# Management and diagnosis of malignancies after transplantation

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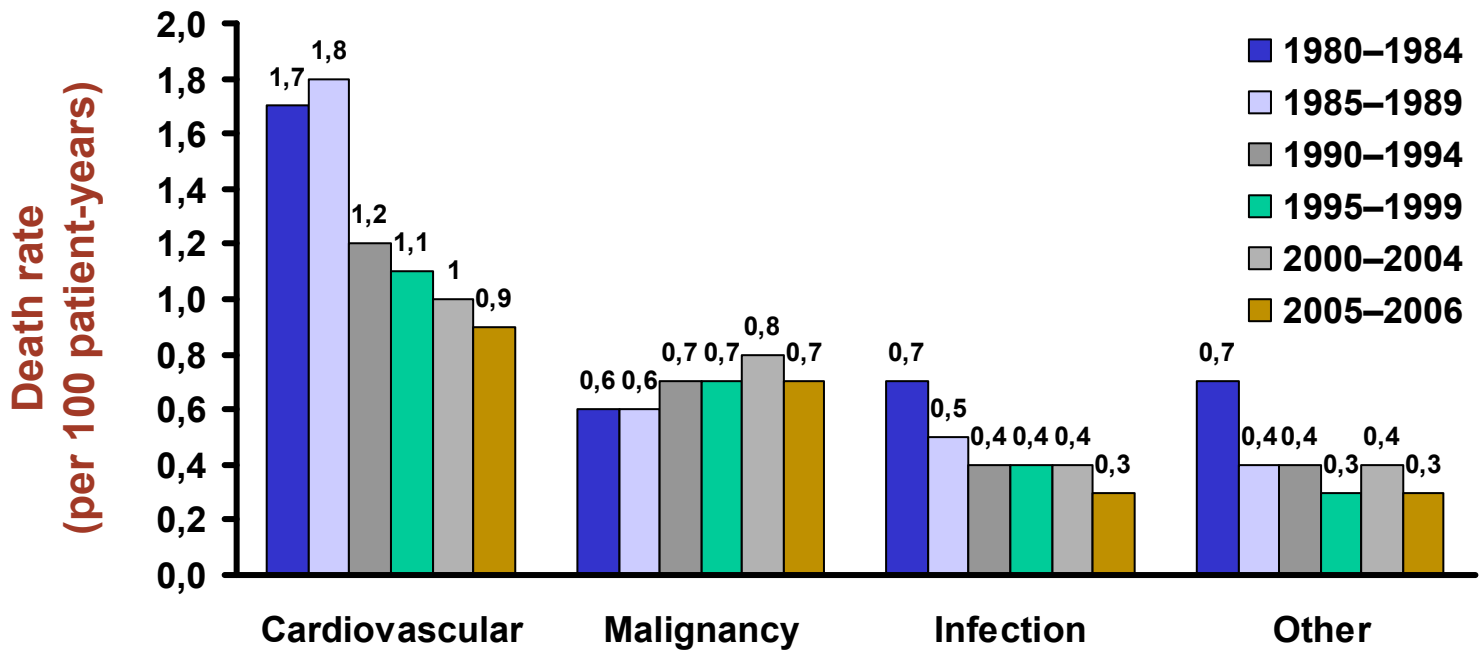
# CVD is a leading cause of death with a functioning graft; malignancy second

**Retrospective analysis of ANZDATA between 1980 and 2007**




CVD, cardiovascular disease

Pilmore HL *et al. Transplantation* 2010;89:851–7

# The negative impact of post transplant cancer

- 2nd most common cause of death with a functioning graft
  - AJT 2008; 8:2410-9.
- Survival with cancer is extremely poor
  - < 10% survival / 5 y
  - CJASN 2008; 3:S87-100

# Monitoring cancer after transplantation

**Epidemiology of post transplant cancer**

Risk factors for developing post transplant cancer

Screening for cancer

Prevention and treatment of cancer

mTORi, mammalian target of rapamycin inhibitor

# Relative tumor risk after renal transplantation

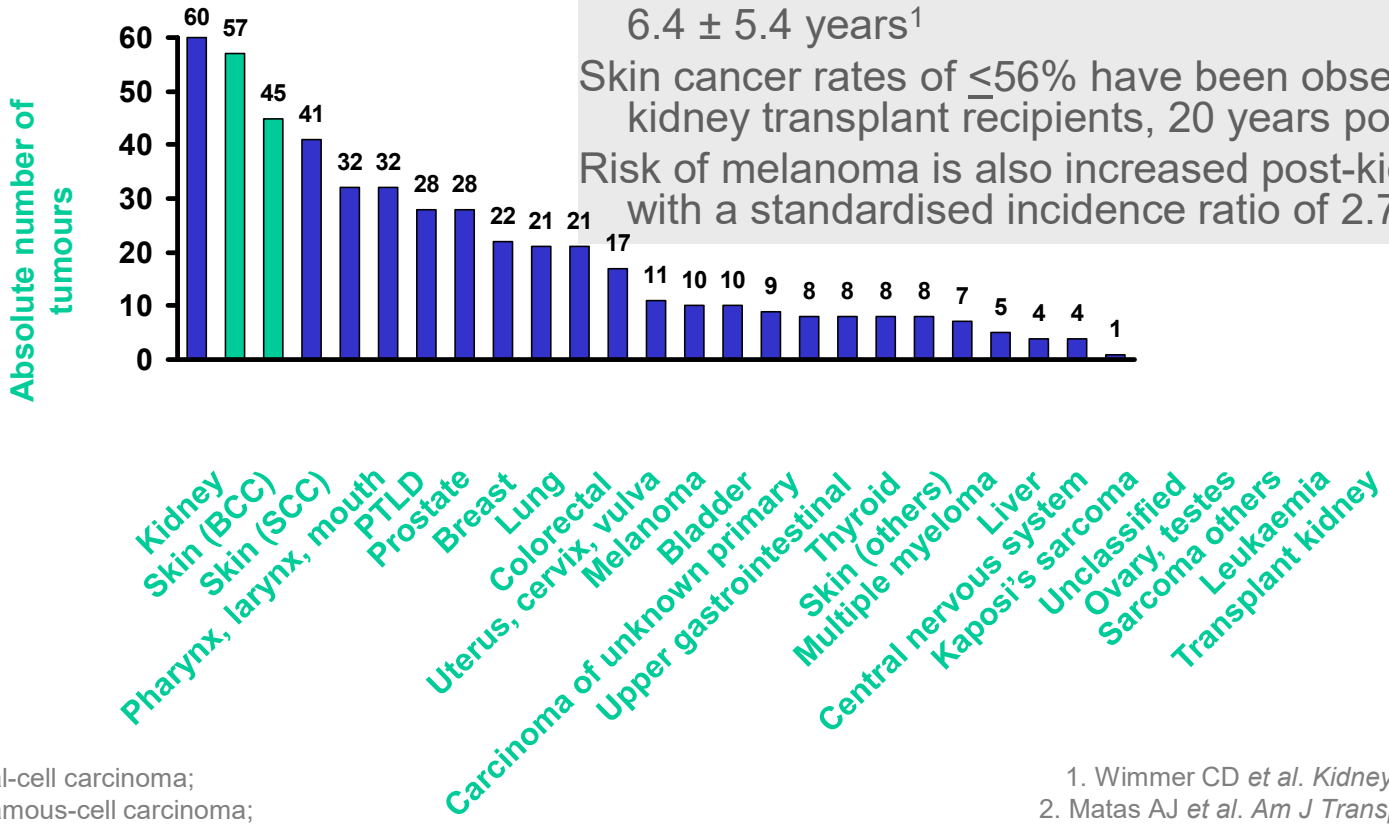
All malignancy
RR = 4.3

| Cancer risk | Cancer site | RR |
|---|---|---|
| Small (RR > 2) | **Lung** | **2.67** |
| | **Bladder, urothel.** | **2.81** |
| | **Sarcoma** | **3.38** |
| | **Liver** | **3.96** |
| | **CNS** | **3.99** |
| | **Melanoma** | **4.13** |
| | **Cervix, vulva,vagina** | **4.42** |
| Intermediate (RR > 5) | **Thyroid** | **5.09** |
| | **Multiple myeloma** | **7.33** |
| | **PTLD (vs. NHL)** | **8.50** |
| | **Farynx, larynx** | **12.85** |
| High (RR > 15) | **Kidney** | **17.60** |
| | **Skin (non-melanotic)** | **52.70** |
| | **Kaposi sarcoma** | **142.32** |

Adapted from Wimmer CD *et al*, *Kidney Int* 2007; 71: 1271

# Skin cancer is common after kidney transplantation

**Absolute numbers of tumours detected in 2419 renal transplant recipients in Munich, Germany[1]**




Mean time from transplantation to malignancy diagnosis was 6.4 ± 5.4 years[1]

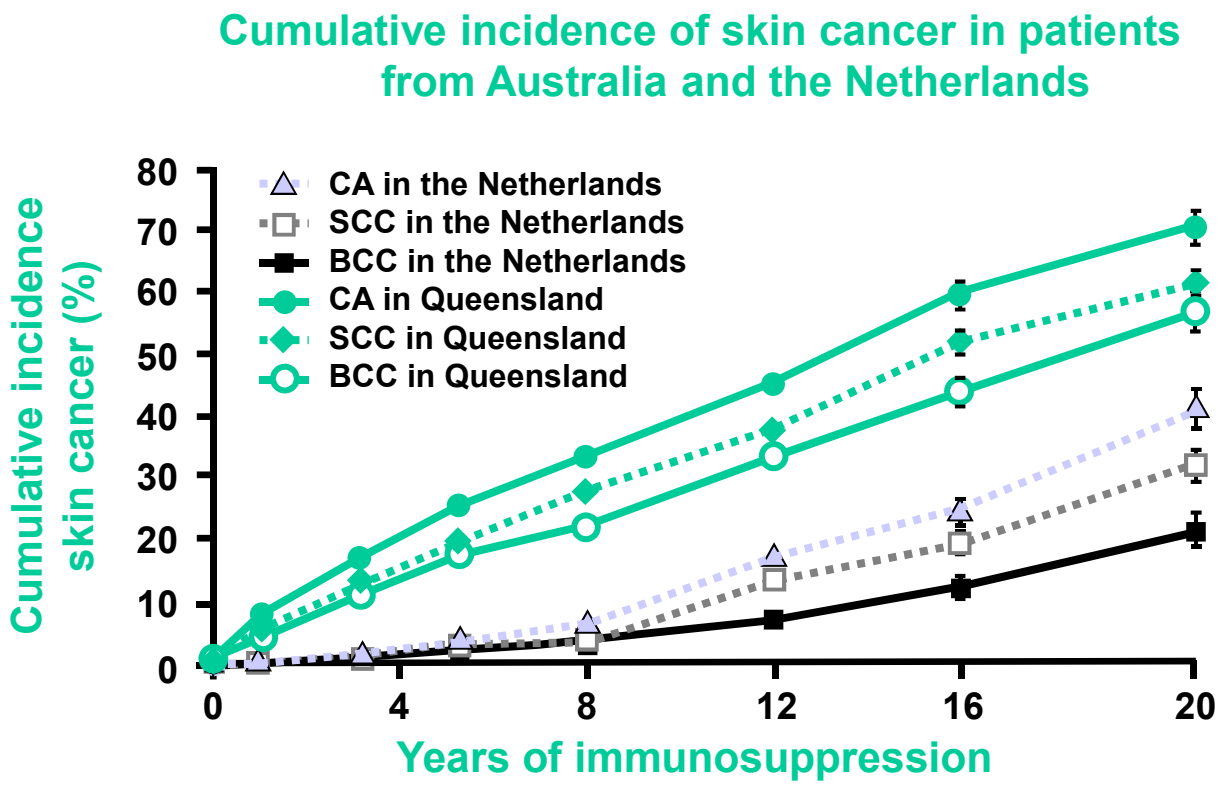
Skin cancer rates of ≤56% have been observed in kidney transplant recipients, 20 years post-transplant[2]

Risk of melanoma is also increased post-kidney transplant, with a standardised incidence ratio of 2.74[3]

BCC, basal-cell carcinoma;
SCC, squamous-cell carcinoma;
PTLD, post-transplant lymphoproliferative disease


1. Wimmer CD *et al*. *Kidney Int* 2007;71:1271–8;
2. Matas AJ *et al*. *Am J Transplant* 2008;8:2410–9;
3. van Leeuwen MT *et al*. *BMJ* 2010;340:c750

# Incidence of skin cancer increases over time




**Cumulative incidence of NMSCs ranges from**

- **2–14% after 5 years**
- **7–33% after 10 years**

NMSC, non-melanomatous skin cancer; CA, all skin cancer; SCC, squamous-cell carcinoma; BCC, basal-cell carcinoma

de Fijter JW. *Nephrol Dial Transplant* 2007;22(Suppl 1):i23–6

# Incidence ratios of various cancers

Table 1 | **Standardized incidence ratios from registry and multicentre studies for various cancers**

| Region (years; number of patients) | Standardized incidence ratios (95% CI) | | | | | | | | | | | Refs |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All cancers | Breast cancer | Cervical cancer | Colorectal cancer | Kidney cancer | Lip cancer | Lung cancer | Malignant melanoma | NHL | NMSC | Prostate cancer | |
| Canada[a] (1981–1998; 11,391) | 2.5 (2.3–2.7) | 1.3 (1.0–1.7)[b] | 1.6 (0.6–3.4) | 1.4 (1.0–1.8) | 7.3 (5.7–9.2) | 31.3 (23.5–40.8) | 2.1 (1.7–2.5) | 1.9 (1.2–3.0) | 8.8 (7.4–10.5) | NA | 0.9 (0.6–1.3) | 13 |
| USA[c] (NS; 113,038) | NA | 0.95 (0.86–1.0) | 1.1 (0.8–1.5) | 1.2 (1.1–1.3) | 6.4 (5.9–6.8) | 18 (15–22) | 1.6 (1.1–1.3) | 2.8 (2.5–3.2) | 5.9 (5.5–6.3) | NA | 0.92 (0.85–0.98) | 15 |
| Italy[d] (1997–2007; 7,217) | 1.7 (1.6–1.9)[e] | 0.8 (0.5–1.2)[b] | NA | 0.8 (0.5–1.2) | 4.9 (3.4–6.8) | 9.4 (3.1–22.0) | 1.1 (0.8–1.6) | 1.8 (0.9–3.3) | 4.5 (3.2–6.1) | NA | 1.7 (1.2–2.3) | 9 |
| Italy[f] (1980–2011; 3,537) | 1.5 (1.3–1.8)[g] | 1.2 (0.8–1.8) | 8.9 (4.4–17.7) | 1.2 (0.7–1.9)[h] | 7.0 (5.0–9.8) | NA | 1.1 (0.1–1.7) | 1.0 (0.4–3.0) | 7.9 (6.0–10.5) | 29.3 (26.0–33.1) | 1.3 (0.8–2.1) | 11 |
| Sweden[i] (1970–2008; 7,952) | 6.5 (6.3–6.8) | 1.2 (0.9–1.8) | 2.4 (1.2–4.4) | 2.3 (1.8–2.9)[h] | 6.2 (4.8–7.9) | 46 (35–59) | 1.7 (1.3–2.2) | 2.3 (1.7–3.1) | 4.8 (3.8–5.9) | 121 (116–127)[j] | 1.1 (0.9–1.3) | 6 |
| UK[k] (1980–2007; 25,104) | 2.4 (2.3–2.5)[e] | 1.0 (0.8–1.2) | 2.3 (1.4–3.5) | 1.8 (1.6–2.1) | 7.9 (6.7–9.3) | 65.5 (49.9–84.6) | 1.4 (1.2–1.6) | 2.6 (2.0–3.3) | 12.5 (11.2–13.8) | 16.6 (15.9–17.3) | 1.1 (0.9–1.4) | 4 |
| Australia and New Zealand[l] (1982–2003; 10,180) | 3.3 (3.1–3.5) | 1.0 (0.8–1.3) | 2.5 (1.3–4.3) | 2.4 (1.9–2.9)[h] | 5.0 (3.4–7.1) | 47.1 (41.8–52.9) | 2.5 (2.0–3.0) | 2.5 (2.1–3.1) | 9.9 (8.4–11.5) | NA | 1.0 (0.7–1.3) | 10,12 |

# Monitoring cancer after transplantation

Epidemiology of post transplant cancer

**Risk factors for developing post transplant cancer**

Screening for cancer

Prevention and treatment of cancer

mTORi, mammalian target of rapamycin inhibitor

# Risk factors associated with post-transplant malignancy

| Conventional | Transplant specific |
| --- | --- |
| Increasing age[1,2] | Immunosuppressive regimen, eg CsA[3] or tacrolimus[6] |
| Exposure to UV light[1] | Chronic viral infection[2] |
| Previous exposure to carcinogens[1] | Previous treatment with cytotoxic agents, e.g. cyclophosphamide[2] |
| Genetic predisposition[1,2] | Transmission of malignancy from donor[2] |
| History of malignancy[1] | Levels of immune system components, eg high regulatory T-cells[4] |
| Cigarette smoking[2] | MMP-26 and MMP-9 levels[5] |
| Analgesic abuse[2] | Time after transplant[6] |
| | Duration of haemodialysis[6] |
| | Race[6] |
| | Age at time of transplant[6] |

UV, ultraviolet; CsA, cyclosporin; MMP, matrix metalloproteinase

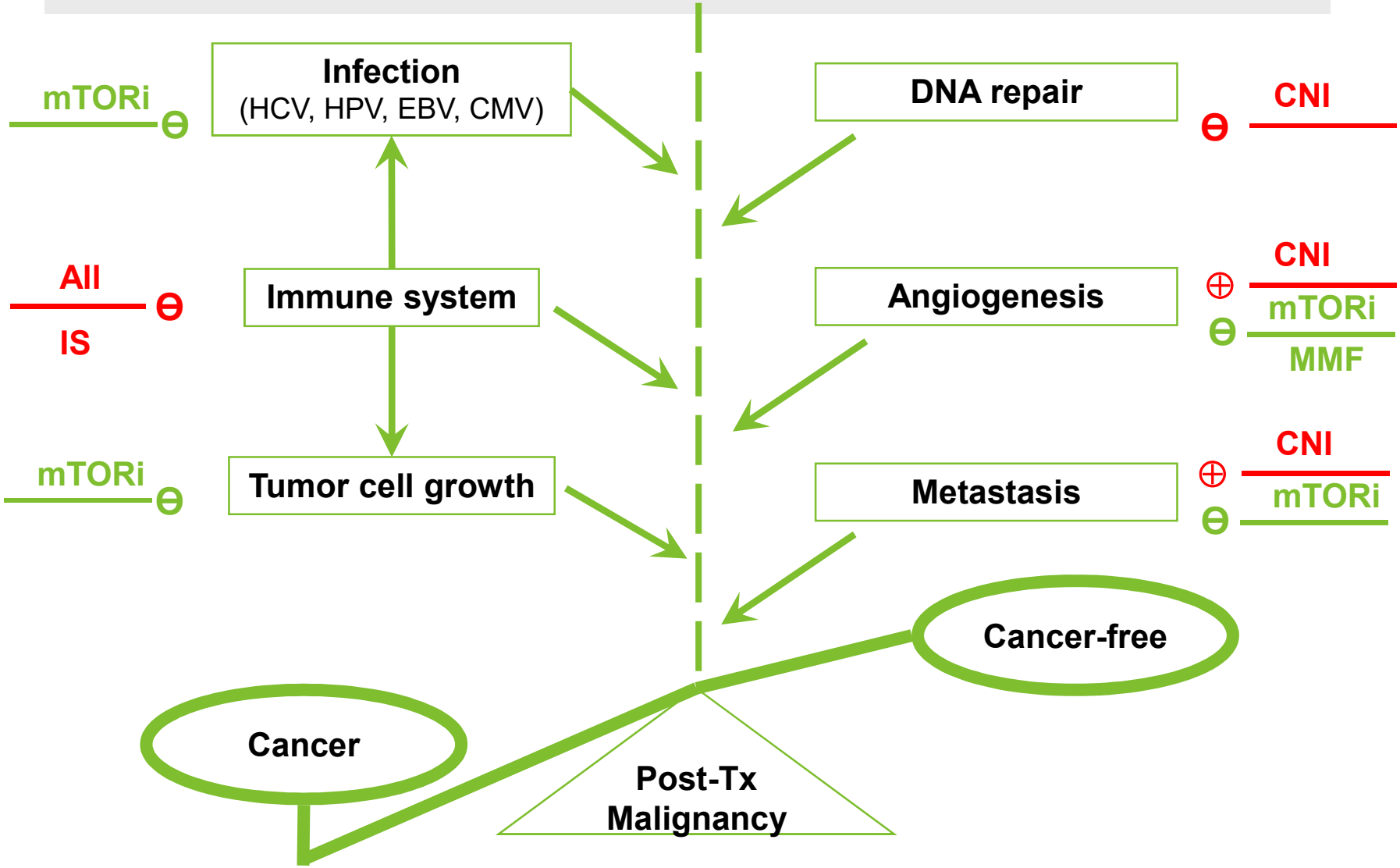
1. Valantine H. *J Heart Lung Transplant* 2007;26:557–64; 2. Morath C *et al. J Am Soc Nephrol* 2004;15:1582–8; 3. Hojo M *et al. Nature* 1999;397:530–4; 4. Carroll RP *et al. J Am Soc Nephrol* 2010;21:713–22; 5. Kuivanen T *et al. J Cutan Pathol* 2009;36:929–36; 6. Imao T *et al. Cancer* 2007;109:2109–15

# Risk factors for post-transplant cancer

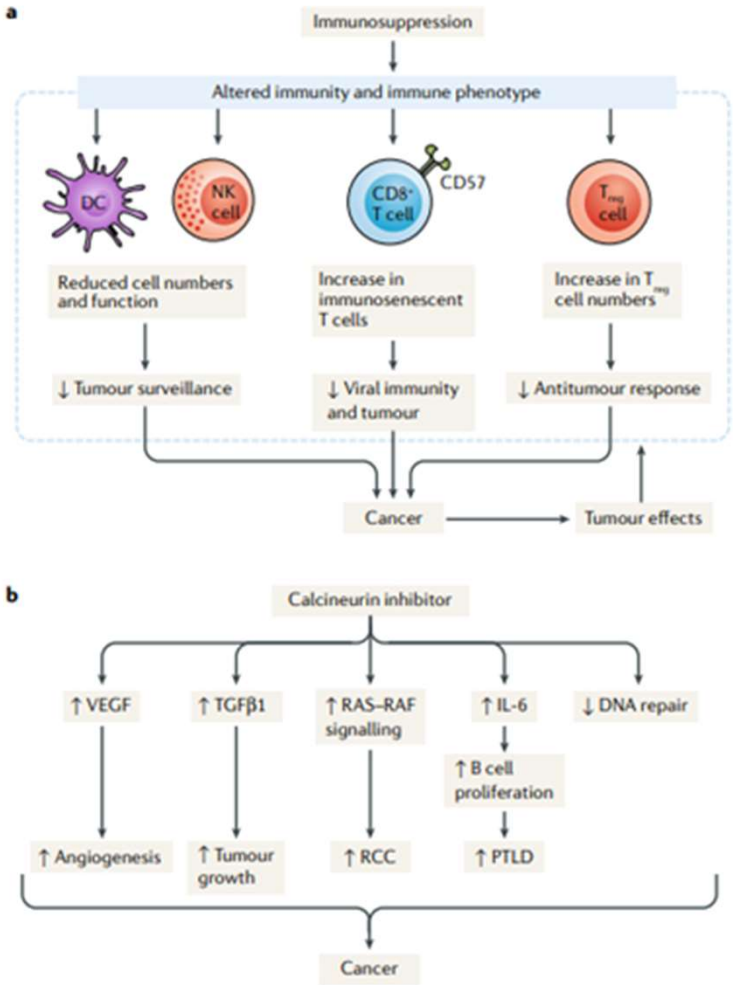
Table 2 | **Factors that influence the risk of cancer after kidney transplantation**

| Factors | Change in risk | Refs |
|---|---|---|
| ***Patient-related factors*** | | |
| Older age (>50 versus <35 years) | 3–6 times increase | 22,23 |
| Male gender | 20–30% increase | 23 |
| White versus non-white ethnicity | 20–35% increase | 22,23 |
| ***Medical history*** | | |
| Smoking | 2–3 times increase | 138 |
| Time on dialysis (>4.5 years versus <1.5 years) | 40% increase | 21 |
| Prior history of cancer | 40% increase | 22 |
| Diabetes mellitus | 20–40% decrease | 22,23 |
| Polycystic kidney disease | 20% decrease | 27 |
| ***Transplant factors*** | | |
| Peak PRA score (80% versus 0%) | 2 times increase | 49 |
| HLA-DR mismatches (2 versus 0) | 25% increase | 50 |
| Deceased expanded criteria donor versus living donor | 50% increase | 52 |
| Donor and recipient CMV status | No difference | 53 |
| ***Immunosuppression*** | | |
| Azathioprine | 2–9 times increased risk of SCC | 139 |
| T cell-depleting agents | ~30–80% increased risk of NHL | 35–38 |
| IL-2 inhibitors | No increase | 41 |
| mTOR inhibitors | 30–50% decrease | 43,45 |

# CANCER DEVELOPMENT/ EFFECTS OF IMMUNOSUPPRESSANTS



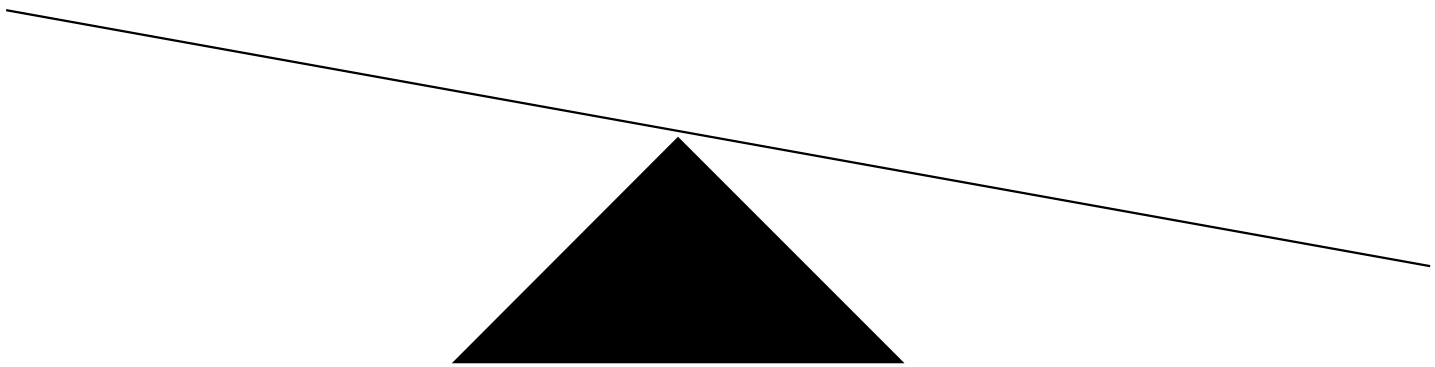
# Effect of immunosuppression



# The paradox of transplantation

COMPLICATIONS

REJECTION



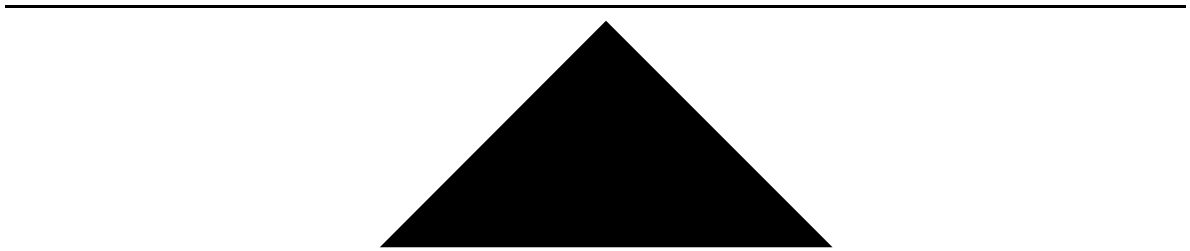
OVER-IMMUNOSUPPRESSION

UNDER-IMMUNOSUPPRESSION

# The ideal situation

COMPLICATONS

REJECTION



# Viral pathogenesis of Cancer

## HPV

**Carcinomas skin & lips, vulva, perineum cervix and uterus**

## EBV

**Post transplant Lymfoproliferative Disorder PTLD**

## HBV – HCV

**Hepatocellular carcinoma**

## HHV-8

**Kaposi's sarcoma**

# Virus associated cancers

Box 1 | **Viruses and associated cancers**

**Epstein–Barr virus (EBV)**

- Post-transplant lymphoproliferative disorder

**Human herpesvirus 8 (HHV-8)**

- Kaposi sarcoma
- Primary effusion lymphoma

**Human papillomavirus (HPV)**

- Head and neck cancers
- Skin cancers
- Cervical cancer
- Vulval cancer
- Penile cancer

**Hepatitis B and C virus (HBV and HCV)**

- Hepatocellular carcinoma

**Merkel cell polyoma virus**

- Merkel cell carcinoma

# Prior cancer – critical risk factor

- 54% of recurrent tumors occur in first 2 y
- 33% in 2-5 y
- 13% after 5 y of transplant

AJT 2001; Suppl 1: 12

# Cancer is a transmittable disease

Risk of a donor with cancer: **1.3%**

Risk of transmitting the cancer: **0.2%**

Cincinnati Tumor Registry

22 Heart + Lung **donors**

- 45% developed cancer
- Depends on the type + extend of the cancer
  - e.g. RCC – capsular invasion vs. vascular invasion
  - Melanoma – choriocarcinoma: early + high transmission

Surgery 2001; 130:660

# Transmission risk

| | | | | | |
|---|---|---|---|---|---|
| Cancer type | Benign tumours | • Skin BCC and SCC<br>• Non-melanoma skin cancer in situ<br>• Cervical carcinoma in situ<br>• Non-invasive papillary carcinoma<br>• Resected solitary RCC[a] (≤1 cm) | • Low-grade[a,b] CNS tumour<br>• Resected solitary RCC[a] (>1–4 cm)<br>• Treated non-CNS malignancy ≥5 years prior with >99% probability of cure | • Breast or colon carcinoma in situ<br>• Resected solitary RCC[a] (4–7 cm)<br>• Treated non-CNS malignancy ≥5 years prior with 90–99% probability of cure | • Malignant melanoma<br>• Breast, colon or lung cancer<br>• RCC[c] (>7 cm)<br>• High-grade[d] CNS malignancy<br>• Leukaemia, lymphoma or sarcoma |
| Cancer grade | | | | | |
| Risk category | No significant risk | Minimal | Low | Intermediate | High |
| Transmission risk estimate | 0% | <0.1% | 0.1–1% | 1–10% | >10% |
| Recommended clinical use | Standard | Clinical judgement with informed consent | Use in recipients at significant risk without transplant with informed consent | Use generally not recommended | Use not recommended |

# Monitoring cancer after transplantation

Case Study

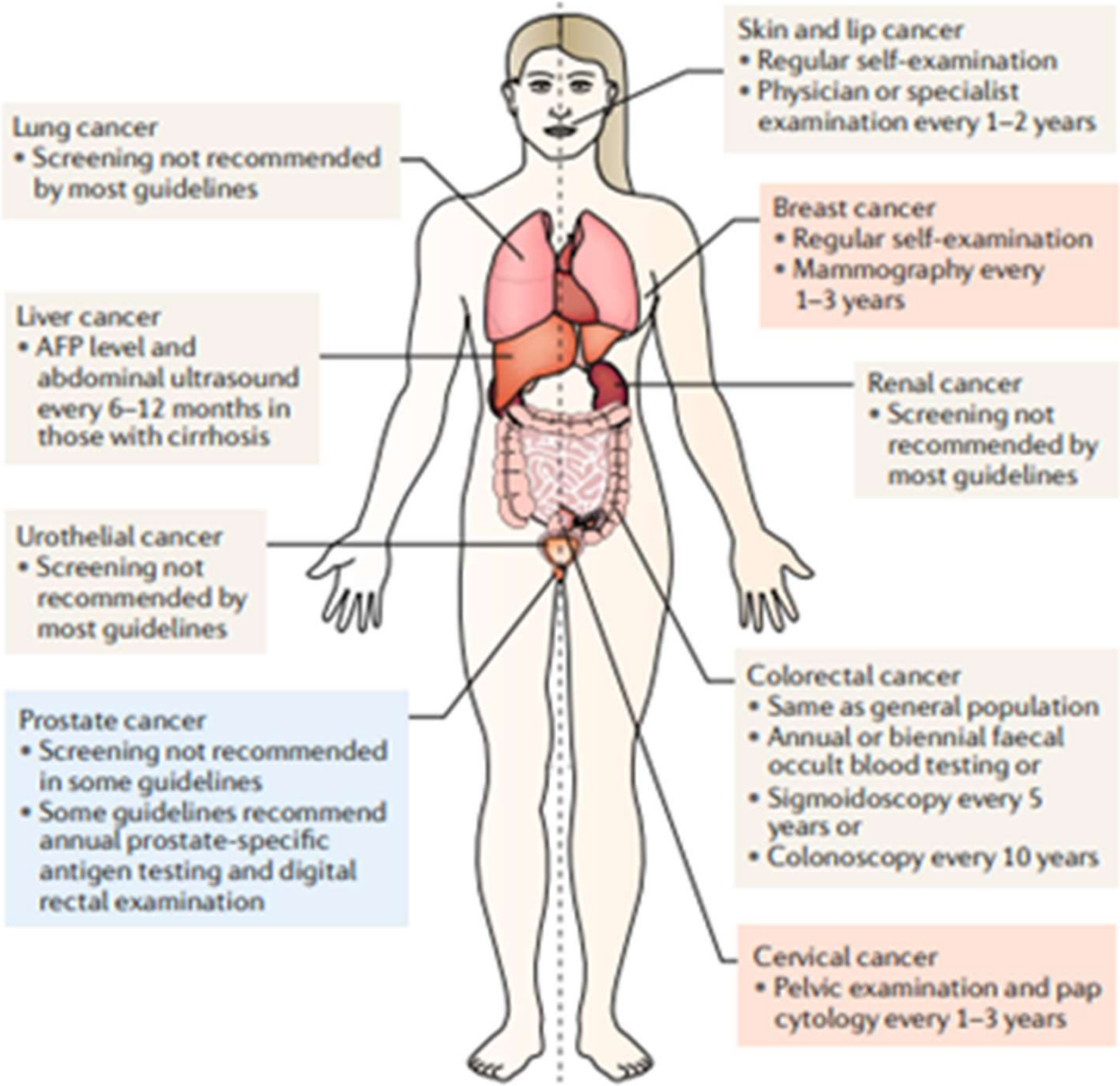
Epidemiology of post transplant cancer

Risk factors for developing post transplant cancer

**Screening for cancer**

Prevention and treatment of cancer

mTORi, mammalian target of rapamycin inhibitor


Skin and lip cancer
• Regular self-examination
• Physician or specialist examination every 1–2 years
Lung cancer
• Screening not recommended by most guidelines
Breast cancer
• Regular self-examination
• Mammography every 1–3 years
Liver cancer
• AFP level and abdominal ultrasound every 6–12 months in those with cirrhosis
Renal cancer
• Screening not recommended by most guidelines
Urothelial cancer
• Screening not recommended by most guidelines
Colorectal cancer
• Same as general population
• Annual or biennial faecal occult blood testing or
• Sigmoidoscopy every 5 years or
• Colonoscopy every 10 years
Prostate cancer
• Screening not recommended in some guidelines
• Some guidelines recommend annual prostate-specific antigen testing and digital rectal examination
Cervical cancer
• Pelvic examination and pap cytology every 1–3 years

# Cancer screening in General Population

All

- Rectal exam
- > 50-y : colonoscopy /10 y

♂

- > 40-y : gynaecologic exam - cervix smear / 2 y
- > 40-y : mammography / 2 y

♀

- 50-y: PSA / y

# Cancer screening in the transplanted population

- **ALL**
  - SKIN
    - MONTHLY **self** exam
    - **Dermatologist** YEARLY
    - EARLY **referral** for suspected lesions
  - KS / Sarcoma
    - Exam of **skin**, **conjunctivae**, **oropharyngeal** mucosa ANNUALLY
    - Including **pelvic** exam + **cytology** for ♀
    - For **high risk patients** MORE FREQUENT screening
      - Ethnicity
      - Geography of residence
      - HHV-8 positivity

# Skin cancer screening – integrated care

Pretransplant screening: ONCE

Posttransplant

- YEARLY
  - full skin exam FSE + Patient education PE
- In-situ: EVERY 6 MONTHS
  - FSE + PE + topical treatment
- Early cutaneous carcinogenesis 1-4 NMSC/y: EVERY 6 MONTHS
  - FSE + PE + topical treatment + surgical removal + retinoids oral

Swiss Med WKLY 2009; 139: 407-415.

# Skin cancer screening – integrated care

## Posttransplant

- Moderate cutaneous carcinogenesis 5-10 NMSC/y: EVERY 2-4 MONTHS
  - FSE + PE + topical treatment + surgical removal + retinoids oral + recommend reduced immunosuppression + mTORi switch
- Severe cutaneous carcinogenesis > 10 NMSC/y: EVERY 1-3 MONTHS
  - FSE + PE + topical treatment + surgical removal + retinoids oral + recommend reduced immunosuppression + mTORi switch

Swiss Med WKLY 2009; 139: 407-415.

# Cancer screening in the transplanted population

- **ALL**
  - COLORECTAL
    - > 50-y
    - ANNUAL **fecal occult blood testing**
    - Either **sigmoidoscopy**/ 5 y or **colonoscopy** / 10 y
    - MORE FREQUENT if at risk
  - PTLD
    - Complete **history** + **physical exam** / 3 M (especially in first YEAR)
    - MORE FREQUENT if at risk
    -
  - LUNG
    - In former smokers

# Cancer screening in the transplanted population

- **PARTICULAR SITUATIONS**
  - HBV – HCV
    - Liver transplant recipients + HBV/HCV+
    - Serum **&-foetoprotein** AFP / 6-12 m
    - **Echography** / 6-12 m
  - RENAL CELL CARCINOMA
    - Kidney transplantation recipients
    - Cytology/ imaging: Not recommended
      - Except in high risk patients e.g. analgesic nephropathy, ..

# Urinary tract – transitional epithelioma

High frequency in case of

- Analgesic nephropathy
- Chinese herbs nephropathy - AA
- Balkan nephropathy - AA
- CYP > SLE/LN – MN – FSGS - …
- Aniline derivates

# Renal Cell Carcinoma - RCC

- 1%/year in CKD stage 5d > acquired multicystic disease

- 100 x more important than expected >< general population

# Cancer screening in the transplanted population

- ♂ - MEN
  - PROSTATE
    - > 50-y ANNUAL (if prognosis > 10 y)
      - **digital rectal exam**
      - **PSA**
    - If positive familial history start at 45-y
  - ANOGENITAL
    - YEARLY **inspection**
    - Insufficient evidence for/against anuscopy screening + biopsy

# Cancer screening in the transplanted population

- ♀ - WOMEN
  - BREAST
    - 40-49-y:
      - benefit of screening is less clear – at the discretion of patient and physician
    - 50-59-y:
      - ANNUAL -> 3y screening **mammography**
      - **Clinical** examination
      - **Self** examination
    - > 70-y: ANNUAL->3y above if life expectancy ≥ 8 years

# Cancer screening in the transplanted population

- ♀ - WOMEN
  - CERVICAL
    - All > 18-y-old or < 18-y sexually active YEARLY
      - **Annual pelvic exam**
      - **PAP** smear
      - More frequent if indicated
  - ANOGENITAL
    - YEARLY **inspection**, including the above pelvic
    - Insufficient evidence for/against anuscopy screening + biopsy

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# Smoking – Obesity  ERBP 2013

We recommend patients stop smoking before transplantation. (**1B**)

Smoking cessation programmes should be offered. (**Ungraded Statement**)

# Strategies for managing **skin cancer** in the transplant population

**Organ transplant recipients with actinic keratoses have been treated with topical immunomodulation with limited results[1]**

**Treatment of these patients using PDT has achieved a response rate of 71%[2]**

**Excision is recommended for patients with invasive SCC, with complete removal at an early stage being the best way to avoid metastasis[3]**

**Chemoprevention with the retinoid acitretin has proven beneficial in both the general population and the high-risk group of solid organ transplant recipients[3]**

PDT, photodynamic therapy; SCC, squamous-cell carcinoma


1. Ulrich C *et al*. *Br J Dermatol* 2007;157(Suppl 2):25–31;
2. Piaserico S *et al*. *Transplant Proc* 2007;39:1847–50;
3. Hofbauer GF *et al*. *Swiss Med Wkly* 2009;139:407–15

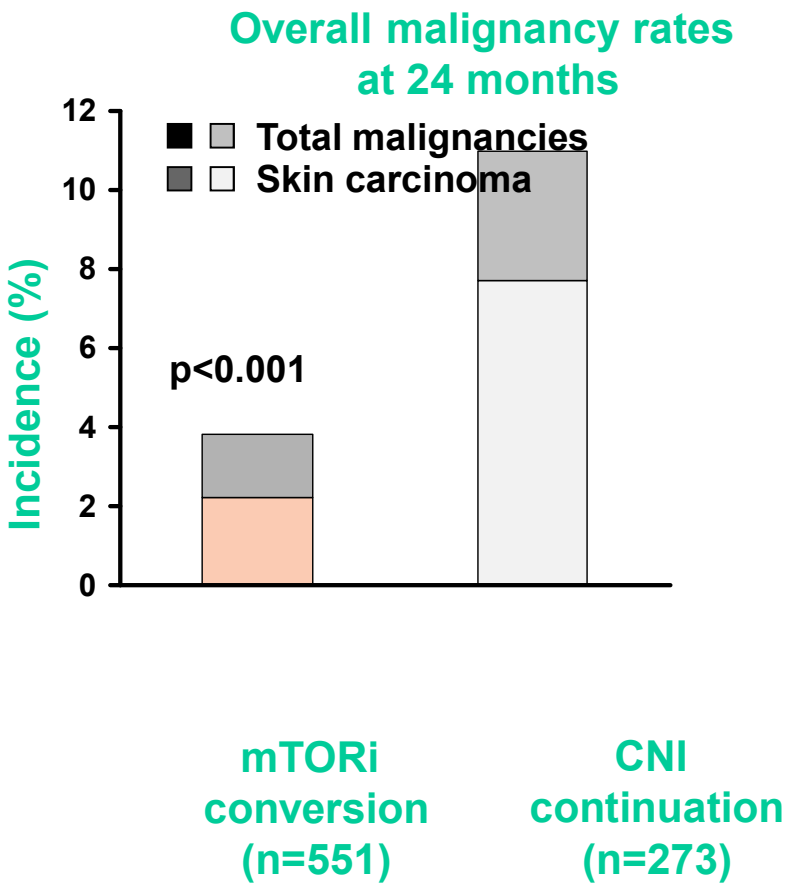
# Conversion from CNIs to mTORi is associated with lower rate of malignancy at 2 years

830 renal allograft recipients 6–120 months post-transplant receiving CNIs were randomly assigned to continued CNIs or sirolimus

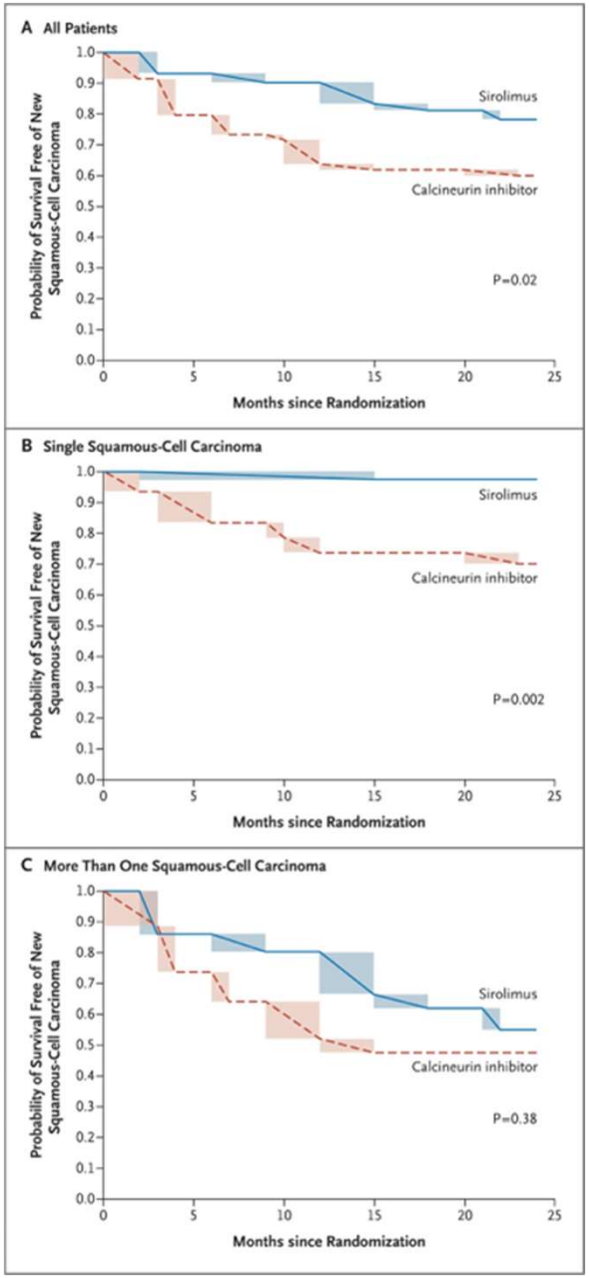
- Incidence of malignancy also significantly lower with mTORi if patients with prior history of malignancy at baseline excluded

Schena FP *et al. Transplantation* 2009;82:233–42

CONVERT-trial



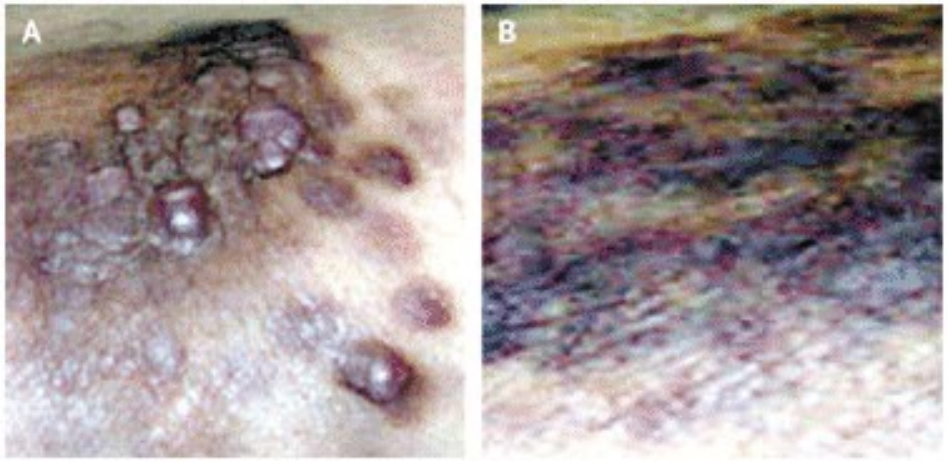

CNI, calcineurin inhibitor;
mTORi, mammalian target of rapamycin inhibitor





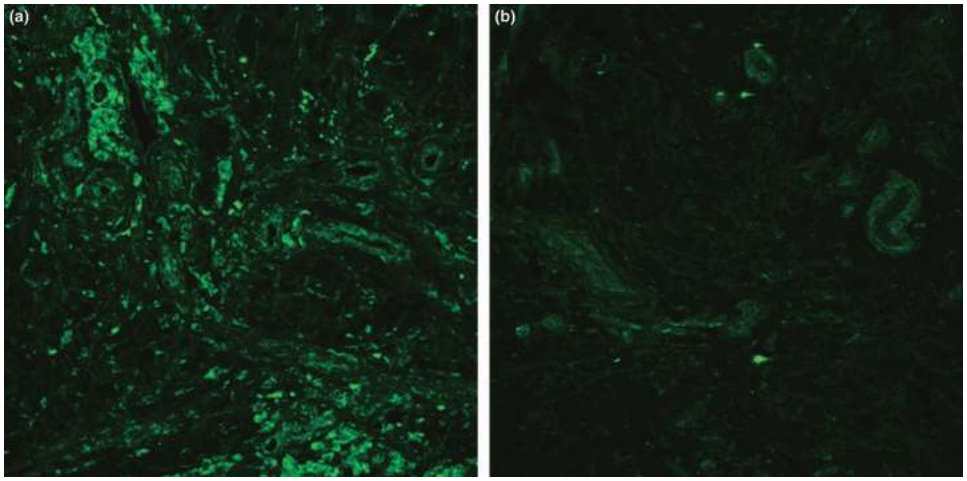

**Euvrard S et al. N Engl J Med 2012;367:329-339. TUMORAPA**

# Kaposi's sarcoma: efficacy of mTORi conversion




Stallone G et al. NEJM 2005; 352: 1317

VEGF






Stallone G et al. *Transplant Int* 2008; 21: 825-832

# Post Tx Kaposi's sarcoma: efficacy of mTORi conversion

**Table 1. Characteristics of the Patients.***

| Characteristic | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 | Patient 7 |
|---|---|---|---|---|---|---|---|
| Age (yr) | 57 | 69 | 53 | 61 | 61 | 64 | 55 |
| Sex | Male | Male | Male | Female | Female | Female | Male |
| Cause of ESRD | Chronic glomerulo-nephritis | Diabetic ne-phropathy | Interstitial nephropathy | Vasculitis | Polycystic kidney disease | Idiopathic | Focal and seg-mental glomer-ulonephritis |
| Initial immunosuppressive therapy | CSA, AZA, and P | BA, CSA, MMF, and P | CSA, MMF, and P | CSA and P | BA, TAC, MMF, and P | BA, CSA, MMF, and P | CSA, MMF, and P |
| Time to development of KS after transplantation (mo) | 6 | 3 | 36 | 36 | 27 | 5 | 8 |
| Site of cutaneous involvement | Lower legs and wound site | Lower legs, hands, abdomen, neck, and ears | Left lower leg and left foot | Left lower leg | Lower legs and wound site | Left lower leg | Lower legs, abdomen, and forearms |
| Creatinine before withdrawal of calcineurin inhibitors (mg/dl) | 2.0 | 2.8 | 2.3 | 1.1 | 1.1 | 2.2 | 1.6 |
| Follow-up since change to sirolimus (mo) | 32 | 13 | 29 | 28 | 10 | 9 | 48 |
| Serum creatinine at last visit (mg/dl) | 2.0 | —† | 2–0 | 0–9 | 1–2 | 1–5 | 1–6 |

* ESRD denotes end-stage renal disease, CSA cyclosporine, AZA azathioprine, P prednisone, BA basiliximab, MMF mycophenolate mofetil, TAC tacrolimus, and KS Kaposi's sarcoma.

† Hemodialysis was performed. The patient had sepsis with cardiac failure and acute renal failure without recovery of the graft function.

Gutiérrez-Dalmau A., J.M. Campistol. *NEJM* 2005, 353: 846-847

# Conclusions

Kidney transplant patients are at greater risk of developing malignancies (+ ensuing patient death) than the general population.

Risk factors are many – some of which avoidable.
– some of which modifiable.
The main issues here: immunosuppression and viruses

mTORi-based regimens with CNI tapering/withdrawal might reduce rates of NMSC cancers post-transplant.

Life style adjustment and screening - in all transplanted patients – to limit the cancer risk.

# Management of immunosuppression and post-transplant cancer

**Table 1.** Cancer screening in transplant recipients

| Cancer type | Recommendations |
|---|---|
| Breast | Annual or biennial mammography for all women |
| Gastric and Colorectal | Annual FOBT and 3-yearly oesophagogastroduodenoscopy and flexible sigmoidoscopy for individuals older than 50 years and with a positive familial history |
| Cervical | Annual cytological cervical cancer screening and pelvic examination |
| Prostate | Annual digital rectal examination and PSA measurement in all male renal transplant recipients older than 40 years |
| Hepatocellular | α-Fetoprotein and ultrasound performed every 6 months in high-risk individuals |
| Skin | Monthly self-skin examination, total body skin examination every 12 months by expert physicians and dermatologists |
| Renal | Ultrasonography of the native kidneys every 6–12 months |
| PTLD-virus-related | Viral nucleic acid dosage every month until 6 months post-transplant, and every 6–12 months thereafter |

Table 3 | **Absolute and relative risks of cancer by age for Australian and New Zealand kidney transplant recipients**

| Age at cancer diagnosis (years) | Gender | Number of kidney transplant recipients | Absolute risk[a] in kidney transplant recipients | Absolute risk[a] in the general population | Relative risk[b] |
|---|---|---|---|---|---|
| <35 | Female | 1,712 | 6.5 | 0.7 | 9.9 (7.8–12.5) |
| | Male | 2,519 | 3.7 | 0.6 | 6.9 (5.3–8.8) |
| 35–44 | Female | 1,926 | 9.1 | 2.2 | 4.2 (3.4–5.2) |
| | Male | 3,035 | 7.4 | 1.3 | 5.8 (4.8–7.0) |
| 45–54 | Female | 2,247 | 15.5 | 4.7 | 3.3 (2.8–3.9) |
| | Male | 3,392 | 11.7 | 3.5 | 3.4 (3.0–4.0) |
| ≥55 | Female | 2,111 | 23.7 | 9.2 | 2.6 (2.3–2.9) |
| | Male | 2,857 | 24.2 | 13.2 | 1.9 (1.7–2.1) |
| All ages | Female | 5,192 | 14.3 | 4.5 | 3.2 (3.0–3.5) |
| | Male | 7,441 | 11.6 | 4.6 | 2.6 (2.4–2.8) |