RENAL CELL CARCINOMA

(Blog by Dr. S. UMA devi)

Renal cell carcinoma (RCC)

Introduction
Synonyms Renal adenocarcinoma, Hyper nephroma
A relatively rare and serious disease
The cancerous process starts in certain areas of the kidney.
Early stage renal cancers grow and spread slowly - have a better prognosis,
advanced/metastatic cancers rapidly progress and have a worse prognosis.

Facts and Figures about Renal Cell Carcinoma

- Approximately 210,000 new cases were diagnosed worldwide.
- 20-30 percent of RCC patients present with advanced (metastatic) disease at diagnosis.
- Five-year survival rates
  - If the tumor is confined to the kidney as high as 80-95 percent.
  - If with metastatic disease much lower - 20 percent.
- Until 2005, only limited treatment options were available.
- Interleukin-2 or interferon alfa was widely used as first-line treatment of metastatic disease.
  Overall survival rates in these patients was approximately 12 months.

Risk Factors

Smoking:
smoking doubles the risk of developing RCC.

Obesity:
obese people have a higher risk of developing many types of cancer, including RCC.
In 20 percent of RCC - obesity is a factor.

Age group
50-70yrs
Rare in young age.

Gender:
Men: women ratio 3:1

Family history and genetics:
a strong family history has a higher chance of developing RCC.
Certain genetic conditions including von Hippel-Lindau disease, a rare inherited disorder in
which there is abnormal growth of blood vessels in certain parts of the body, increase the risk of
developing RCC.
Other risk factors
Long term dialysis
Tuberous sclerosis

Histological sub types of RCC
Clear cell renal carcinoma  most common,less favorable prognosis
Papillary -15%
Chromophobe4%
Collecting duct carcinoma
And Medullary are aggressive and carry poor prognosis

Other types
Sarcomatoid(high grade end of all subtypes)
Heridity cancer syndrome
Multilocular
Mucinous,tubular and spindle cell carcinoma
Neuroblastoma associated RCC
Unclassified
Different subtypes have distinct genetic abnormalities
Genetic testing helps accurate diagnosis and detects recurrence

Biology of Renal Cell Carcinoma
• Two Proteins found at high levels in RCC
  1. Vascular endothelial growth factor (VEGF)
  2. Platelet-derived growth factor (PDGF)
• Overproduction of these proteins is caused by a genetic mutation,
• Most common of mutation is the inactivation of the von Hippel-Landau gene.
• VEGF and PDGF are important to the growth and survival of tumors.

High VEGF levels lead to angiogenesis –that feed the tumor.
High PDGF levels lead to the maturation and survival of newly formed and existing blood
vessels and supporting tissue.and thus to tumor progression
This knowledge is utilized for new therapeutic ventures

Clinical features
Symptoms of RCC
Hematuria – may be painless/blood clots can cause uretric colic
lump or a mass in the lumbar region with dull pain
Back pain /flank pain
Tiredness,
Loss of appetite,
Weight loss,
anemia,
Recurrent fever
Hypertension in advanced cases
May be asymptomatic at times.

**Signs**
1. Abdominal mass 25%
2. Varicocele on left side 2%
   (Tumor invasion of left renal vein leads to blocking of left testicular vein)
   Rt gonadal vein drains directly into IVC
3. Hypertension (secretion of rennin by the tumor)
4. Hirsutism (in females)
5. Stauffes syndrome-Paraneoplastic non metastatic liver disease

**Stages of renal cell carcinoma**
Stage I  Tumor confined to kidney; measures about 7 cm
Stage II  spread to fat tissue around kidney measures above 7 cm
Stage III  has 3 possible situations
INVESTIGATIONS
CT scan abdomen
MRI
Ultra sound KUSB area
Intravenous pyelography
Biopsy

Treatment
Cure is related to degree of dissemination and stage of tumor
Early-stage tmt-survival .prolonged (even when regional lymphatics involved)

Rare Variations in course
1. Sometimes locally advanced /metastatic cases show indolent course lasting several years
2. Late recurrence many years after treatment posible
3. Well documented case of spontaneous regression exists but may not survive long
Mainstay of therapy
Surgical removal
In disseminated cases-local regional therapy –is palliative
Systemic therapy-only limited effectiveness

Summary of treatment
Surgery -most common modality
  o Partial nephrectomy is as beneficial as total nephrectomy
  o Partial nephrectomy reduces chance of kidney failure

Radiation not very effective
Chemotherapy not very effective
Biological therapy
Immunotherapy
Biotherapy
Biological response modifier therapy
Biological therapy uses body’s immune system directly or indirectly
Can be complementary to surgery,radiation and chemotherapy
Hormone therapy

DETAILS OF TREATMENT
Treatment varies from patient to patient
Treatment approach takes 5 factors into consideration
1.RCC type
2.Tumorsize and location
3.Stage of cancer
4.General condition of the patient
5.Patients age

Treatment option
Surgery
Radiotherapy
Chemotherapy
Hormone therapy
Arterial embolisation
Target therapy
Biological therapy

SURGERY
2 types
1.Nephrectomy
2.Metastatic removal

Types of Nephrectomy

1.Partial nephrectomy-only part of kidney i.e.site of tumor
   Indications:
Patients with only one kidney
Bilateral RCC
Small tumor

2. **Radical nephrectomy**
Entire kidney, adrenal gland, tissues around the kidney and regional lymph nodes-removed

3. **Simple nephrectomy**
Removal of just kidney; no other additional tissues

**Nephrectomy** can be

I. **Open nephrectomy**

II. **Laprosopic nephrectomy**

*Common side effects of nephrectomy*

- Bleeding
- Wound infections
- Pneumothorax
- Damage to nearby organs—(Spleen, pancreas, aorta, vena cava, small large bowel)
- Kidney failure
- Laproscopic nephrectomy – I when tumor is small, confined

**ARTERIAL EMBOLISATION**

Embolisation of renal artery-
Using small pieces of gelatin sponge, or plastic microspheres or ethanol or chemotherapy— injected into renal artery

approach via femoral artery

this procedure shrinks the tumor before surgery

used for cases unfit for surgery.

Side effects; back pain, fever, nausea, vomiting

**CHEMO THERAPY**

Single drug /combination of several drugs

Administered in cycles (treatment period followed by recovery period)

- Route of administration— Oral or/Im or IV

But chemotherapy is not very effective

Drugs used— Vinblastin, Gemcitabin, 5-flurouracil

**RADIOTHERAPY**

Usually in the form of external beam therapy

1. Before surgery—to reduce size of tumor

2. After surgery—as adjuvant to destroy any remaining cancer cells

3. as palliative therapy

Radiation therapy is not very effective for RCC
**HORMONE THERAPY**
used in advanced stages
e.g. Medroxyprogesterone

**BIOLOGICAL THERAPY or IMMUNOTHERAPY**
Systemic therapy
Acts by improving body’s immune system
Used in cases of metastatic cancer
Interleukin2
Interferonalfa2a
Bevaci zumab
Side effects - Flu like symptom, kidney damage, breathing difficulty, intestinal bleed
Not very effective

**TARGETED THERAPY**
New approach
Targets only the tumor
Mechanism of action:
stop the new blood vessels from growing by blocking vascular endothelial growth factor
and platelet derived growth factor VEGF/PDGF
And targets certain factors which cause the cancerous cells to grow
Only 2 drugs have been approved by FDA.
**SORAFENIB** orally effective/in advanced stagess
Side effects; rashes, diarrhea, high BP, erythema/blistering of skin over palms and soles
**SUNITINIB** orally effective
S.E; Diarrhoea, high BP, altered taste, bleeding, hypothyroidism, skin colour change

**ANNEXURE**
Therapeutic Targets for RCC—Cell Proliferation and Angiogenesis

HIF = Hypoxia-induced factor; mTOR = Mammalian target of rapamycin; VEGF = Vascular endothelial growth factor; PDGF = Platelet-derived growth factor; TGF = Transforming growth factor.

Adapted from Kaclin WC. *Nat Rev Cancer*, 2002,2(9):673-682.
ss Fig2. VEGF as a molecular targeting factor in the treatment of RCC

**BEYOND VEGF INHIBITION**

**OPTIONS:**

INHIBITION OF OTHER MAJOR PATHWAYS

**mTOR as a molecular target**

mTOR stands for Mammalian Target of Rapamycin
Conclusions

- 30% of patients have distant metastases at RCC diagnosis
  - Metastatic disease is the principal cause of death
- Limitations of current therapies exist for RCC treatment
  - Cytotoxic treatments are minimally effective
  - Immunotherapy is associated with high treatment-related toxicities
- Targeted molecular therapies have demonstrated promising activity in RCC treatment
  - VEGF inhibitors (eg, bevacizumab, sunitinib, sorafenib)
  - mTOR inhibitors (eg, temsirolimus, everolimus [RAD001])
- Treatment landscape for mRCC is evolving
  - A need exists for new, effective, therapeutic options, especially in patients with TKI-refractory mRCC