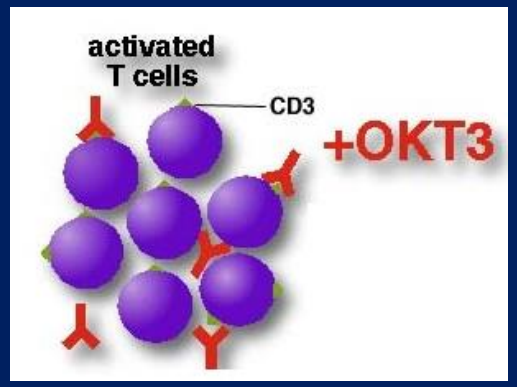
PATHOGENESIS

- Sun exposure
- Extent and duration of immunosuppression
- Concomitant viral infection
- Pre-transplantation dialysis
- Malignancy has been transplanted from the donor.

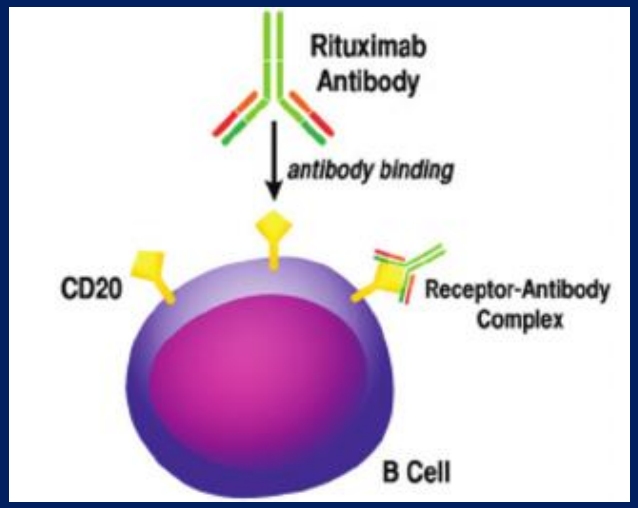


Type, extent, and duration of immunosuppressive therapy

Antibody therapy



Thymoglobulin®
Anti-thymocyte Globulin (Rabbit)



Antibody therapy directed against T lymphocytes (as with OKT3 or antilymphocyte serum) specifically predisposes to PTLD induced by EBV.

- Antibody therapy targeting B lymphocytes (as with rituximab) may reduce the incidence of lymphoproliferative disorders.

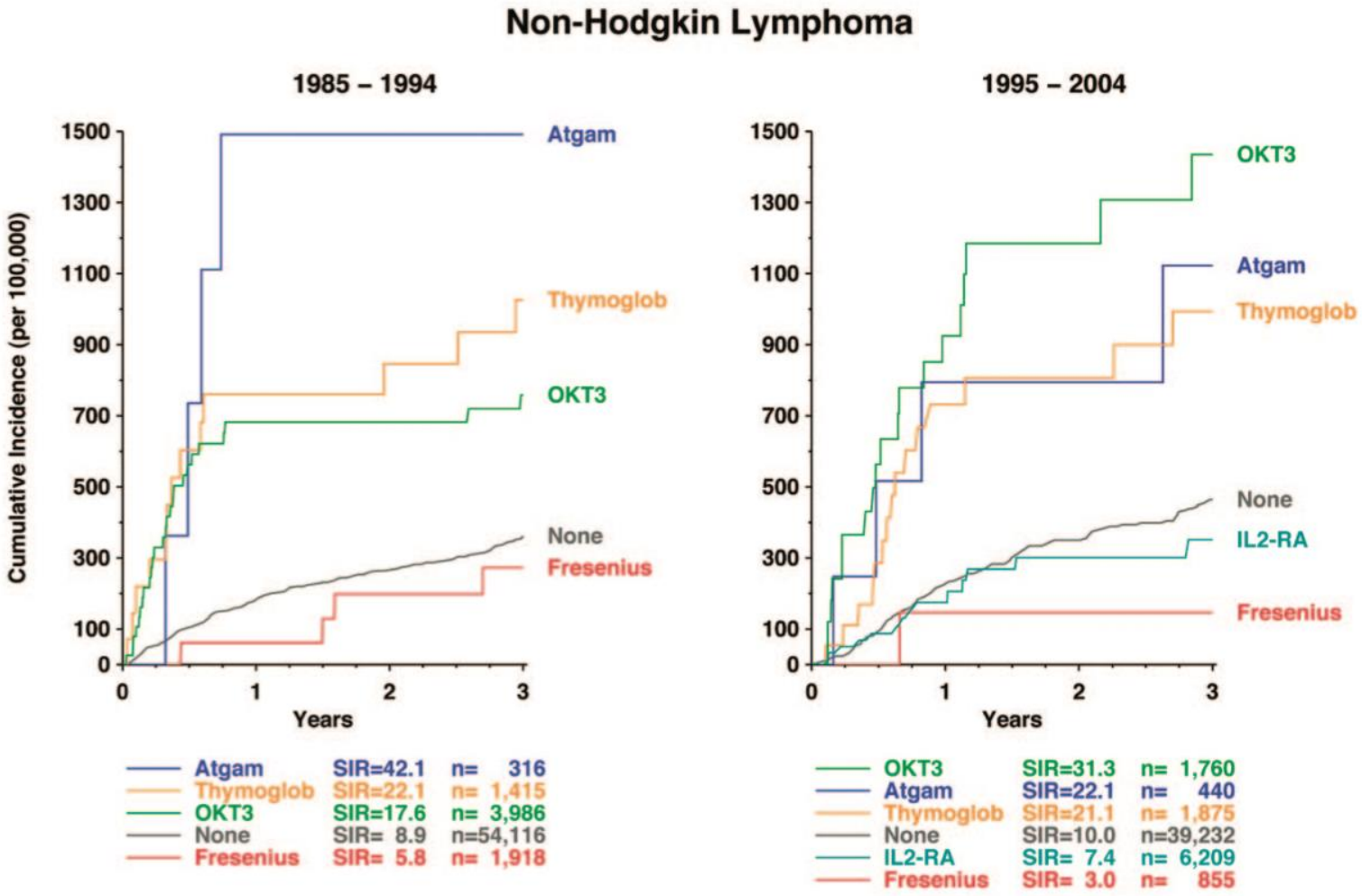
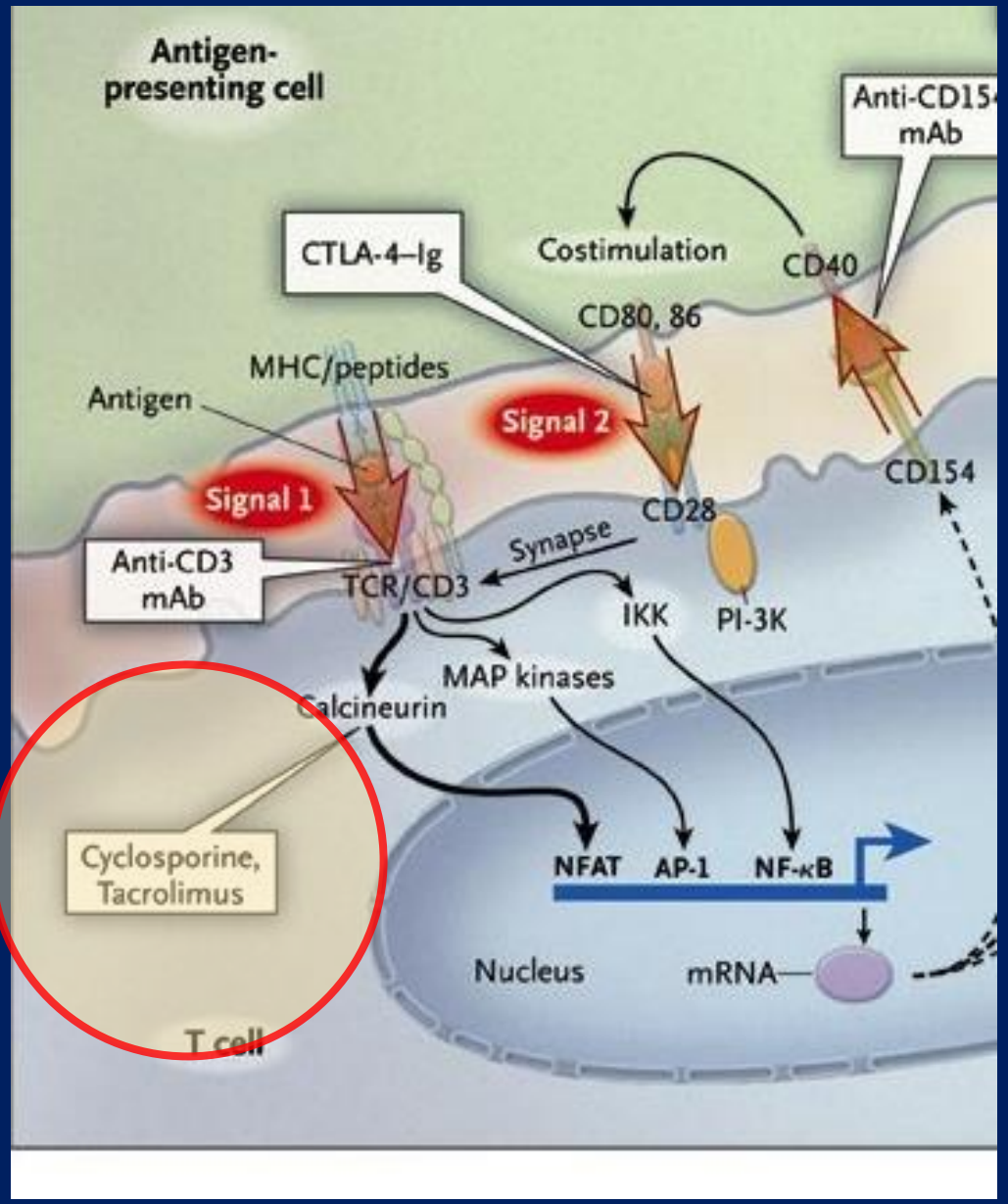


FIGURE 4. Cumulative incidence of non-Hodgkin lymphoma (NHL) after renal transplantation from a deceased donor according to type of induction therapy for patients receiving a transplant during 1985 to 1994 and 1995 to 2004. Standardized incidence ratio (SIR) values compare the observed risk of lymphoma versus the estimated risk in the nontransplant control population

Calcineurin inhibitors



Calcineurin inhibitors

- There is a dose-dependent relationship between calcineurin inhibitors and secondary malignancies.

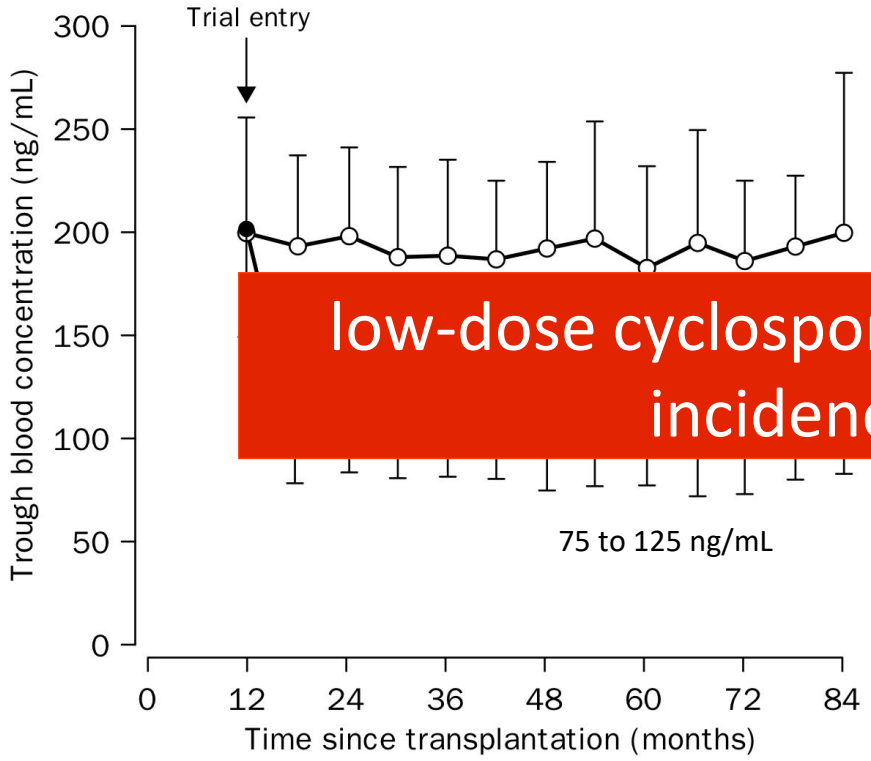


Figure 2: **Cyclosporin dose and trough blood concentrations**
Bars=SD.

low-dose cyclosporine regimen had a significantly lower incidence of all secondary cancers

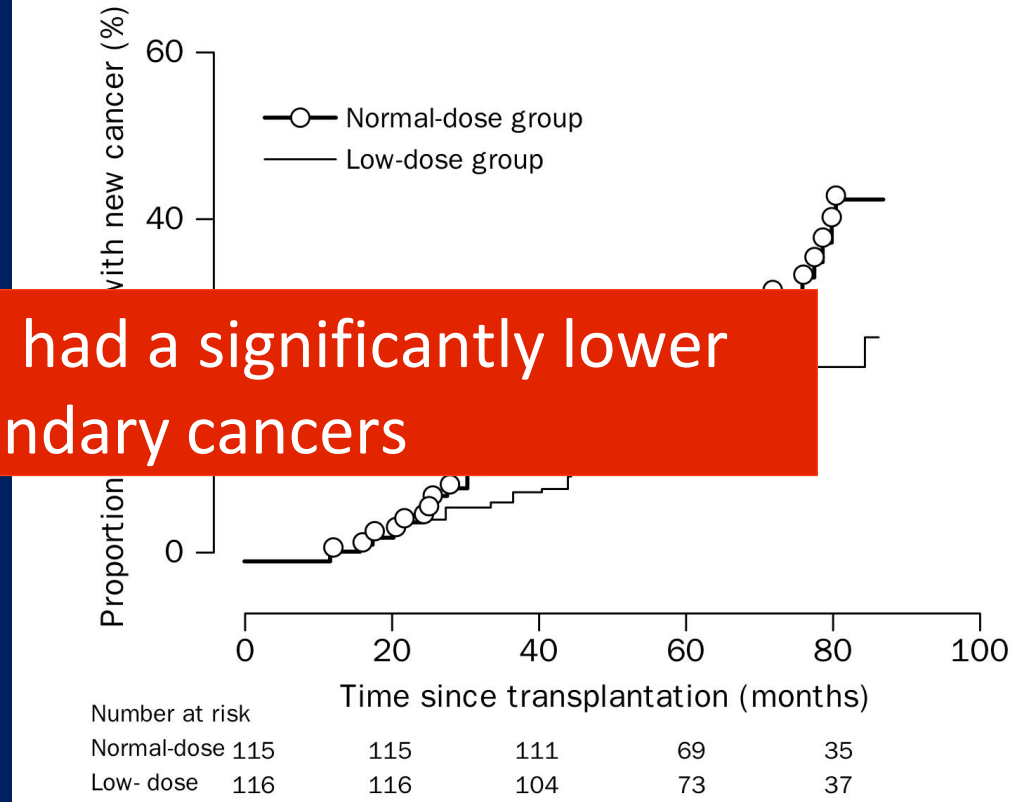


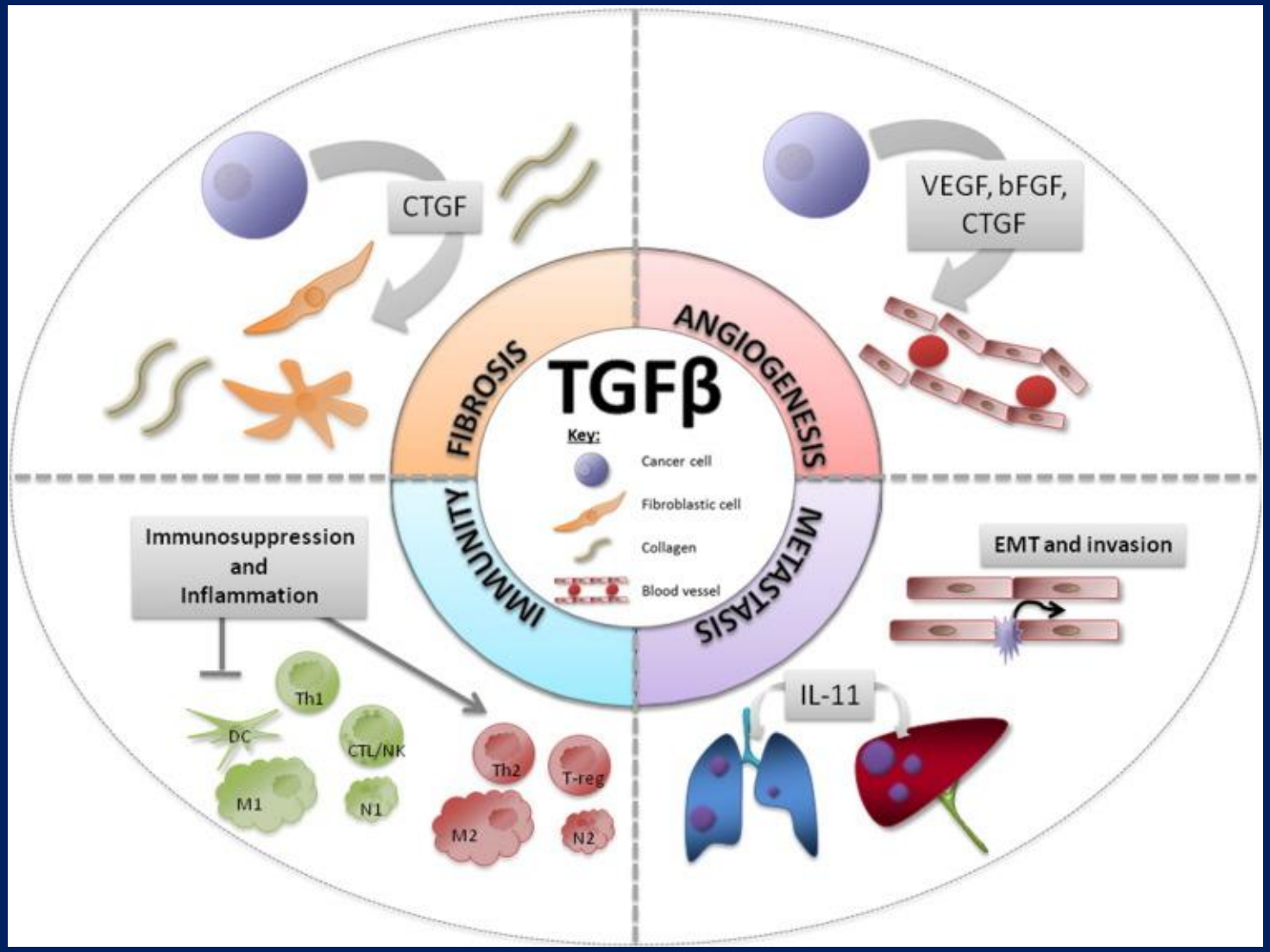
Figure 4: **Frequency of cancer**

Dantal. 1998. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyc

Cyclosporine

- May promote cancer progression, principally via the production of TGF-beta.

- Both the in vitro and in vivo changes were prevented by the administration of anti-TGF-beta antibodies.



Risk Factors for Malignancy in Japanese Renal Transplant Recipients

TABLE 3
Multivariate Analysis: Risk Factors for Malignancies

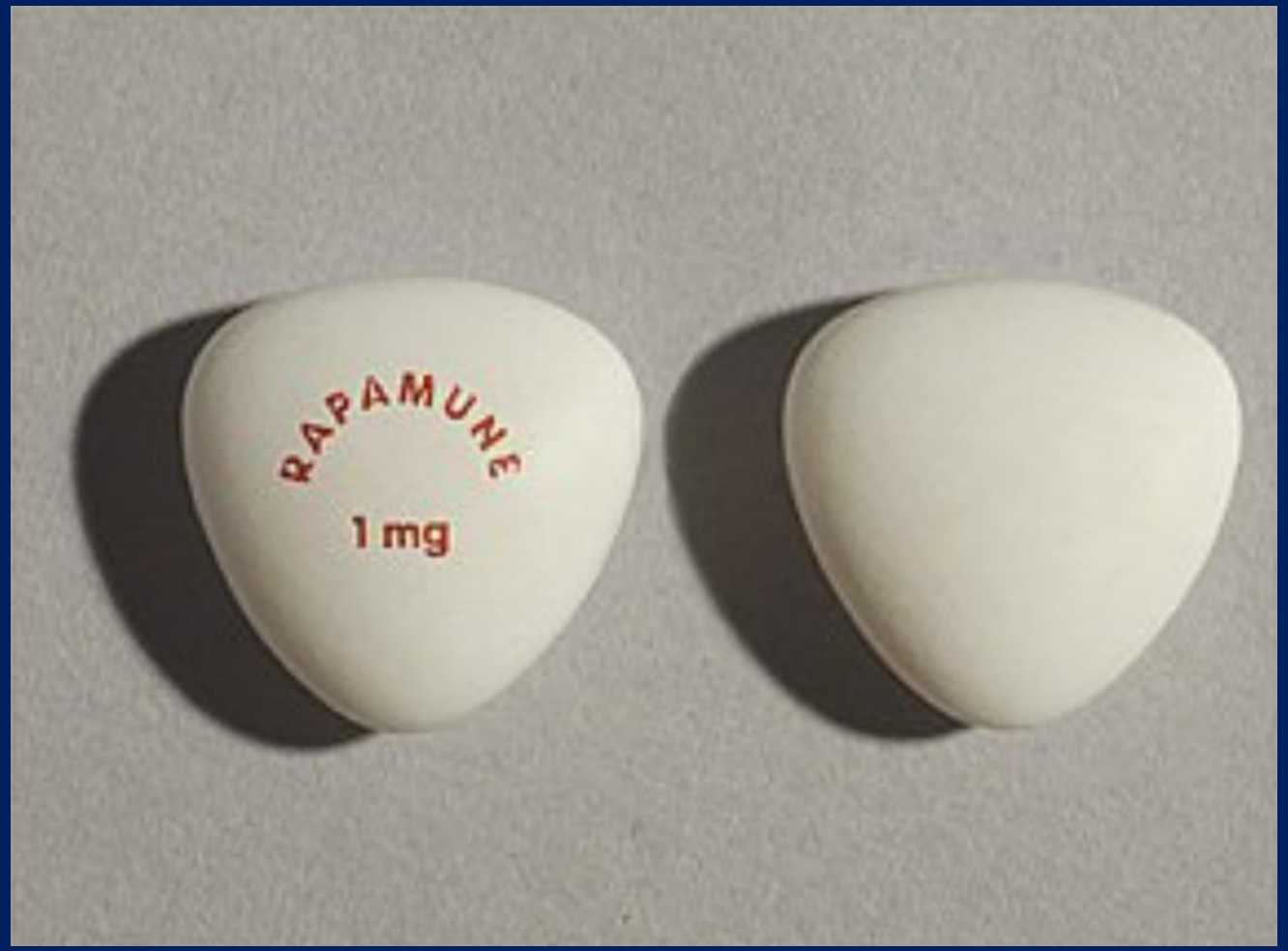
Tacrolimus increases the risk of malignancy following kidney transplantation

Sex (women vs men)	0.983–5.196	2.260	.0549
Age (per 10 y older)	1.089–2.240	1.562	.0155
Dialysis before transplantation (<2 y vs ≥2 y)	0.170–1.007	0.413	.0519
Tacrolimus	1.647–11.627	4.376	.0031
Mycophenolate mofetil	0.771–11.078	2.922	.1148

CI indicates confidence interval.

Imao T, Ichimaru N, Takahara S, et al. Risk factors for malignancy in Japanese renal transplant recipients. Cancer 2007; 109:2109.

Sirolimus



Sirolimus

- Some data suggest that sirolimus suppresses the growth and proliferation of tumors in various animal models.

Possible mechanisms of actions includes inhibition of:

- p70 S6K (thereby decreasing cell proliferation)
- interleukin-10 (IL-10, decreasing tumor cell Jak/STATs activity)
- Cyclins (blocking cell cycle activity)
- Lymphangiogenesis (impaired signaling of VEGF A and C)

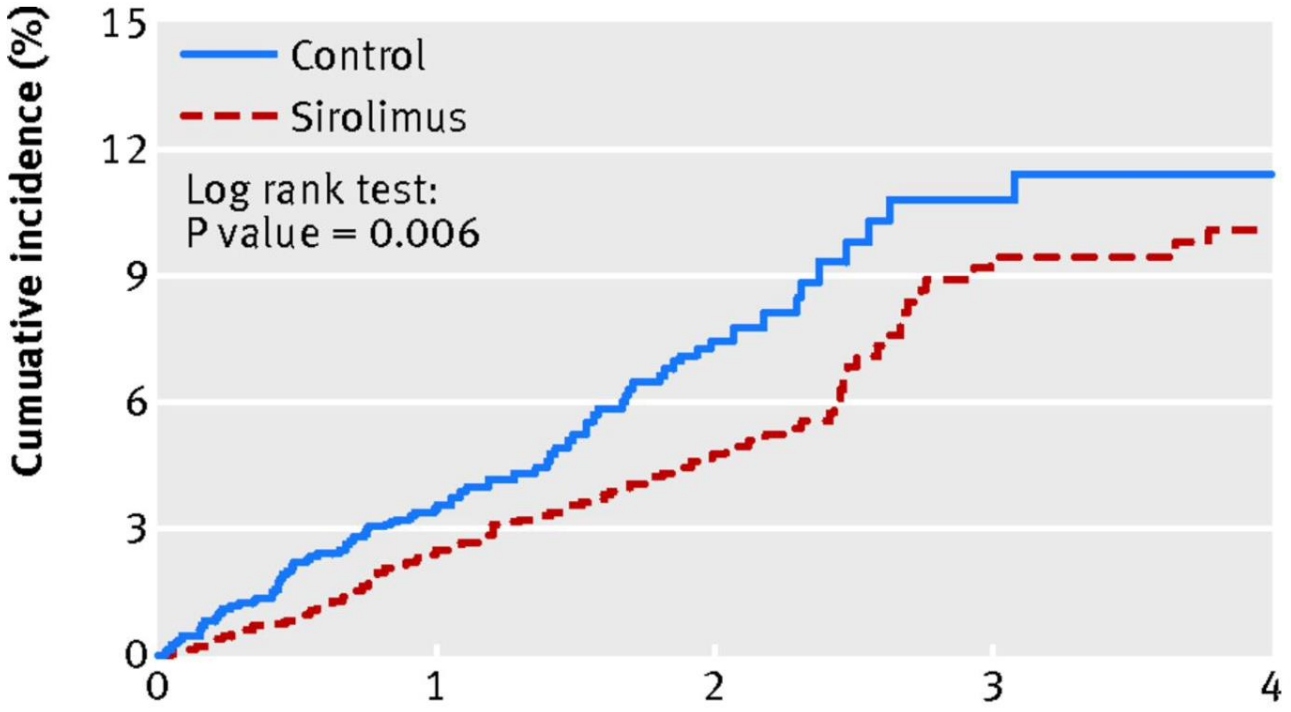
BMJ 2014;349:g6679 doi: 10.1136/bmj.g6679 (Published 24 November 2014)

RESEARCH

Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data

Greg A Knoll *nephrologist*[1 2], Madzouka B Kokolo *research coordinator*[1], Ranjeeta Mallick *statistician*[1], Andrew Beck *research assistant*[1], Chieny D Buenaventura *research assistant*[1], Robin Ducharme *methodologist*[1 2], Rashad Barsoum *professor*[3], Corrado Bernasconi *medical director*[4], Tom D Blydt-Hansen *nephrologist*[5], Henrik Ekberg *professor*[6], Claudia R Felipe *transplant coordinator*[7], John Firth *consultant nephrologist*[8], Lorenzo Gallon *professor of medicine*[9], Marielle Gelens *nephrologist*[10], Denis Glotz *nephrologist*[11], Jan Gossmann *nephrologist*[12], Markus Guba *professor of surgery*[13], Ahmed Ali Morsy *professor of urology*[14], Rebekka Salgo *consultant dermatologist*[15], Earnst H Scheuermann *nephrologist*[12], Helio Tedesco-Silva *nephrologist*[7], Stefan Vitko *nephrologists*[16], Christopher Watson *professor of transplantation*[17], Dean A Fergusson *epidemiologist*[1 2]

Fig 2 Time to first malignancy in patients with kidney transplant according to immunosuppressive treatment group.

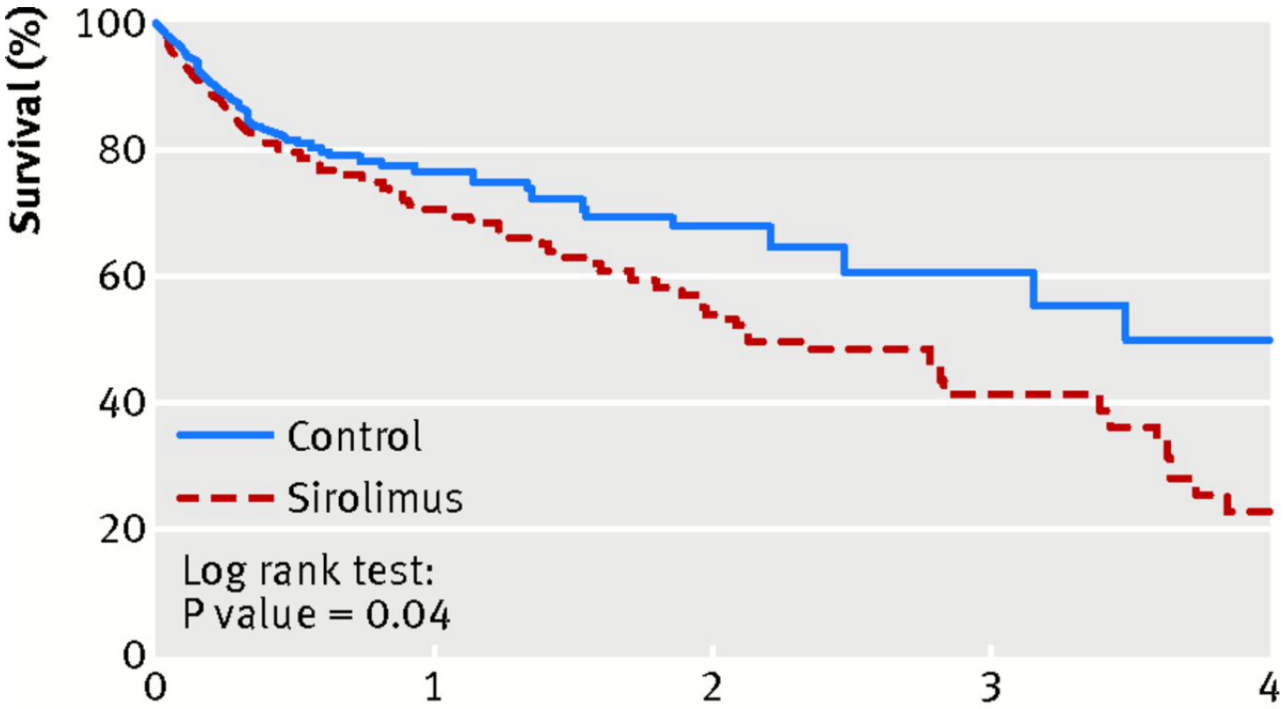


No at risk

Control				
	2600	1741	571	157
Sirolimus				
	3276	2318	1314	333

Greg A Knoll et al. BMJ 2014;349:bmj.g6679

Fig 4 Overall survival in patients with kidney transplant according to immunosuppressive treatment group.

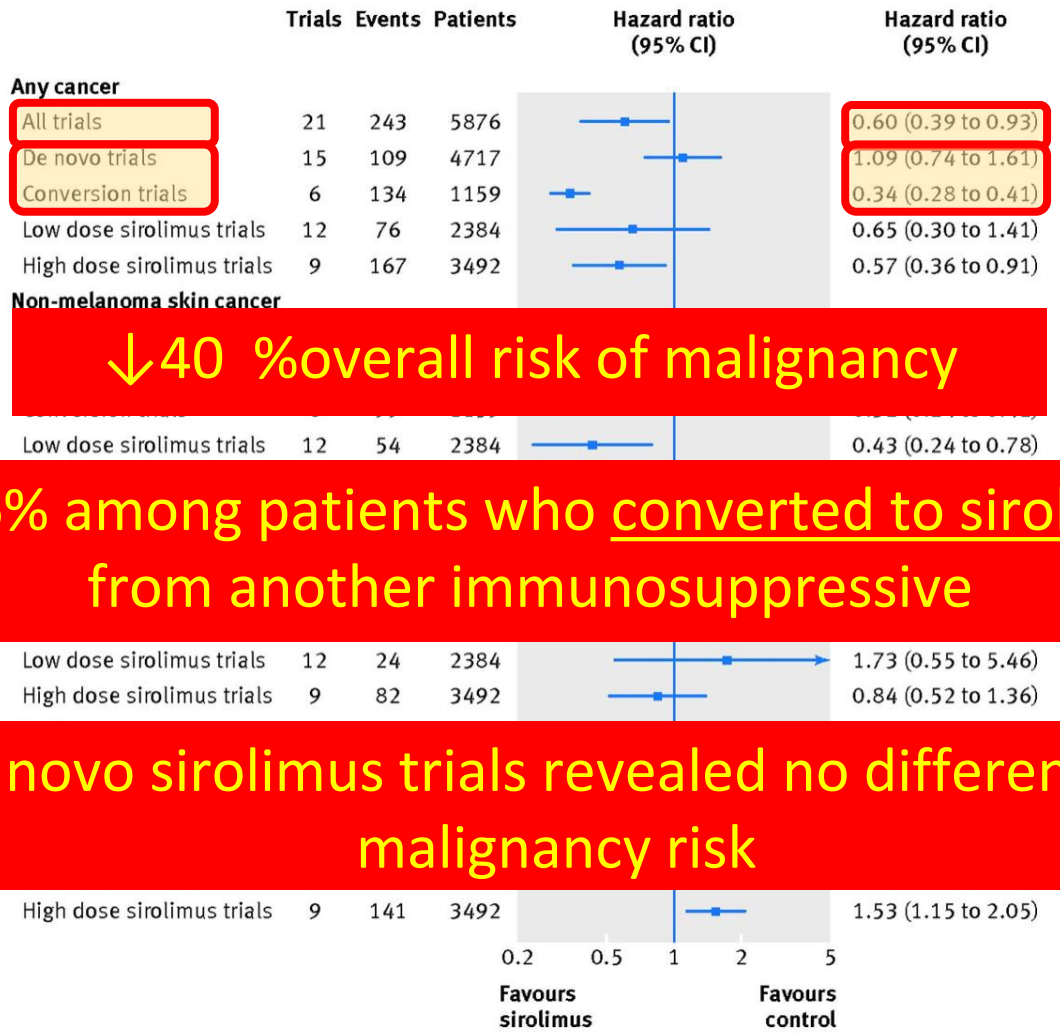


No at risk

Control				
	2600	1809	613	184
Sirolimus				
	3276	2375	1362	363

Greg A Knoll et al. BMJ 2014;349:bmj.g6679

Fig 5 Risk of cancer and death in patients with kidney transplant treated with sirolimus versus control.



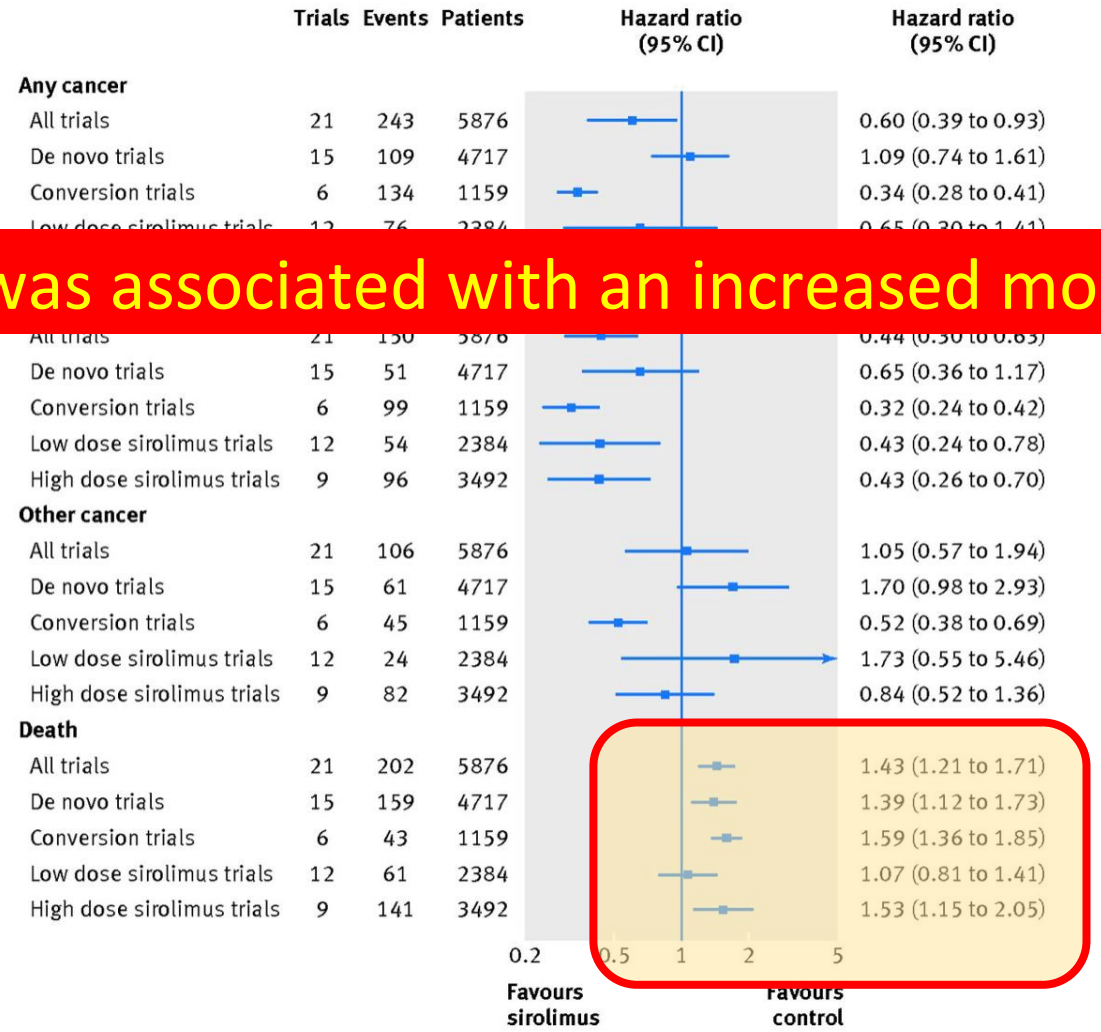
↓40 %overall risk of malignancy

↓ 66% among patients who converted to sirolimus from another immunosuppressive

De novo sirolimus trials revealed no difference in malignancy risk

Greg A Knoll et al. BMJ 2014;349:bmj.g6679

Fig 5 Risk of cancer and death in patients with kidney transplant treated with sirolimus versus control.



sirolimus was associated with an increased mortality risk

Greg A Knoll et al. BMJ 2014;349:bmj.g6679

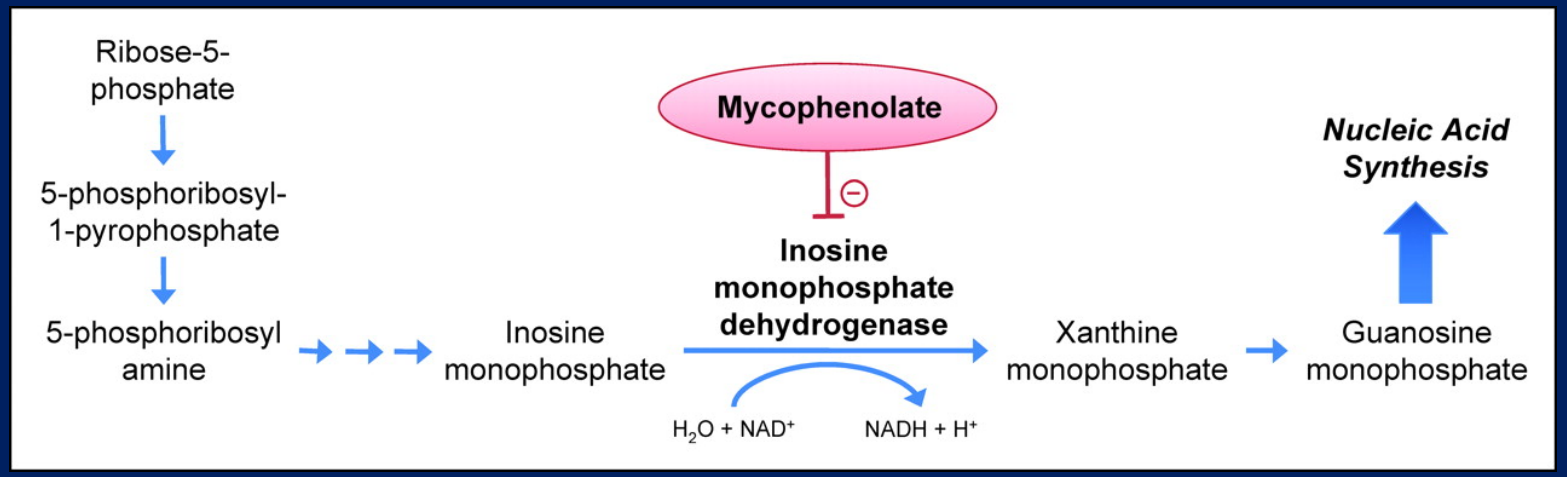
Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data

Conclusions Sirolimus was associated with a reduction in the risk of malignancy and non-melanoma skin cancer in transplant recipients. The benefit was most pronounced in patients who converted from an established immunosuppressive regimen to sirolimus. Given the risk of mortality, however, the use of this drug does not seem warranted for most patients with kidney transplant. Further research is needed to determine if different populations, such as those at high risk of cancer, might benefit from sirolimus.

Kaposi sarcoma

- The substitution of sirolimus for cyclosporine in renal transplant recipients has been associated with complete regression of Kaposi sarcoma.

Mycophenolate mofetil



Some malignancies, including some solid tumors, have dramatic elevations of this enzyme, suggesting that this agent may have some antiproliferative activity .

American Journal of Transplantation 2005; 5: 2954–2960
Blackwell Munksgaard

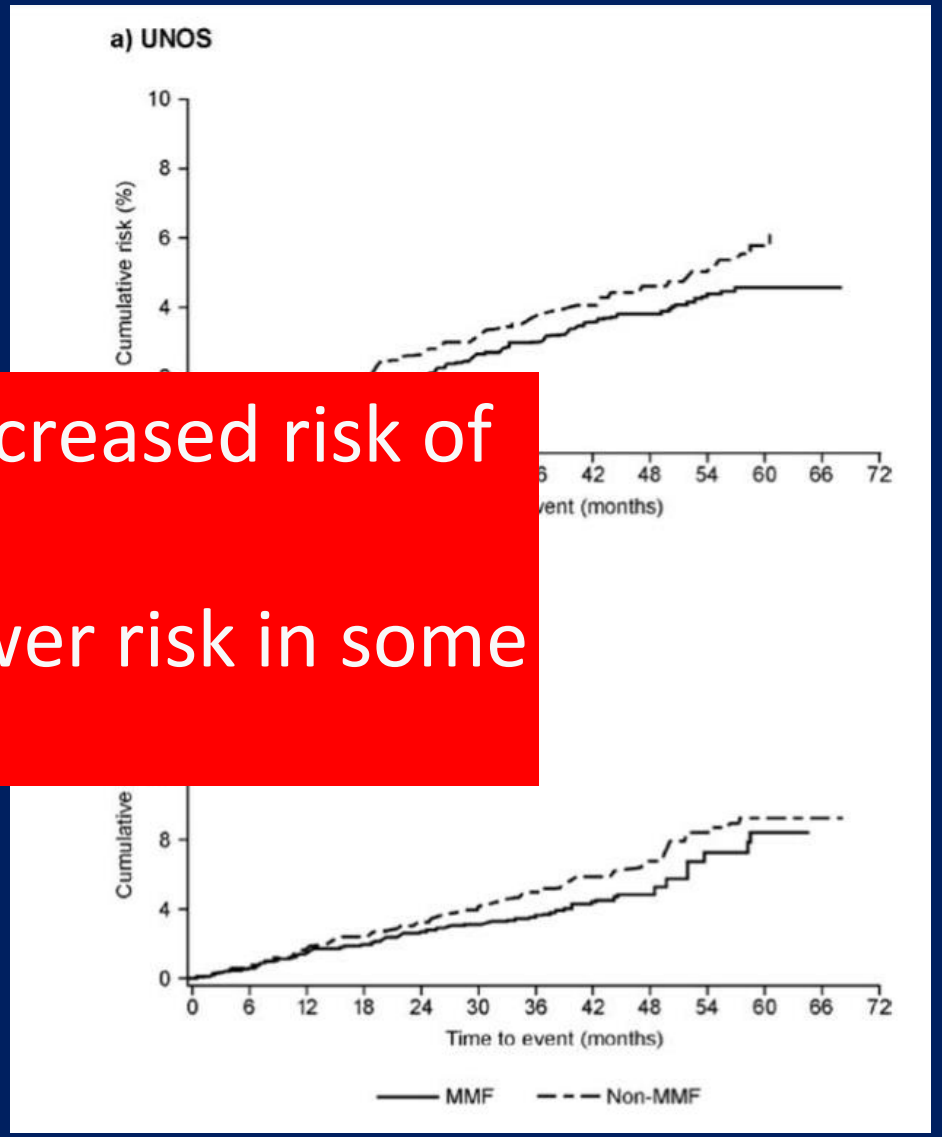
doi: 10.1111/j.1600-6143.2005.01125.x

Prospective Registry-Based Observational Cohort Study of the Long-Term Risk of Malignancies in Renal Transplant Patients Treated with Mycophenolate Mofetil

R. Robson[a,*], J.M.
and S. Sacks[e]

MMF is not associated with an increased risk of malignancies.
May even be associated with a lower risk in some populations.

- Tim
  development of any
  malignancy



Robson R, Prospective registry-based observational cohort study of the long-term risk of malignancies in renal transplant patients treated with mycophenolate mofetil. American journal of transplantation : 2005, 5(12):2954-2960.

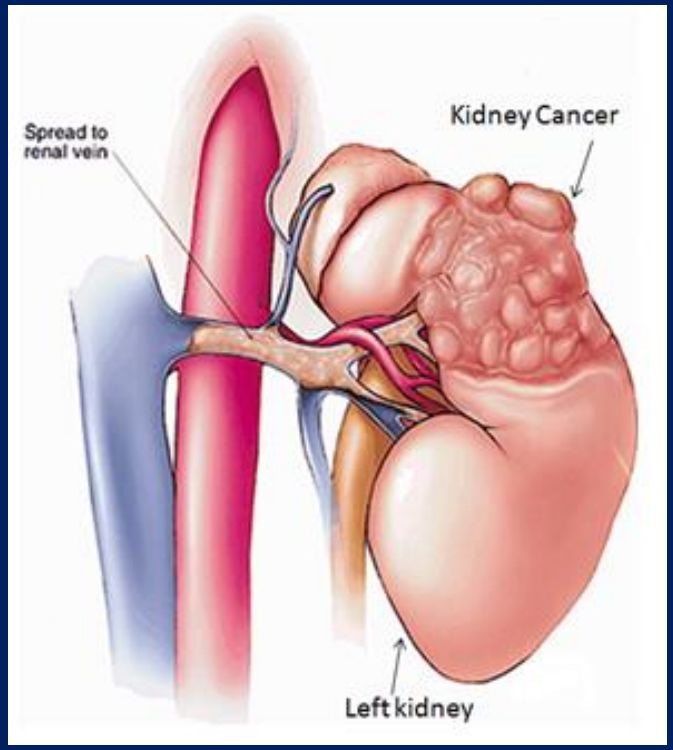
Mycophenolate mofetil

- A principal mechanism of a lower malignancy risk with MMF, to the degree that it occurs, may be due to the decreased incidence of acute rejection.

- This results in a reduced need for increased doses of immunosuppressive agents.

Renal tumors in kidney transplant recipients

↑ risk of carcinoma of the native kidneys (×100)

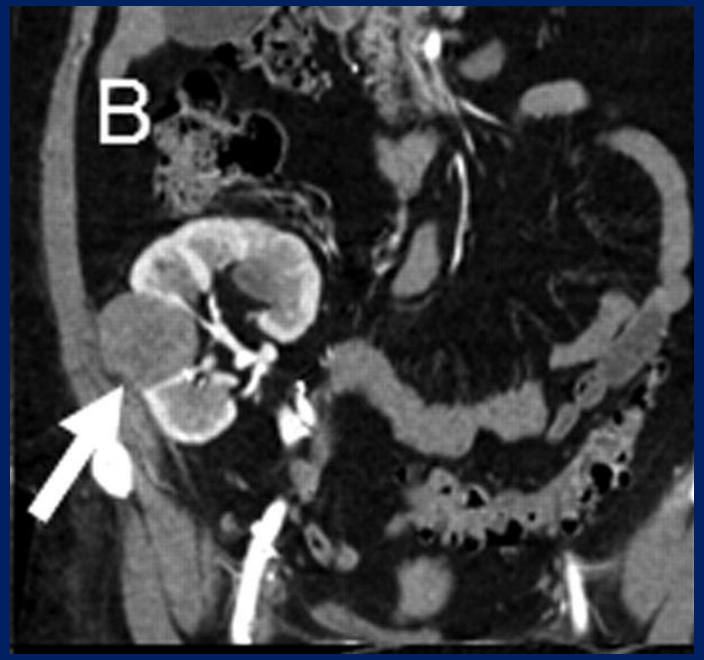


- Particularly if they have undergone prolonged periods of dialysis.

Transplanted kidneys tumors

- Renal tumors are **rare** in transplanted kidneys.

A retrospective, multicenter study identified **20 patients** with histologically confirmed tumors in a survey of **11 European centers** .



Cornelis F, Buy X, André M, et al. De novo renal tumors arising in kidney transplants: midterm outcome after percutaneous thermal ablation. Radiology 2011; 260:900.

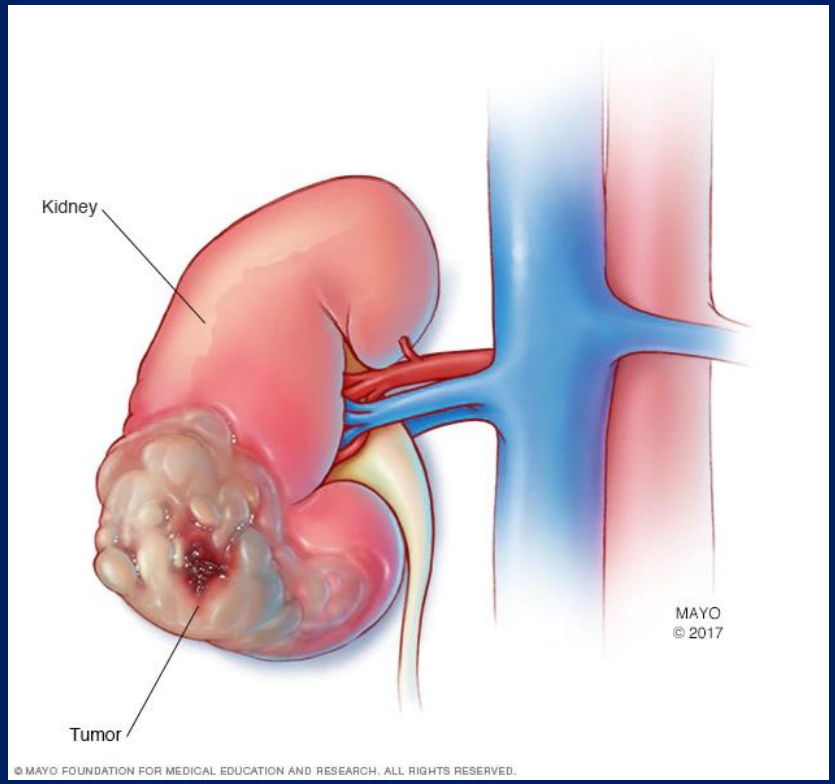
CANCER SCREENING

Suggested guidelines for cancer screening in patients undergoing solid organ transplantation

Cancer type	Recommendation
Breast	Women 50 to 69 years: annual screening mammography with or without clinical breast examination; age 40 to 49 years: the benefit of screening is less certain and should be left to the decision of the clinician and patient; ≥70 years of age: annual screening is appropriate as long as estimated life exectancy is ≥8 years.
Skin	Monthly self-examination; clinician examination annually, with early referral for suspected lesions.
Cervical	All women ≥18 years old and sexually active girls <18 years old should undergo an annual pelvic examination and Pap smear.
Anogenital	Yearly physical examination of the anogenital area, including pelvic examination and cytologic studies for women. Insufficient evidence to recommend for or against screening anoscopy and biopsies of anal epithelium.

Renal carcinoma

All transplant patients should, at minimum, undergo ultrasonography of the native kidneys once a year.



Patients with ACKD according to bosniak:

- I or II cysts: renal ultrasonography twice a year and CT scan for progressive lesions.
- IIF cysts: four times per year and yearly CT scan or magnetic resonance imaging (MRI).
- Nephrectomy and CT scan for progressive lesions should be performed if progression is observed, even if category III and IV cysts are not reached.
- III or IV cysts should undergo nephrectomy.

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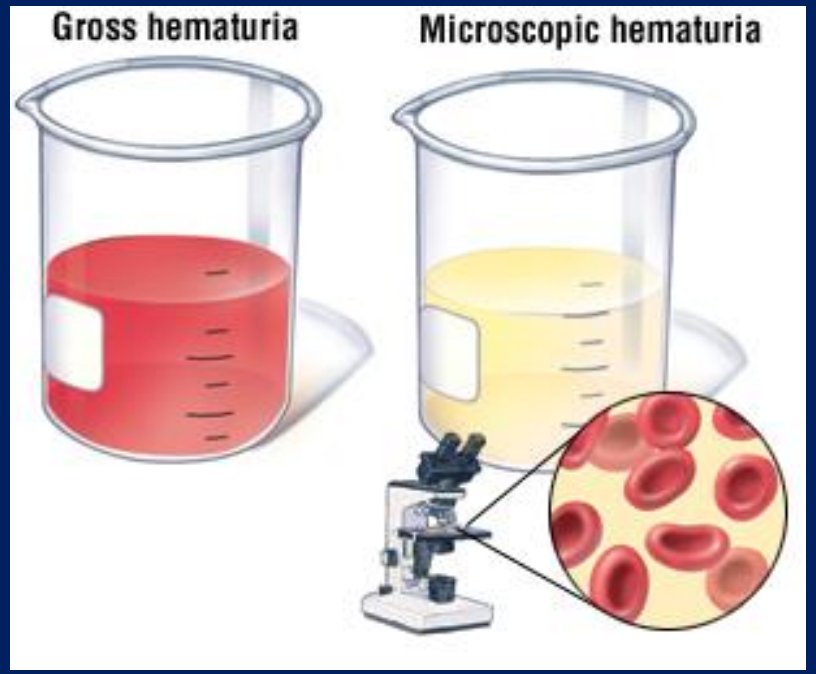
Hematuria

Monitor for hematuria using urinalysis (q 3-6 months).

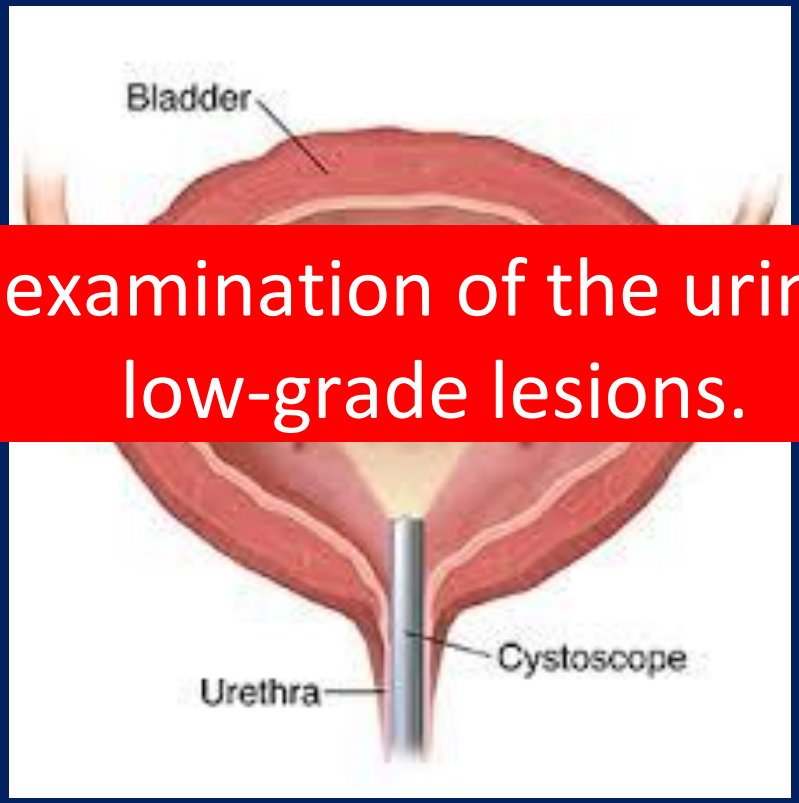
If positive

- Urine culture
- Morning urine cytology (×3)
- KUB ultrasonography
- Urine for BK PCR
- PSA



Cyclophosphamide

Patients with nonglomerular hematuria should undergo cystoscopy.



Cytologic examination of the urine may miss low-grade lesions.

Gynecologic malignancies

- Gynecologic examinations should be performed annually.

- This is more frequent screening than is generally recommended for the general population since immunosuppression can reactivate viral infection such as human papillomavirus (HPV).

PREVENTION AND TREATMENT

Reduction of immunosuppressive therapy

Reduction or cessation of immunosuppressive therapy is useful since loss of the graft to rejection is not a fatal event in these patients.

Such measures may result in tumor regression in some cases of:

- Lymphoma
- Some skin cancers
- Kaposi sarcoma
- Donor-derived malignancies

Wolters Kluwer UpToDate®

Our first approach in serious malignancy is to discontinue the antimetabolite.

Pred. + CNI + ~~MMF~~ → Pred. + ~~CNI~~ → Pred. + Sirolimus

Because rejection is less likely to occur with double therapy with a calcineurin inhibitor and prednisone than the combination of an antimetabolite with prednisone.

Some clinicians would substitute sirolimus for the CNI and antimetabolite.

Kaposi sarcoma

Converting to sirolimus from a CNI

Nonmelanoma skin cancer

The use of sirolimus for transplant recipients with nonmelanoma skin cancer may not be justified, given the overall increase in associated mortality.

Sharif A: Sirolimus after kidney transplantation. BMJ 2014, 349:g6808.

TRANSPLANTATION IN PATIENTS WITH PRE-EXISTING MALIGNANCY

Waiting period	
No waiting period	• Incidentally discovered RCC • In situ carcinoma • Skin BCC • Low-grade bladder cancer
5 years	• Melanoma (some recommend 10 years [102]) • Breast • Colorectal cancer
2 years	• Most other tumors

Malignancy in renal transplantation. J Am Soc Nephrol 2004, 15(6):1582-1588.

Take home messages

- There is a dose-dependent relationship between CNI and malignancies.
- Sirolimus reduced malignancy risk among patients who converted to sirolimus from another immunosuppressive but not in De novo sirolimus trials.
- All transplant patients should, at minimum, undyergo ultrasonography of the native kidneys once a year.
- Patients with nonglomerular hematuria and hx of cyclophosphamide should undergo cystoscopy.
- Reduction or cessation of immunosuppressive therapy is useful since loss of the graft to rejection is not a fatal event in these patients.