Renal Tumors

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Anatomy of Kidney

- pair of organs located in the abdominal cavity on either side of the spine in a retroperitoneal position.
- Adrenal glands rest on top of each kidney
- Approx. at vertebral level T12 to L3, right kidney being slightly lower than the left.
- Long axis of kidney is directed downward and laterally
- Approx. 11–14 cm in length, 6 cm wide and 4 cm thick
- Weighs around 150 gm in males & 135 gm in females.
- Mobile Organ, move vertically within retroperitoneum 0.9 cm to 1.3 cm., as much as 4 cm during normal respiration.
• The kidney is surrounded by tough fibrous tissue, the renal capsule, which is itself surrounded by perinephric fat, renal fascia (of Gerota) and paranephric fat.

• parenchyma, of the kidney is divided into two major structures: renal cortex and renal medulla.
Anat contd

• Blood Supply
  • Approx. 20% of the cardiac output.
  • From renal arteries, left and right, which branch directly from the abdominal aorta.
    • renal vein emerges from hilum and drains into the inferior vena cava.

• Lymph Drainage: to the lateral aortic lymph nodes around the origin of the renal artery.

• Nerve Supply:
  • Through renal sympathetic plexus (T10 – L1) fibres, mainly vasomotor.
  • Afferent nerves T10 to T12 thoracic nerves.

• Functions
  • Excretion of wastes,
  • Acid-base homeostasis,
  • Osmolality regulation, Blood pressure regulation and Hormone secretion
Renal Tumors

- 51,000 cases diagnosed and more than 12,900 deaths annually in the US

- Account for approx. 3% of adult malignancy
Renal tumors...

- **Benign**
  - Oncocytoma
  - Papillary adenoma
  - Angiomyolipoma

- **Malignant**
  - Renal Cell Carcinoma (Adenocarcinoma of Kidney)
Renal Cell Carcinoma

- First described by König in 1826.

- In 1883 Grawitz, noted the fatty content of cancer cells similar to that of adrenal cells.

- All these tumors arise from Renal tubular epithelium.

- Accounts for 80–85% of kidney cancer

- 2% to 4% increase in incidence per year
Epidemiology

• Male predominance (1.6:1.0 M:F)

• Highest incidence between age 50-70
  - Median age of diagnosis is 66 years
  - Median age of death 70 years

• Majority of RCC occurs sporadically

• Highest incidence in Scandinavia and North America, lowest in Africa
Risk Factors

- Tobacco smoking contributes to 24-30% of RCC cases
  - Tobacco results in a 2-fold increased risk
- Environmental:
  - Cadmium, thorium-di-oxide, petroleum and phenacetin analgesics.
- Occupational:
  - Leather tanners, shoe workers, asbestos workers.
- Hormonal:
  - diethylstilbestrol,
- Obesity, HTN
- 35% - 47% pt on long term dialysis develop Acquired polycystic kidney disease, out of which 5.8% develops Renal cancer.
RCC is not one disease...

It is made up of no. of different types of cancers with different histology, different clinical courses and caused by different gene.

<table>
<thead>
<tr>
<th>Type</th>
<th>Incidence (%)</th>
<th>Associated mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear cell</td>
<td>75%</td>
<td>VHL</td>
</tr>
<tr>
<td>Papillary type 1</td>
<td>5%</td>
<td>c-Met</td>
</tr>
<tr>
<td>Papillary type 2</td>
<td>10%</td>
<td>FH</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>5%</td>
<td>BHD</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>5%</td>
<td>BHD</td>
</tr>
</tbody>
</table>

A sarcomatoid variant represents 1% to 6% of renal cell carcinoma and these tumors are associated with a significantly poorer prognosis.

BHD=Birt-Hogg-Dubé; FH=fumarate hydratase; VHL=von Hippel-Lindau.
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Chromosome Location (Gene)</th>
<th>Renal Manifestations</th>
<th>Other Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Von Hippel-Lindau (VHL)</td>
<td>3p25 VHL</td>
<td>Clear cell renal carcinoma: solid and/or cystic, multiple and</td>
<td>Retinal and central nervous system hemangioblastomas; pheochromocytomas; pancreatic cysts and neuroendocrine tumors; endolymphatic sac tumors; epididymal and broad ligament</td>
</tr>
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<td>Syndrome</td>
<td>Chromosome Location</td>
<td>Renal Manifestations</td>
<td>Other Manifestations</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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<td>---------------------------------------</td>
</tr>
<tr>
<td>Hereditary papillary renal carcinoma type 1 (HPRC)</td>
<td>7q31 MET</td>
<td>Papillary renal carcinoma type 1: solid, multiple and bilateral</td>
<td>None</td>
</tr>
<tr>
<td>Hereditary leiomyomatosis and renal cell</td>
<td>1q42-43 FH</td>
<td>Papillary renal carcinoma type 2, collecting duct</td>
<td>Uterine leiomyomas and leiomyosarcomas;</td>
</tr>
<tr>
<td>Syndrome</td>
<td>Chromosome Location</td>
<td>Renal Manifestations</td>
<td>Other Manifestations</td>
</tr>
<tr>
<td>----------------------------------</td>
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<td>-------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------</td>
</tr>
<tr>
<td>Birt-Hogg-Dubé syndrome (BHD)</td>
<td>17p11.2 BHD</td>
<td>Hybrid oncocytic renal tumors, chromophobe and clear cell renal carcinomas,</td>
<td>Benign tumors of hair follicle (fibrofolliculomas); lung cysts,</td>
</tr>
<tr>
<td>Constitutiona l chromosome 3</td>
<td>3p; Not known; VHL</td>
<td>Clear cell renal carcinoma: multiple, bilateral</td>
<td>None</td>
</tr>
</tbody>
</table>
Consequences of VHL Gene Mutation

- Elongin B/C
- Cul2
- Rbx1

Ubiquitin Ligase Complex Disrupted

HIF-1α Accumulation

- VEGF, PDGFβ
- Glut-1, Erythropoietin
- PDGF

Angiogenesis
Increased metabolism
Endothelial stabilization
Autocrine growth stimulation
Natural History

- 7% diagnosed incidentally
- 45% present with localized disease, 25% with locally advanced disease, 30% with metastatic disease
- Lymph node metastases- 9% to 27% (renal hilar, para-aortic and paracaval)
- Renal vein – 21% & IVC 4%
- Distant metastases- lung (75%), soft tissue (36%), bone (20%), liver (18%), skin (8%) and CNS (8%)
Clinical Presentation

- Clinically occult for most of its course.
- Classic triad (occur in 5%-10% of patients)
  - flank pain,
  - hematuria,
  - palpable abdominal mass
- Hematuria present 40% of patients
- Systemic symptoms
  - Anaemia, Fatigue, Cachexia, Wt. Loss, Hypercalcemia, Hepatic Dysfunction
- Paraneoplastic Syndrome
  - Parathyroid like hormones, erythropoietin, renin, gonadotropins, placental lactogen, prolactin, enteroglucagon, insulin like hormones, adrenocorticotropic hormone and prostaglandins identified in RCC pt.
Diagnostic Work-Up

• General-History, Physical examination

• Laboratory studies
  • CBC, LFT's, alkaline phosphatase, BUN, creatinine, urinalysis

• Radiographic studies- Increased use of imaging has increased the detection of renal lesions most of which are simple cysts.
  • X-Ray KUB region
  • Ultrasonography- Excellent in distinguishing cystic from solid masses
  • Intravenous Urography - Starting point for hematuria evaluations and function of contralateral kidney
  • Computed tomography- Provides an excellent assessment of the parenchyma and nodal status.
  • Magnetic Resonance Imaging - excellent demonstration of solid renal masses and is image test of choice to demonstrate extent of vena caval involvement with tumor. Useful in patients with renal insufficiency
Metastatic Work-Up

- Chest X-ray or Chest CT
- CT/MRI scan of abdomen or pelvis
- Bone scan with plan films (for elevated alkaline phosphatase or bone pain).
Figure: Computed tomography demonstrates a right renal carcinoma (m) with a large contralateral adrenal metastasis (a).

Figure: CT scan shows large left renal mass with calcification (m) invading the left renal vein (arrow).
Figure: T1-weighted magnetic resonance image demonstrates tumor (m) and vascular invasion (arrow). Flowing blood (v) in the left renal vein is

Figure A: Axial T1-weighted image demonstrates a large left renal carcinoma with extension into the left renal vein (m) with protrusion into the IVC (v). B: Sagittal T1-weighted image shows the relation of the tumor thrombus (m) to the IVC (v) in the lateral projection.
## Robson Modification Of the Flocks & Kadesky Staging of RCC

<table>
<thead>
<tr>
<th>Tumor Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Renal cell carcinoma is confined to the kidneys</td>
</tr>
<tr>
<td>II</td>
<td>Renal cell carcinoma extends through the renal capsule but is confined to Gerota’s fascia</td>
</tr>
<tr>
<td>III</td>
<td>Renal cell carcinoma involves the renal vein or inferior vena cava (IIIA) or the renal hilar lymph nodes (IIIB)</td>
</tr>
<tr>
<td>IV</td>
<td>Renal cell carcinoma has spread to local adjacent organs (other than adrenal gland) or to distant sites</td>
</tr>
<tr>
<td></td>
<td>T - primary tumour</td>
</tr>
<tr>
<td>---</td>
<td>--------------------</td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour confined to kidney, &lt;7cm</td>
</tr>
<tr>
<td>T1a</td>
<td>≤4cm, confined to kidney</td>
</tr>
<tr>
<td>T1b</td>
<td>&gt;4cm but &lt;7cm, confined to kidney</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour &gt;7cm, confined to kidney</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour extends into major veins or adrenal or perinephric</td>
</tr>
<tr>
<td>T3a</td>
<td>Direct invasion of adrenal gland, perirenal and/or sinus fat</td>
</tr>
<tr>
<td>T3b</td>
<td>Gross extension into renal vein or IVC</td>
</tr>
<tr>
<td>T3c</td>
<td>Extends into IVC above diaphragm or wall of IVC</td>
</tr>
<tr>
<td>T4</td>
<td>Invasion beyond Gerota’s fascia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>N - regional lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>Regional lymph nodes not involved</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single regional lymph node</td>
</tr>
<tr>
<td>N2</td>
<td>Metastases in &gt;1 regional lymph node</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>M - distant metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Metastases cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases</td>
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</table>
## Staging

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>T1</td>
<td>No</td>
<td>Mo</td>
</tr>
<tr>
<td>II</td>
<td>T2</td>
<td>No</td>
<td>Mo</td>
</tr>
<tr>
<td>III</td>
<td>T3</td>
<td>No</td>
<td>Mo</td>
</tr>
<tr>
<td>III</td>
<td>T1</td>
<td>N1</td>
<td>Mo</td>
</tr>
<tr>
<td>III</td>
<td>T2</td>
<td>N1</td>
<td>Mo</td>
</tr>
<tr>
<td>IV</td>
<td>T4</td>
<td>No</td>
<td>Mo</td>
</tr>
<tr>
<td>IV</td>
<td>T4</td>
<td>N1</td>
<td>Mo</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>N2</td>
<td>Mo</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>
Prognostic factors for RCC

- Pathologic stage 5 yr survival
  - T1 - 2 organ confined 70-90%
  - T3 50-70%
  - N+, M1 5-30%

- Tumour size
  - < 4 cm > 90%
  - 4 - 10 cm 50%
  - > 10 cm 0%

- Histological type
  - Clear cell 70%
  - Papillary, Chromophobe 85%
  - Multilocular cystic 100%
  - Medullary, Collecting duct 0%
Management

• Localized disease
• Metastatic disease
Management of Localized disease

Localized disease

- Surgery
- Radio Therapy
Surgery- Radical nephrectomy

Gold standard treatment for localized RCC with contralateral normal kidney, adequate surgical margin.

Indications
1. Bilateral RCC
2. RCC in a solitary functioning kidney
3. Unilateral RCC with contralateral kidney under threat of its future function
   (Renal artery stenosis, Chronic pyelonephritis, Hydronephrosis, Ureteral reflux, Calculus disease, Systemic disease such as diabetes)
4. Tumor less than 4cms with normal opposite kidney.
   5. Five year survival rate 75% to 85%
   6. Local tumor recurrence of 10% is reported.

Other Approaches
1. Radio frequency ablations
2. Cryo ablation
Radiotherapy

- Radiosensitivity of RCC is variable
- Animal experiments suggest a theoretical benefit to preoperative RT (Reduce intra-operative seeding)
- Historically several series suggested clinical benefit to adjuvant (post-op) RT
  - Limited applicability because of long time span, improvements in staging, surgery, changing RT technology
Management of Metastatic Disease

- Surgery
- Radio Therapy
- Chemo Therapy
- Targeted Therapy
- Immuno Therapy
Surgery

- Palliative Nephrectomy – Indicated in patients with
  - Severe hemorrhage,
  - Severe pain,
  - Paraneoplastic syndrome
  - or compression of adjacent viscera
  - Solitary metastasis can be resected and may show some survival advantage
- Therapeutic:
  - Not curative but produce some long-term survivors.
  - The possibility of disease-free survival increases after resection of primary tumor and isolated metastasis excision.
  - to decrease tumor burden in preparation for subsequent therapy
Surgery...

- Resection of met’s
  - in pt. not relieved from palliative RT
  - In solitary mets.

- Spontaneous regression of met’s
  - < 1 % of cases
  - only 4 (0.8%) of 474 patients in 9 series who underwent nephrectomy experienced regression of metastatic foci
Radio Therapy

• Palliation
  • Used for local or symptomatic metastatic disease, such as painful osseous lesions or brain metastasis.
  • Treatment field encompasses metastatic deposit (or local recurrence) with 2-3cm margins
  • Higher doses (up to 35-40Gy) may be required to overcome radioresistance
  • Symptomatic relief in 64-84% of patients
Chemotherapy

- RCC is a chemo resistant tumor. Phenomenon due to presence of multi drug resistant glycoprotein (MDR) in tumor cell - causes extrusion of the drug

- Conventional therapy has little to offer

- 5-FU alone has a response rate of 10%,

- On-going clinical trials of combination chemotherapy including Gemcitabine and 5-FU

- Limited data reveals some response in non-clear cell RCC to Carboplatin, Cisplatin plus Gemcitabine
Targeted Molecular Therapy

• New treatment approach that targets only the cancer.

• In renal cell carcinoma patients, this type of therapy uses drugs that stop the new blood vessels from growing, and targets certain factors that cause the cells to grow.

• Tyrosine kinase (TK) inhibitors block the intracellular domain of the VGEF receptor
  - Sunitinib (Sutent)
  - Sorafenib (Nexavar)
Targeted Molecular Therapy...

- Monoclonal antibody that binds circulating VEGF preventing the activation of the VEGF receptor
  - Bevacizumab (Avastin)
- Mammalian target of rapamycin (mTor) inhibitors
  - Temsirolimus (TMSR)
Immunotherapy

• Systemic type of treatment used to improve the body’s natural defenses.
• Boosts the immune system and slows down the cancer growth
• Clinical response to immunotherapy seen in patients with
  1. Good performance status
  2. Had a prior nephrectomy
  3. Non bulky pulmonary or soft tissue metastasis
  4. Asymptomatic patient
• Interferon (IFN)
• Interleukin (IL -2)
Summary

- RCC is relatively rare but increasing incidence
- Associated with tobacco and inherited disorders
- Hematuria is a common symptom.
- Surgery is the only curative modality for Stage I, II, and III
- RCC is radio resistant, RT’s role in palliation
- Stage IV disease holds poor prognosis despite advancements in molecular understanding
- IL-2, Sorafenib, Sunitinib, and Temsirolimus are FDA approved treatments for advanced RCC
Thank you!

- Questions