VON HIPPEL-LINDAU DISEASE: SURGICAL POSSIBILITIES

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Von Hippel – Lindau Disease

- In 31-45% one can detect renal cancer
- Bilateral and multifocal forms are more common
- 20% metastatic cancer, in 50% of vHL the cause of death
- Age: 29-69 y, mean: 33 y
- First ophtalmic lesions, than CNS, than renal

Pathologic Background

- Poston CD et al. J Urol 153: 22-6, 1995
- vHL kidneys: 7,8 cystic and 3,0 solid lesions in average
- cystic lesions:
  21% carcinoma, 26% atypic, 53% benign
- solid lesions:
  90% carcinoma
- in the „normal” parts:
  microscopic cysts, clear cell neoplasia

Multicentric U.S. Study

- Steinbach F et al. J Urol 153: 1812-6, 1995
- 8 USA centers, follow-up: 68 months
- 65 vHL patients: 54 bilateral, 11 unilateral resection, (1 patient had metastatic disease)
- radical nephrectomy: 16 patients (25%)
  nephron sparing surgery (NSS): 49 patients (75%)
- 5 y survival: 95% NSS: 100% RN: 73%
  10 y survival: 77% NSS: 81% RN: 36%

Multicentric U.S. Study

- I. stage 75%, II. stage 17%,
  III. stage 6%, IV. stage 2%
- 89% clear cell renal carcinoma
- 12% died because of metastases (after 104 months)
  9% because of vHL and non-vHL causes (50-50%)
- One can observe metastases in 50% at sporadic cases
  Is vHL another type of cancer?
- 63% was detected by prophylaxis and control!

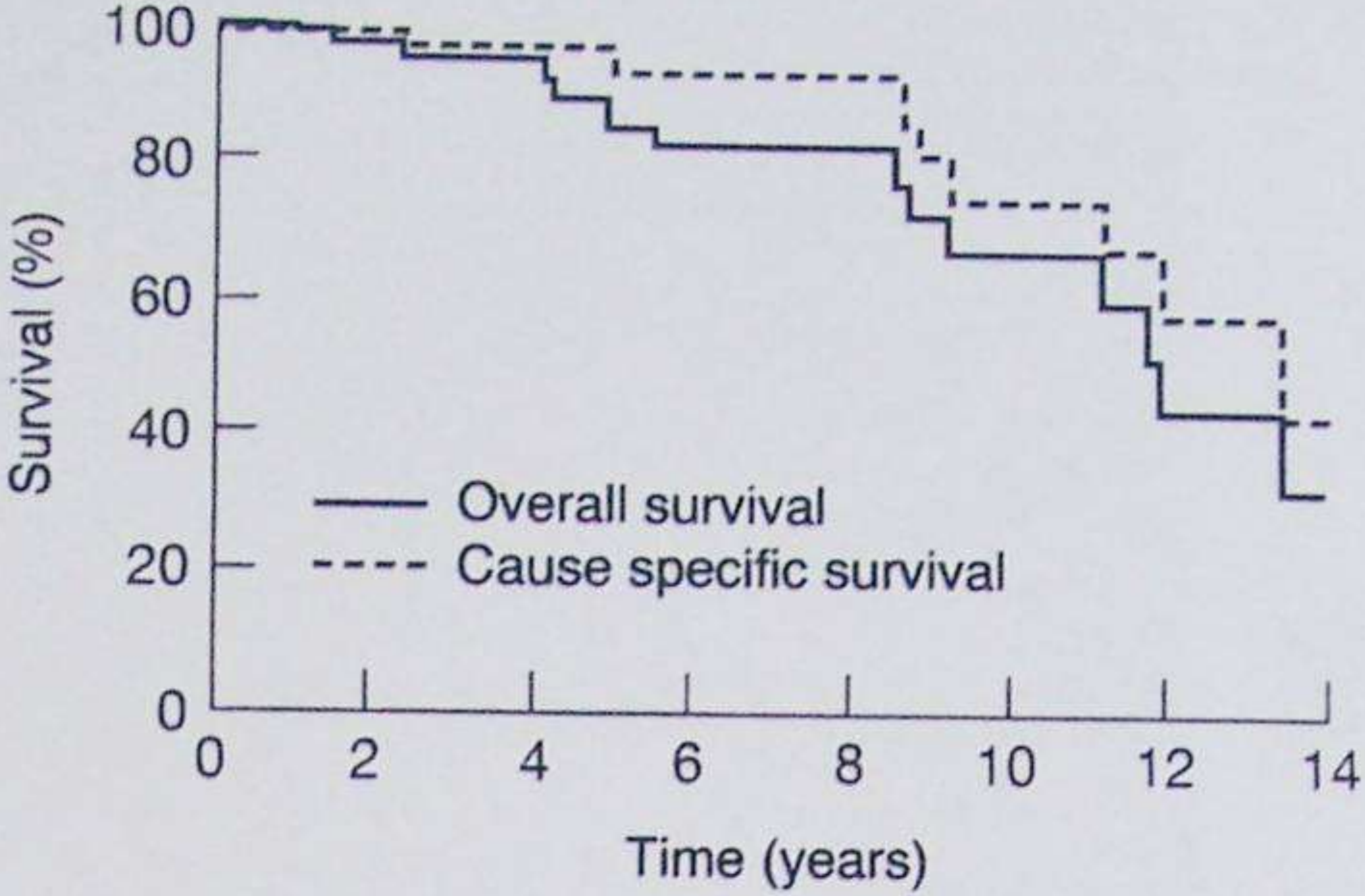


Fig. 1 Overall and cancer-specific survival rates for renal cell carcinoma in patients with von Hippel–Lindau disease [5].

NEPHRON SPARING SURGERY

- 25 patients (51%!) local tumor recurrence, metastatic disease in two of them
- 5 year recurrence free status: 71%,
  10 year recurrence free status: 15%!
- 15 patients became uremic (23%)
- 6 got transplanted
- 9 were dialysed, 6 were tumor free

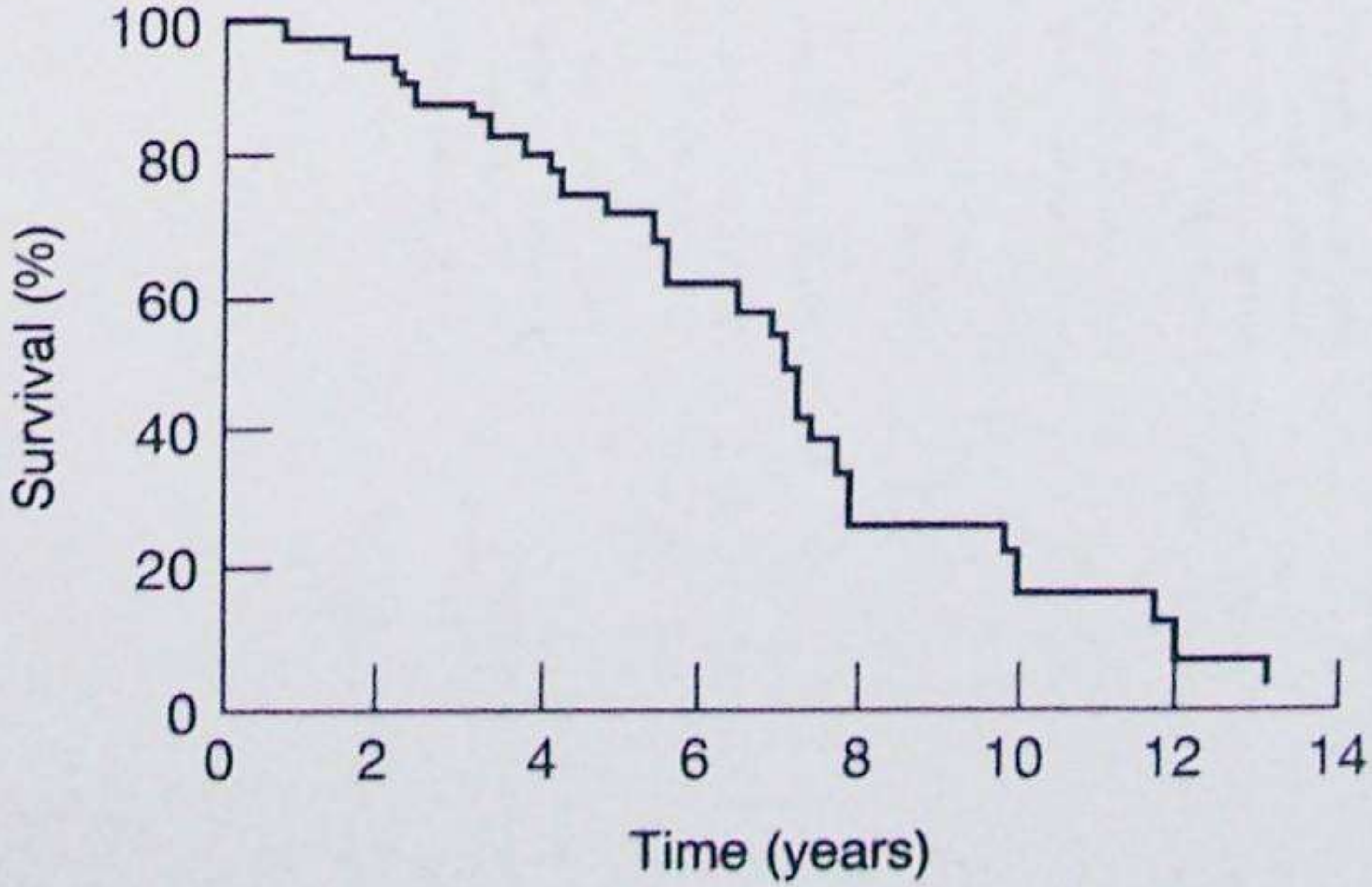


Fig. 2 Survival free of local tumour recurrence following nephron-sparing surgery for renal cell carcinoma in patients with von Hippel–Lindau disease [5].

The First Transplanted vHL Patient

- Peterson GJ et al. Arch Surg 112: 841-2, 1977

- 12 y ophtalmic symptoms, 30 y removal of the first, a year later of the second kidney

- Estimation:
  13-25% of the vHL patients manifest tumor

- Recommendation:
  bilateral nephrectomy, a year later tx

VHL AND KIDNEY TX

- Penn I: Transplantation 55: 742-7, 1993
- 304 RCC: 12 vHL
- Goldfarb DA, Novick AC, Penn I, Neumann HPH: J Urol 157: 327, 1997
- 28 Pt: 31 y cancer, 37 y tx (28 months dialysis)
- 23 tumor free 51 months after tx,
  3 died of metastases 33 months after tx
  2 died of non-cancer related causes
- This is equal to non-cancer tx survival!

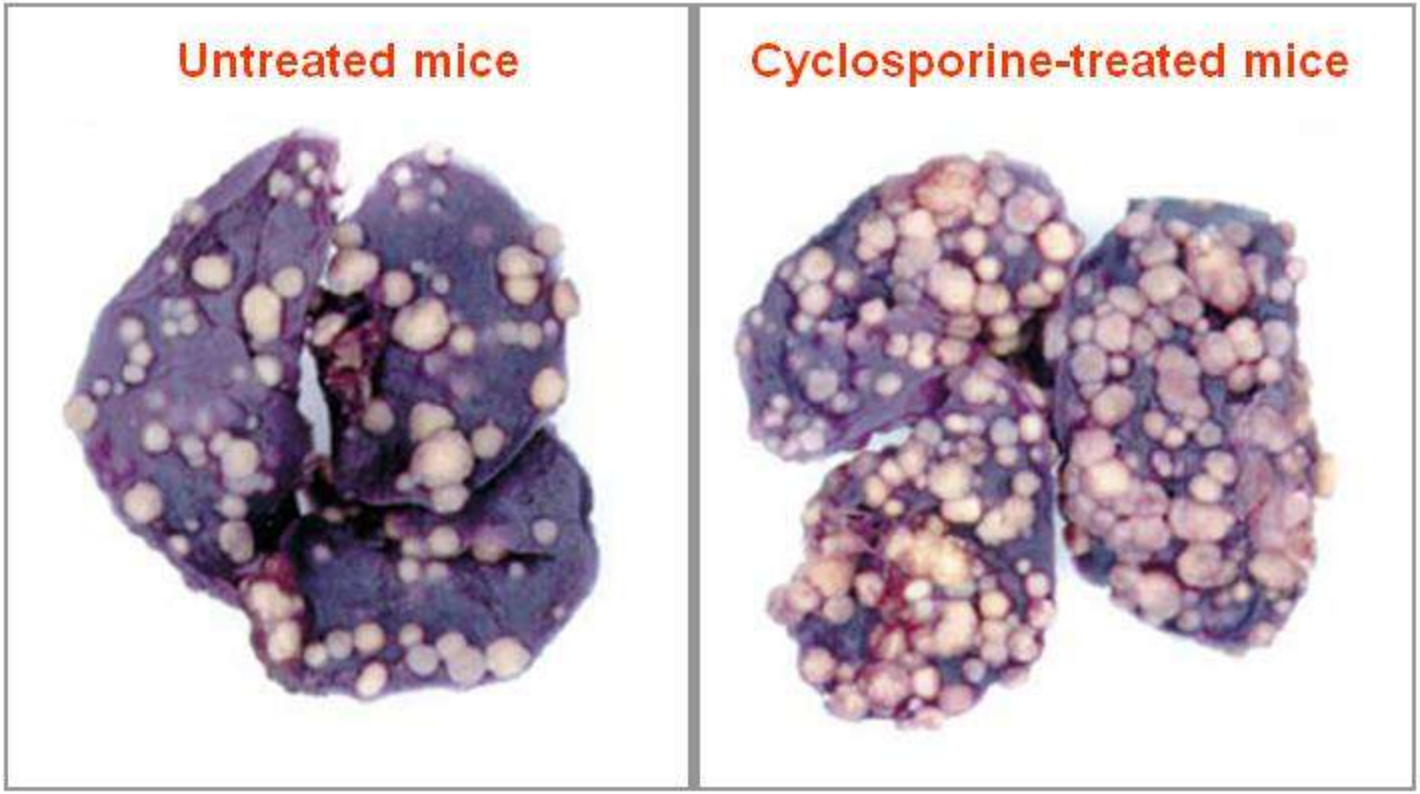
RCC AND KTX

- Penn I: Transplantation 55: 742-7, 1993
- 56 incidentalomas (tx within 2 years): 0 recurrence!
- 152 patients with symptoms of RCC:
  51 recurrences: 39 metastases caused deaths
- 31/51 patients (61%) were within 2 years to tx
- Conclusion: low-grade, symptom free RCC no waiting, otherwise 2 years recommended WT

Listing of Living Donors for VHL

- Undetected disease in a relative represents a risk
- Symptom free carrier?
- MRI, opthalmology, abdominal CT,
  24 h urine collection

Increase in renal cell cancer metastases in SCID-beige mice with CsA



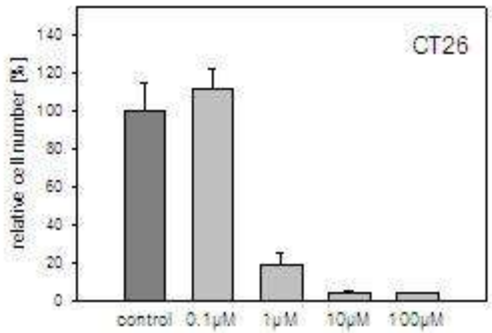
Hojo M *et al. Nature* 1999; **397**: 530–534.

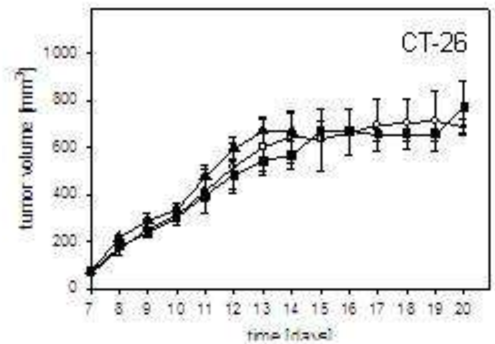
MMF inhibits tumors *in vitro*, BUT NOT *in vivo* at relevant concentrations

In vitro √

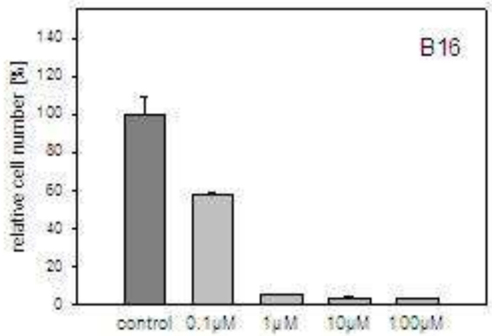
In vivo ø

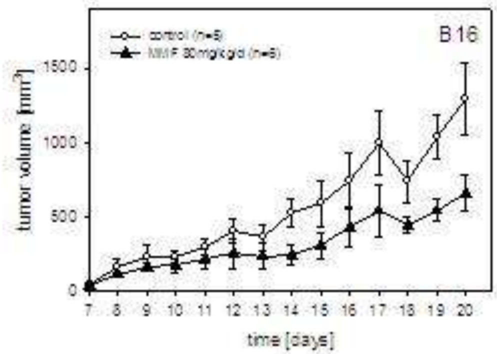
Colon CA



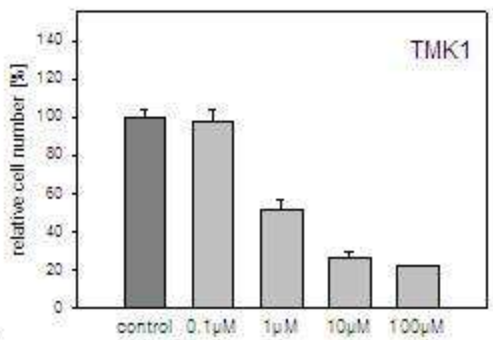


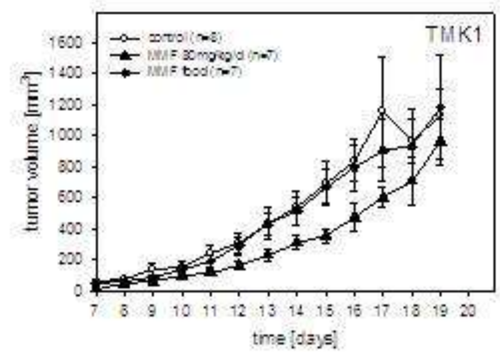
Melanoma





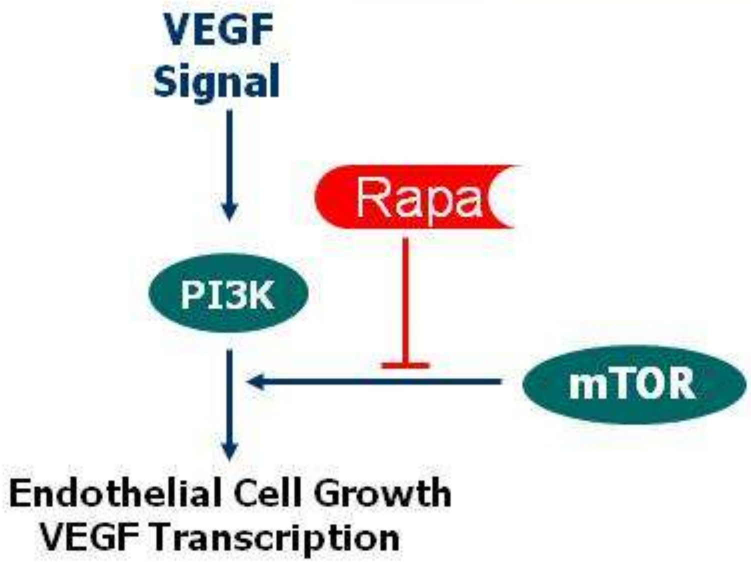
Gastric CA



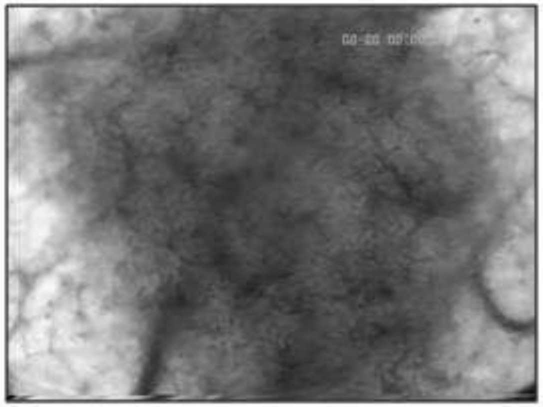


Koehl et al. *Transplantation*, 2007

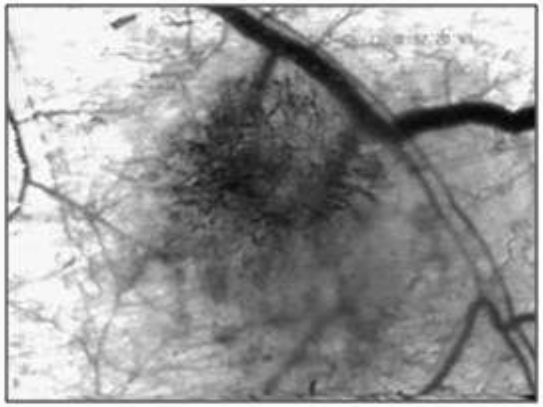
mTOR has a central role in cancer: **I - Angiogenesis**



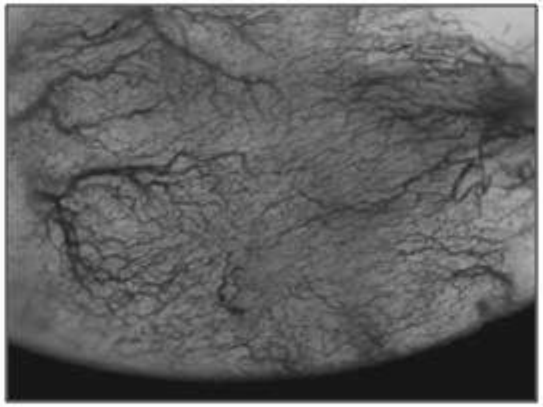
Control



Rapamycin 1.5 mg/kg

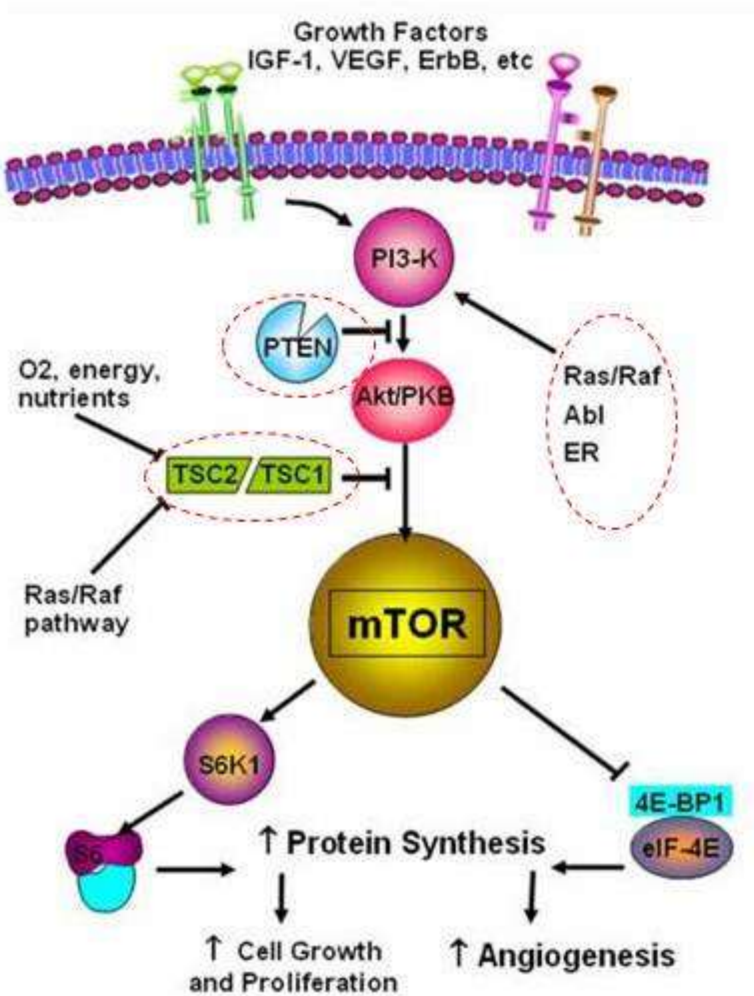


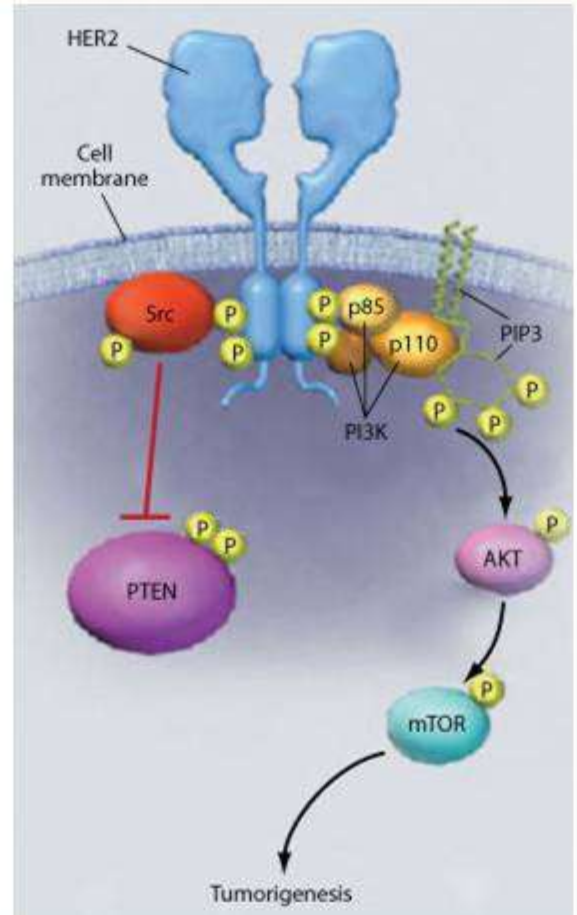
Cyclosporine 10 mg/kg



Nature Med 2002

mTOR has a central role in cancer: **II - Oncogenes/Tumor suppressors**





- Breast Cancer (HER2)
- Leukemia (Abl)
- Tuberous sclerosis (TSC1/2)
- Colon cancer (APC^{min})
- Skin cancer (p53)

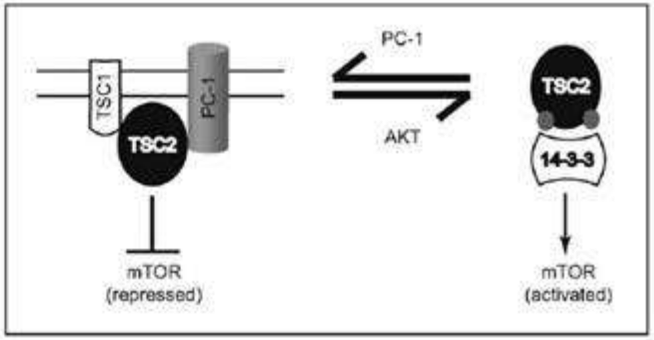
mTOR has a central role in cancer: **II – Proliferative Diseases**

Polycystic Kidney Disease

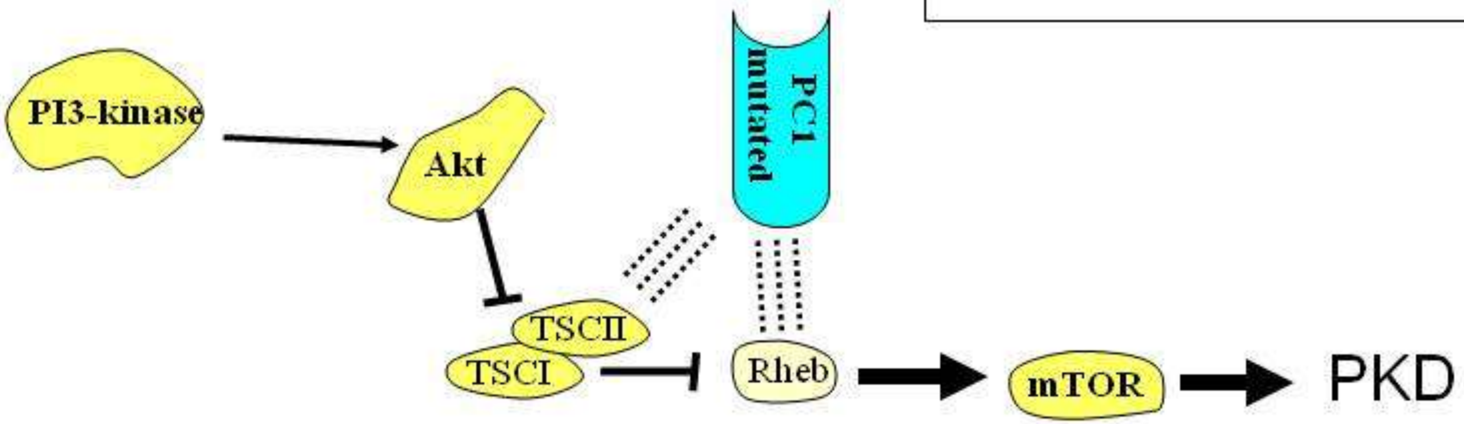
PKD1 gene mutation

Mutated PKD1 may interact with tuberin in such a way that mTOR is activated

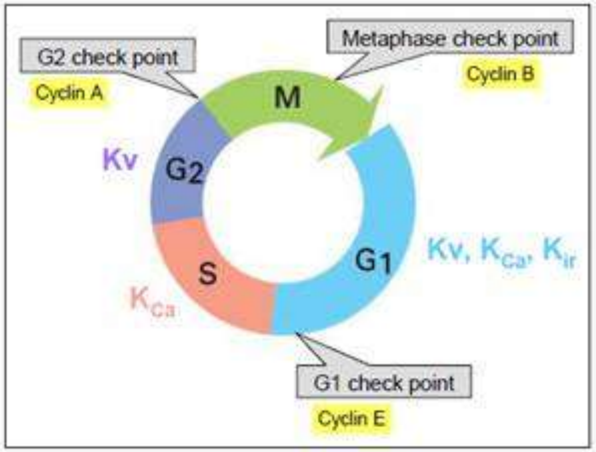
Dere et al., *PLoS ONE*, Feb 2010



Polycystin-1 regulates TSC2 localisation



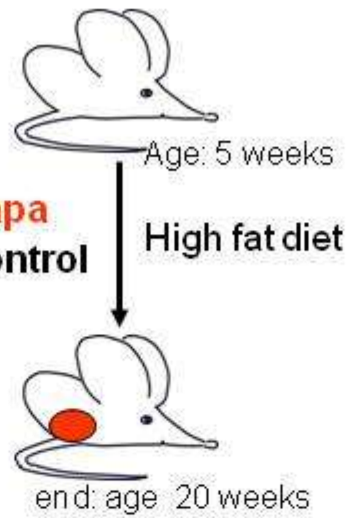
mTOR has a central role in cancer: **III - Oncogenic ion channels**

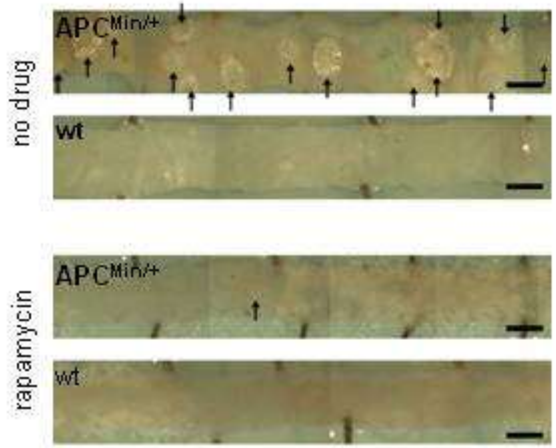


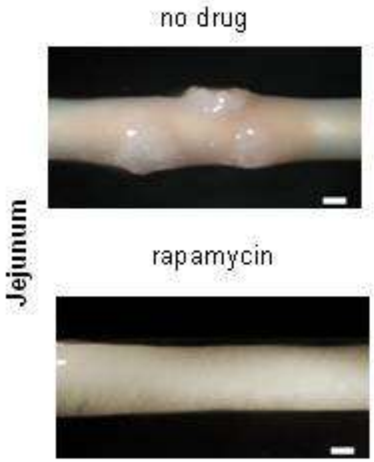
family	subfamily	members	type of tumor cell line	type of tumor
Kv channels	Kv1	Kv1.3, Kv1.5	prostate cancer cells, colonic cancer cells	neuroblastoma, breast carcinoma, small lung cell carcinoma, melanoma, lymphoma, hepatocarcinoma
	Kv3	Kv3.3, Kv3.4		colonic carcinoma
	Kv10	Eag1 Eag2	NIH 3T3, HeLa	cervix carcinoma, neuroblastoma, mammary gland carcinoma, ductal carcinoma, breast carcinoma
	Kv11	Erg1	atrial tumor cells (HL-1), breast cancer cells (SK-BR-3), colonic cancer cells	myeloid leukemia, neuroblastoma, colorectal cancer
	Kv12	Elk1, Elk2		astrocytoma
K_{Ca} channels	BK_{Ca}	BK, SK	prostate cancer cells (PC3)	glioma, pituitary GH3 lactotroph
K_{2P} channels	K_{2P}	TWIK TASK	melanoma cell line (SK-MEL-28)	glioma, neuroblastoma, medulloblastoma, leukemia, insulinoma
	K_{ATP}	K_{ATP}	liver epithelial cell lines (HepG2, HuH-7, HFL), U-373 MG, SK-N-MC	astrocytoma, neuroblastoma, insulinoma, urinary bladder carcinoma, medulloblastoma
K_{ir} channels	K_{ir}	Kir 4.1	neuroblastomaxglioma hybrid cells (NG108-15), basophilic leukemia cells (RBL-2H3)	

mTOR has a central role in cancer: **III - Oncogenic ion channels**

APC$^{min/+}$ - wt siblings

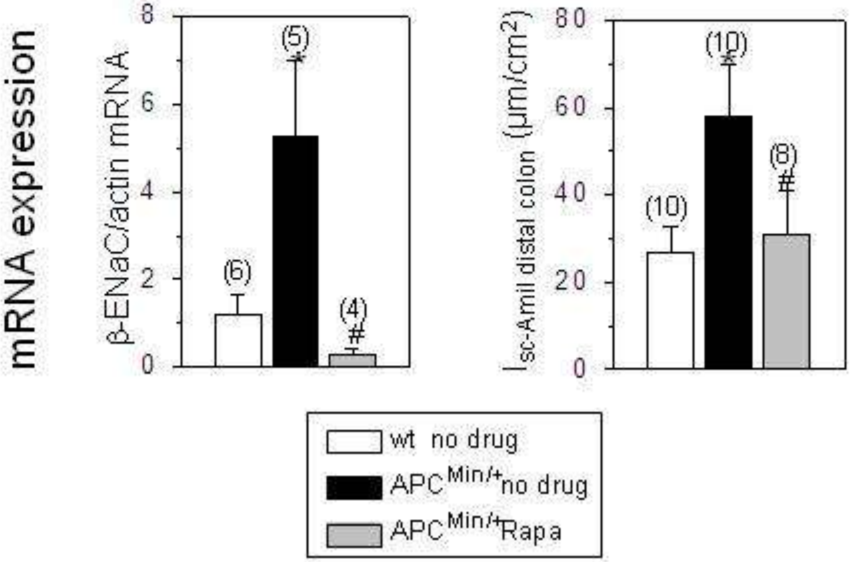






ENaC
(amilioride sensitive
Na^+ channel)

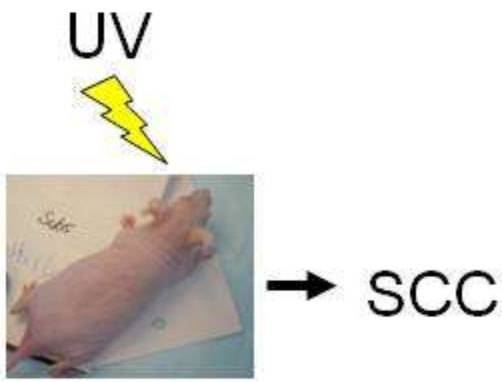
Inflammation | **DSS colitis**



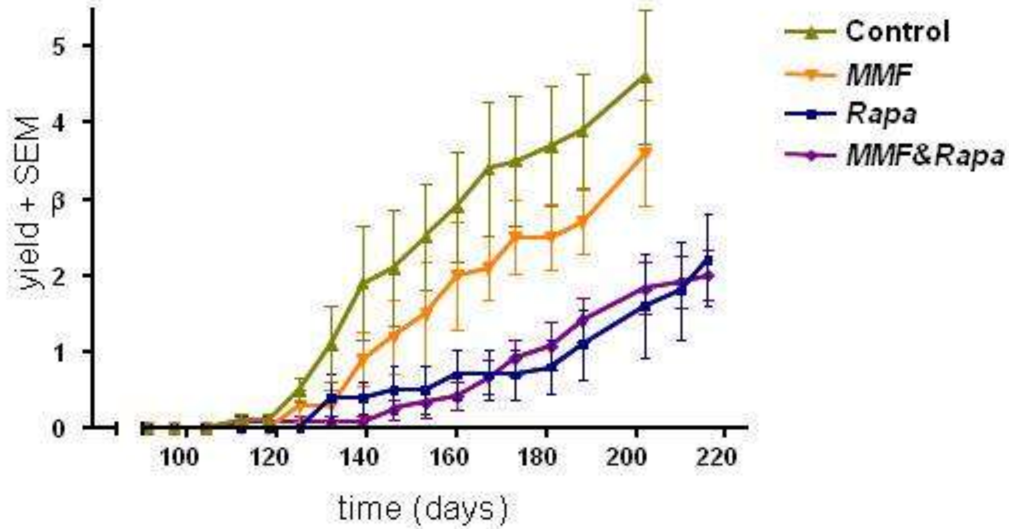
Koehl *et al*, *Oncogene*, Mar 2010

mTOR has a central role in cancer: **IV - UV DNA damage**

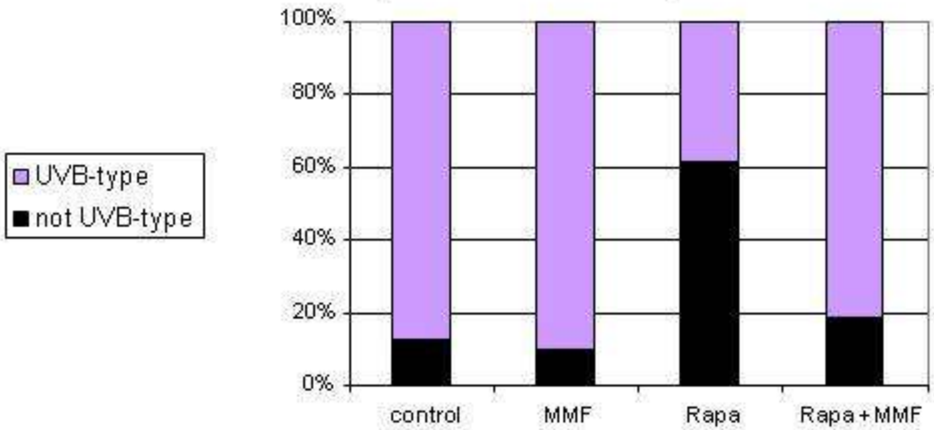
Experimental Model



Hairless Mice



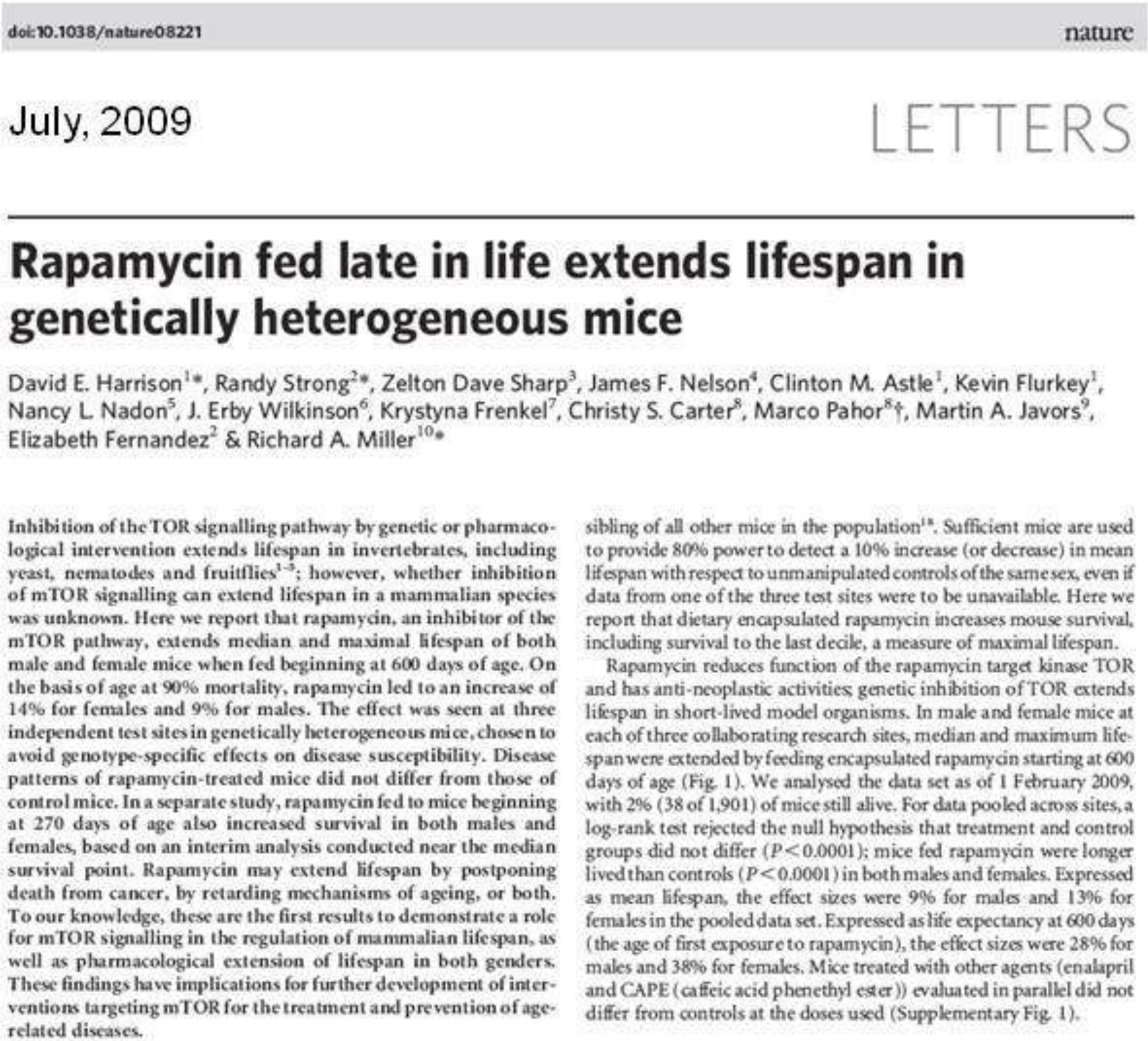
Alters p53 mutation pattern in SCC



Also, fewer p53 patches

de Gruijl et al. *Int J Cancer* Dec 2010

TOR pathway: metabolism regulation → lifespan effects


doi:10.1038/nature08221 nature

July, 2009

LETTERS

Rapamycin fed late in life extends lifespan in genetically heterogeneous mice

David E. Harrison[1]*, Randy Strong[2]*, Zelton Dave Sharp[3], James F. Nelson[4], Clinton M. Astle[1], Kevin Flurkey[1], Nancy L. Nadon[5], J. Erby Wilkinson[6], Krystyna Frenkel[7], Christy S. Carter[8], Marco Pahor[8]†, Martin A. Javors[9], Elizabeth Fernandez[2] & Richard A. Miller[10]*

Inhibition of the TOR signalling pathway by genetic or pharmacological intervention extends lifespan in invertebrates, including yeast, nematodes and fruitflies[1–3]; however, whether inhibition of mTOR signalling can extend lifespan in a mammalian species was unknown. Here we report that rapamycin, an inhibitor of the mTOR pathway, extends median and maximal lifespan of both male and female mice when fed beginning at 600 days of age. On the basis of age at 90% mortality, rapamycin led to an increase of 14% for females and 9% for males. The effect was seen at three independent test sites in genetically heterogeneous mice, chosen to avoid genotype-specific effects on disease susceptibility. Disease patterns of rapamycin-treated mice did not differ from those of control mice. In a separate study, rapamycin fed to mice beginning at 270 days of age also increased survival in both males and females, based on an interim analysis conducted near the median survival point. Rapamycin may extend lifespan by postponing death from cancer, by retarding mechanisms of ageing, or both. To our knowledge, these are the first results to demonstrate a role for mTOR signalling in the regulation of mammalian lifespan, as well as pharmacological extension of lifespan in both genders. These findings have implications for further development of interventions targeting mTOR for the treatment and prevention of age-related diseases.

sibling of all other mice in the population[18]. Sufficient mice are used to provide 80% power to detect a 10% increase (or decrease) in mean lifespan with respect to unmanipulated controls of the same sex, even if data from one of the three test sites were to be unavailable. Here we report that dietary encapsulated rapamycin increases mouse survival, including survival to the last decile, a measure of maximal lifespan.

Rapamycin reduces function of the rapamycin target kinase TOR and has anti-neoplastic activities; genetic inhibition of TOR extends lifespan in short-lived model organisms. In male and female mice at each of three collaborating research sites, median and maximum lifespan were extended by feeding encapsulated rapamycin starting at 600 days of age (Fig. 1). We analysed the data set as of 1 February 2009, with 2% (38 of 1,901) of mice still alive. For data pooled across sites, a log-rank test rejected the null hypothesis that treatment and control groups did not differ ($P < 0.0001$); mice fed rapamycin were longer lived than controls ($P < 0.0001$) in both males and females. Expressed as mean lifespan, the effect sizes were 9% for males and 13% for females in the pooled data set. Expressed as life expectancy at 600 days (the age of first exposure to rapamycin), the effect sizes were 28% for males and 38% for females. Mice treated with other agents (enalapril and CAPE (caffeic acid phenethyl ester)) evaluated in parallel did not differ from controls at the doses used (Supplementary Fig. 1).

CONCLUSION

- VHL: RCC determines morbidity and mortality
- Surgery: if possible NSS, (less than four lesions) which can lead to long time survival
- Because of recurrence nephrectomy may be necessary
- KTX can be the final solution given the discussed criteria