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 on average

- Cystic lesions:
  - 21% carcinoma, 26% atypical, 53% benign

- Solid lesions:
  - 90% carcinoma

- In the „normal” parts:
  - Microscopic cysts, clear cell neoplasia
Multicentric U.S. Study


- 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


- 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


- 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

MMF inhibits tumors \textit{in vitro}, BUT NOT \textit{in vivo} at relevant concentrations

\textbf{In vitro }\checkmark

\begin{itemize}
\item Colon CA
\item Melanoma
\item Gastric CA
\end{itemize}

\textbf{In vivo }\varnothing

\textit{Koehl et al. Transplantation, 2007}
mTOR has a central role in cancer: I - Angiogenesis

VEGF Signal

PI3K

mTOR

Endothelial Cell Growth
VEGF Transcription

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\textsuperscript{min})
- Skin cancer (p53)
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

![Diagram](image)
**mTOR has a central role in cancer: III - Oncogenic ion channels**

![Cell cycle diagram](image)

<table>
<thead>
<tr>
<th>family</th>
<th>subfamily</th>
<th>members</th>
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<th>type of tumor</th>
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<td>Kv1</td>
<td>Kv1.3, Kv1.5</td>
<td>prostate cancer cells, colonic cancer cells</td>
<td>neuroblastoma, breast carcinoma, small lung cell carcinoma, melanoma, lymphoma, hepatocarcinoma</td>
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<tr>
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<td>Kv3</td>
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<tr>
<td></td>
<td>Kv10</td>
<td>Eag1, Eag2</td>
<td>NIH 3T3, HeLa</td>
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<td>Erg1</td>
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<td>myeloid leukemia, neuroblastoma, colorectal cancer</td>
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<td>Elk1, Elk2</td>
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<td>hydroblastoma, glioma</td>
<td>hybrid cells (NG108-15), basophilic leukemia cells (RBL-2H3)</td>
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mTOR has a central role in cancer: III - Oncogenic ion channels

APC<sup>min/+</sup> - wt siblings

- Age: 5 weeks
- High fat diet
- End: age 20 weeks

Rapa Control

ENaC (amiloride sensitive Na<sup>+</sup> channel)

Inflammation → DSS colitis

mRNA expression

Koehl et al., Oncogene, Mar 2010
**mTOR has a central role in cancer:** IV - UV DNA damage

**Experimental Model**

UV → SCC

Hairless Mice

**Alters p53 mutation pattern in SCC**

Also, fewer p53 patches

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de Grujl et al. *Int J Cancer* Dec 2010
Rapamycin fed late in life extends lifespan in genetically heterogeneous mice


Inhibition of the TOR signalling pathway by genetic or pharmacological intervention extends lifespan in invertebrates, including yeast, nematodes and fruitflies; 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.
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