ISSN 0975-6299 Vol.1/Issue-3/Jul-Sep.2010

International Journal of Pharma and Bio Sciences

OVERVIEW ON RENAL CELL CARCINOMA

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ABSTRACT

Cancer is a disease with uncontrolled multiplication and spread within the body of abnormal forms of the body's own cell. Renal-Cell Carcinomas (RCC) arises from the renal epithelium and account for about 85 percent of renal cancers accounting approximately 95000 deaths every year. Various types of renal carcinoma are conventional or clear-cell renal-cell carcinoma, papillary renal-cell carcinoma, oncocytoma, chromophobe renal-cell carcinoma, and collecting-duct renal-cell carcinoma. End-stage renal disease (ESRD) increases incidence of cancer at various sites. Common symptom of RCC is flank or abdominal pain, gross hematuria, and an abdominal mass, weight loss etc. Treatment of RCC includes surgery, chemotherapy, immunotherapy, stem cell transplant, tumor vaccine etc. Some molecular targeted therapies are also being used and many are under clinical trials. Diabetes, hypertension, tobacco addiction increases the probability of RCC while the green vegetables, fruits Ca^{++} supplements, vitamin E reduces the risk.

KEY WORDS

Renal-cell carcinomas, Chronic renal failure, End-stage renal disease (ESRD), Hypoxia-inducible factor a (HIFa), Hippel–Lindau tumor suppressor (VHL) gene.

INTRODUCTION

Cancer is a disease in which there is an uncontrolled multiplication and spread within the body of abnormal forms of the body's own cell. It is one of the major causes of death in the developed nations- at least one in five of the population in Europe and North America can expect to die in cancer[1]. According to the reports of the National Cancer Institute, U.S.A, there were about 49096 new cases of renal cancer among which 11033 patients died. Over 200,000 new cases of kidney cancer are diagnosed and more than 100,000 patients are died from the deadly disease each tear globally [2]. Renal Cell Carcinoma (RCC) is most common malignant tumor of the kidney, highly aggressive in nature

and most lethal among urologic malignancies [3]. Renal-cell carcinomas arise from the renal epithelium and account for about 85 percent of renal cancers. It accounts approximately 95000 deaths per year and it is steadily increasing at rate of 2.5% per year across population group [4, 5].

Many prognostic factors involving anatomical, histological and clinical aspects of the disease have been identified in RCC: the TNM staging system, tumor grade, sarcomatoid features, tumor size, performance status etc [6, 7]. approximately one third of the patients present with metastatic disease and up to 40% of the patients recur following surgery for clinically localized disease [8]. However no satisfactory results exist for patients with advanced RCC at present and the response rate with immunotherapy using INFα and IL-2 is less than 20% [9]. Selective advances in diagnosis, staging and treatment of patient with RCC have resulted in improved survival of a selected group of patient and overall change in natural history of the disease [10, 11].

Tumor types and molecular pathogenesis

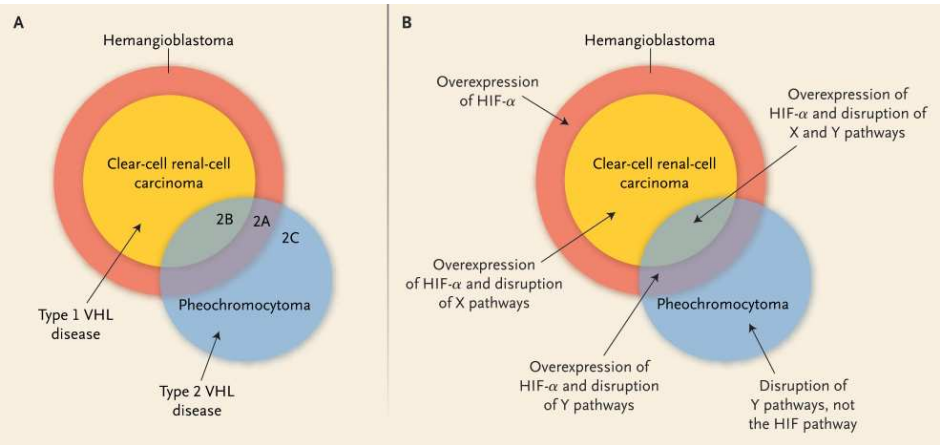
Conventional or clear-cell renal-cell carcinoma (CC-RCC)

Von Hippel–Lindau disease is an autosomal dominant, rare, familial cancer syndrome consisting chiefly of retinal angiomas, hemangioblastomas of the central nervous system, pheochromocytomas, and renal-cell carcinoma of the clear-cell type (Fig. 1). The gene responsible for the disease was identified in 1993 naming von Hippel–Lindau tumor suppressor (VHL) gene [12]. In this disease, one VHL allele is mutated inharitantly. RCC arise from the inactivation or silencing of the remaining normal (wild-type) VHL allele (Fig. 2). Defects in the VHL gene is responsible for about 60 percent of the cases of sporadic clear-cell renal-cell carcinoma, which is a major portion of all cases of renal-cell carcinoma [13].

VHL protein functions as a tumor suppressor, inhibiting growth when reintroduced into cultures of renal-cell carcinoma [14, 15]. Hypoxia-inducible genes are normally inhibited by VHL protein, including several encoding proteins involved in cell growth (e.g., transforming growth factor a [TGFa]), angiogenesis (e.g., vascular endothelial growth factor [VEGF]), acid–base balance (e.g., carbonic anhydrase IX [CA9]) and glucose uptake (e.g., the GLUT-1 glucose transporter)[16]. When VHL protein is lost, these proteins are over expressed, creating a microenvironment favorable for epithelial-cell proliferation. These VHL-regulated pathways are being studied as potential targets of therapies for clear-cell renal-cell carcinoma.

Loss of the translocated chromosome 3p probably implicates VHL protein in the development of these tumors. Additional translocations of chromosome 3 have been associated with clear-cell renal-cell carcinoma [17].

Figure 1
Schematic Representation of the Clinical Spectrum of von Hippel–Lindau Disease and Potential Biologic Mechanisms [18].



In Panel A, 3 major manifestations of von Hippel–Lindau (VHL) disease are central nervous system hemangioblastoma, pheochromocytoma, and clear-cell renal-cell carcinoma — are represented as Venn diagrams. Families affected by it may not have all three conditions, depending largely on the type of mutation in the inherited VHL gene. The most common type is Type 1 VHL disease which includes clear-cell renal-cell carcinoma with central nervous system hemangioblastoma and it is due to major disruptions in the VHL protein, resulting from truncating mutations. Type 2B disease affected patients have all three conditions, whereas type 2A includes hemangioblastoma and pheochromocytoma and type 2C patients suffer only from pheochromocytoma.

In Panel B, the spectrum of manifestations of von Hippel–Lindau disease, along with biochemical studies are shown. The mutations in VHL protein which disrupt the ubiquitination and destruction of hypoxia-inducible factor a (HIFa) are the same as those that correlate with the lesions of hemangioblastoma. Von Hippel–Lindau disease type 2A mutations disrupt HIFa processing but do not cause renal cancer. So additional, unknown VHL pathways (called X pathways) must be disrupted along with HIF pathway for development of clear-cell renal-cell carcinoma. Pheochromocytomas can arise from mutations in the gene for VHL protein that do not affect HIFa processing, suggesting that they arise through the disruption of other unknown VHL pathways (called Y pathways).

Papillary renal-cell carcinoma

Papillary renal-cell carcinoma occurs in several familial syndromes. The survival rate for metastatic papillary renal-cell carcinoma is probably less than that for clear-cell renal-cell carcinoma [19]. End stage renal diseases increase the risk of both types. Chromosome 7 is duplicated in 75 percent of sporadic papillary cases. There are two subtypes of papillary renal-cell carcinoma [20]. In case of Type 1 tumors, the papillary lesions covered by small cells with small oval nuclei with indistinct nucleoli and pale cytoplasm, and papillary lesions are covered by large cells with abundant eosinophilic cytoplasm and large, spherical nuclei with distinct nucleoli in case of type 2 tumors. Type 2 tumors are genetically more heterogeneous, have a poorer prognosis, and may arise from type 1 tumors [21]. Hereditary type is an autosomal dominant

disorder [22] and responsible the mutated gene has been identified at chromosome7 which encodes MET, a tyrosine kinase receptor that is normally activated by hepatocyte growth factors [23]. MET receptor tyrosine kinase domain undergoes auto activating amino acid substitution mutations, which promote cellular transformation [24]. Subsequently, chromosome 7 harboring the *MET* mutation is duplicated, increasing the gene dose [25, 26]. So, the hereditary type of papillary renal Carcinoma differs significantly from that of sporadic type on the point of pathogenesis.

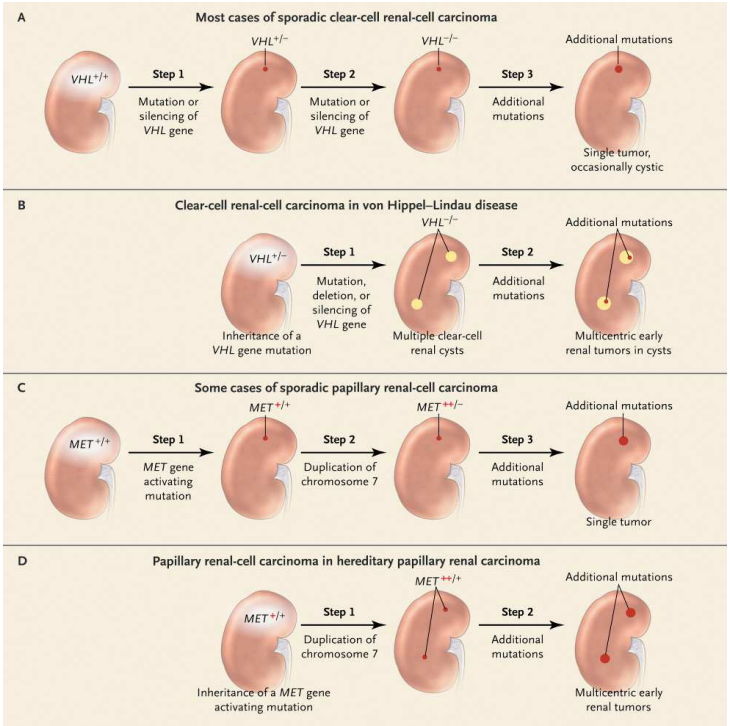
Oncocytoma and chromophobe renal-cell carcinoma

Oncocytoma is thought to originate from type A intercalated cells of the collecting duct, whereas chromophobe renal-cell carcinoma is thought to originate from type B intercalated cells. Both of oncocytomas and chromophobe variant of renal-cell carcinoma accounts for 4% among all cases of renal-cell carcinoma [27] and may also have a benign course after surgery, provided that the tumor stage and grade are favorable [28]. The Birt–Hogg–Dubé syndrome is a rare autosomal dominant disorder which is characterized by hair-follicle hamartomas (fibrofolliculomas) of the face and neck [29- 32]. *BHD,* the gene encodes the protein folliculin [33], a suspected tumor suppressor. In sporadic renal-cell carcinoma, *BHD* mutations occur rarely [34, 35].

Collecting-duct renal-cell carcinoma

Collecting-duct renal-cell carcinoma occurs for less than 1 % of all cases of renal-cell carcinoma and is typically an aggressive tumor. Medullary carcinoma of the kidney, which may be a variant of the collecting-duct type, is associated with sickle cell trait or disease. The collecting-duct form may be most similar to transitional-cell carcinoma of the urothelium [36].

Figure 2
Steps in the Development of Renal-Cell Carcinoma [18]



A plus sign in red type represents a mutated, activated allele; two plus signs in red type represent duplication of that allele. In contrast to sporadic renal-cell carcinoma (Panels A and C), fewer steps are required for the development of renal-cell carcinoma in the inherited forms of the disease (Panels B and D), because all of the patient's cells have a mutation that predisposes the patient to the disease. In von Hippel–Lindau disease, a cellular recessive mechanism is involved, since both copies of the *VHL* gene are inactivated (Panels A and B). In hereditary papillary renal carcinoma, one copy of the *MET* gene has an activating mutation, which is inherited (Panel D). Activated *MET* is a classic oncogene. A plus sign represents the wild-type allele; a minus sign represents a null allele.

Malignancy and chronic renal failure

Increased incidence of cancer at various sites is observed in patients with end-stage renal disease (ESRD). Certain malignant diseases, such as lymphomas and carcinoma of the kidney show an enhanced prevalence compared with the general population. In particular, renal cell carcinoma (RCC) shows an excess incidence in ESRD patients [37]. The prevalence of renal cell carcinoma (RCC) in hemodialysis and renal transplant patients is approximately 40 to 100 times greater than that in the general population [38-40]. On the other hand, we have reported a 2% incidence of end-stage renal disease (ESRD) from unilateral RCC and associated pathology in the contra lateral kidney [41]. The overall incidence of malignancy after transplantation is three to five times higher than in the general population [42-45]. In a high proportion of hemodialysis patients, long-term analgesic abuse is the cause of renal failure, which may be associated with urothelial carcinomas as well as RCC in particular, after renal transplantation [46].

Symptoms and prognosis

RCC exhibits a 2:1 male predominance in adults, but in pediatric group no clear pattern exists
The most common symptom in pediatric RCC is flank or abdominal pain, gross hematuria, and an abdominal mass [47- 49]. Although paraneoplastic signs are infrequently documented in children, but a high frequency of general symptoms (42.5%) such as fever (22.5%), nausea/vomiting (17.5%), pallor (10%), malaise (10%), and weight loss (5%) are found. For metastatic renal-cell carcinoma, poor prognostic factors include a low Karnofsky performance-status score (a standard way of measuring functional impairment in patients with cancer), a high level of serum lactate dehydrogenase, a low hemoglobin level, and a high corrected level of serum calcium [50, 51].

Prognostic biomarkers associated with RCC

During the past decade, a large no of potentially important Prognostic biomarkers have been studied but their clinical uses still remain controversial [52].

Markers	Prognostic value	Possibility as target
Hypoxia inducible factors		
1. HIF 1α	Yes	Not investigated
2. CAIX	Yes	No?
3. VEGF	Yes	Yes
IAP family and related proteins		
1. c-IAP, c-IAP2	Yes	No

2. X IAP	Yes	No
3. Survivin	Yes	Yes
4. Livin	No	Yes
5. Smac/DIABLO	Yes	No
Immunogenic markers		
1. Regulatory T cells	Yes	Yes
2. B7-H1, B7H4	Yes	Yes

Treatment of RCC

Surgery for metastatic disease

Surgical excision of a solitary metastasis in patients with advanced renal-cell carcinoma is recommended in many cases, but this approach has not yet been proved to be effective in prolonging survival. The combination of interferon alfa and nephrectomy is superior to interferon alfa alone, offering a survival advantage of 3 to 10 months [53, 54].

Nephron-sparing partial nephrectomy

Nephron-sparing partial nephrectomy has gained acceptance for treating tumors less than 4 cm in diameter. Results achieved with nephronsparing surgery are similar to those with radical nephrectomy, but a disadvantage is a rate of local recurrence of 3 to 6 % [55].

Laparoscopic nephrectomy

The laparoscopic approach has been used for both radical nephrectomy and partial nephrectomy which has accelerated the evolution toward minimally invasive surgical management of renal-cell carcinoma. The benefits include a shorter hospitalization, decreased postoperative pain and quicker recovery. However, it is a technically demanding procedure with the potential for increased preoperative complications [56].

Robot-assisted partial nephrectomy for large renal tumors

The benefits of robotic assistance in this procedure have been demonstrated in patients with small tumors, but its performance has yet to be evaluated in patients with larger tumors [57]. The total surgical process involves 10 steps including trocar placement, medical mobilization of the bowel, tumor identification, tumor excision, renal reconstruction, specimen retrieval and closure etc [58].

Percutaneous ablative approaches

Percutaneous thermal ablative techniques that use radiofrequency heat ablation [59] or cryoablation [60] to destroy tumor cells are the newer trends. A needle probe is advanced through the skin and directed into the tumor under image guidance. The rates of complications appear to be low, but reported adverse events include intraoperative and postoperative hemorrhage, urinary leakage, and injury to adjacent structures.

Chemotherapy

Chemotherapy option is more suitable for advanced non–clear-cell renal- cell carcinoma, particularly the carcinoma of collecting-duct [61, 62] .Response rates to chemotherapy alone are only 4 to 6 percent [63]. Phase 2 trial on carboplatin and paclitaxel for the collecting-duct carcinoma of the disease is under way.

Immunomodulatory therapies

The immunomodulatory therapy is used to boost either tumor antigenicity or host surveillance. Unique tumor antigens may also be inducible in renal-cell carcinoma [64].

Interferon α

About 14 % of cases of metastatic clear-cell renal carcinoma respond to interferon α alone. Various doses and routes have been used [65]. The side effects of the drug are not onerous; it can be used in combination with other agents in experimental approaches.

Interleukin-2

Interleukin- 2 is a major growth factor and activator of cytotoxic and other T-lymphocytes. It is applied in the therapy of metastasing renal carcinoma and melanoma. Side effects include hypotension, arrhythmias, edema, pruritus, erythema, central nervous symptoms, fever, and many others [66]. High-dose interleukin-2 is the standard therapy for advanced renal-cell carcinoma and is the only regimen for this disease approved by the FDA. High-dose interleukin-2 induces responses in 21 percent of patients, as compared with only 13 percent of patients who receive low-dose interleukin- 2 [67]. Interleukin-2 has also been used in combination with other drugs, but it is unclear whether combined therapy achieves better results than interleukin-2 alone. Thus, interleukin- 2 is a highly effective therapy for a subgroup of patients with metastatic disease.

Stem-cell transplantation

Allogeneic stem-cell transplantation appears promising for treating clear-cell renal cell carcinoma. The Protocols includes myelosuppressive pretreatment, followed by an infusion of donor CD34+ cells and T cells from an HLA-identical sibling [68]. However, results are variable depending on the centers. The drawbacks are severe graft-versushost disease and the need for a haplotype-matched sibling donor.

Tumor vaccines

The promising approach of the treatments to enhance host immunity in advanced clear-cell renal carcinoma is using autologous or donor dendritic cells, which starts a primary immune response by presenting antigen in the context of costimulatory molecules. Dendritic cells can be pulsed with tumor protein [69], DNA or RNA [70], they can even be fused with tumor cell [71, 72] to present tumor antigens in a context favorable for therapy. The vaccines are generally well tolerated and combined administration of cytokines and vaccines may improve the response to vaccines.

Molecular targeted therapy for RCC

The discovery of molecular links underlying the relationship between VHL, hypoxia signaling and the VEGF in the biology of CC- RCC has identified a pathway that is potential treatment target. Many novel molecular targeted therapeutic agents including small molecules, tyrosine kinase inhibitors (TKIS), and human monoclonal antibodies are currently preclinical and clinical trials. The small molecules inhibitor and other monoclonal VEGF anti body have shown anti tumor antitumor activity in randomized clinical trials [73-76]. There is a list of novel therapeutic agents in summarized manner [77].

Agents	Class	Mechanism of action	Clinical trial phase	FDA approved for RCC
Sorefinib	Small molecule	TKI of VEGFR, PDGFR, Ras	II,III	Dec 2005
Sunifinib	Small molecule	TKI of VEGFR, PDGFR	II, III	Jan 2006
AG-0736	Small molecule	TKI of VEGFR, PDGFR	II	
Pazopanib	Small molecule	TKI of VEGFR, PDGFR	II, III	
PTK 787	Small molecule	TKI of VEGFR, PDGFR	I	
Zalmatinib	Small molecule	TKI of PD	II	
Gefitinib	Small molecule	TKI of EGFR	II	
Erlotinib	Small molecule	TKI of EGFR	II ,III	
Lapatinib	Small molecule	TKI of EGFR/ Erb2	II, III	

Bortezomib	Small molecule	Inhibitor of 26S proteosome	II	
RAD 001	Small molecule	mTOR inhibitor	II	
Temsirolimus	Small molecule	mTOR inhibitor	II, III	May 2007
Cetuximab, ABX-EGF	Monoclonal antibody	Antibody of EGFR	II	
G 250	Monoclonal antibody	Antibody of CAIX	II	
Bevacixumab	Monoclonal antibody	Antibody of VEGF	II	
VEGF trap	Monoclonal antibody	Antibody of VEGF	II	

Factors associated with RCC

Diabetes and Hypertension

In hypertension, a variety of angiogenic and other growth factors, the levels of which are increased in persons with hypertensive disease, may be involved in renal carcinogenesis. A similar mechanism may be involved in the development of RCC among diabetic patients [78].

Role of Tobacco

Smoking is a major oxidative stress in addition to being a source of mutagens. In particular, for cancer of the kidney and the urinary tract, the pathogenetic role of smoking has been demonstrated. Furthermore, in some virus-induced malignancies such as cancer of cervix uteri, nicotine has been assumed as a cocarcinogen. In ESRD, the consequences of smoking may be aggravated by the accumulation of nicotine [79, 80].

Dietary factors and chemoprevention

Diet play an important role in cancer etiology and its prevention, cancer can be reduced substantially by dilatory modification [81]. Report of European Prospective Investigation into cancer and Nutrition (EPIC) says that overall non significant association between vegetable and fruits intake and RCC risk were observed, but an inverse relation was found for root vegetables [82]. Some studies shows that the risk of RCC decreased with increasing intake of fruits and vegetables particularly with banana, salad vegetables, dark green vegetables, cruciferous vegetable, vitamin E, Ca^{++} supplements etc [83, 84]. Dietary fibers play a beneficial role on of renal cell carcinoma [85]. Garlic, bitter melon, green tea, fish (fish oil rich with ω_3 fatty acid), fenugreek are the dietary agent that may have both anti obesity and anti cancer affect [86].

CONCLUSION AND FUTURE DIRECTIONS

Over the past 5 years, advances a lot in the understanding of RCC biology. This understanding has translated into development of new medication and therapies with better clinical response. Clinical trials of many promising compounds are on the verge. We are waiting for the fruitful results. Unfortunately, following targeted therapies are not the permanent solution and not all patients benefit clinically from these agents. We are now attempting to identify molecular markers that are associated with good clinical responses. Target over the combination treatment strategies that concurrently inhibit multiple growth factor pathways including RTKs (e.g., receptors for PDGF, VEGF, and EGF), Ras/Map kinase and phosphatidylinositol 3-kinase-AKT-mTOR pathways may be beneficial over conventional dose regimen. Development of specific HIF-1 inhibitors is also a challenging job ahead of us as there are effective HIF-1 inhibitors in animal models still now. Ultimately, we expect to learn that the evolution of RCC is not entirely dependent on HIF-1 and RTKs, and other pathways that drive clear-cell RCC progression will need to be discovered and novel inhibitors synthesized and tested clinically.

ACKNOWLEDGEMENT

We are grateful to Professor Debesh Chandra Majumdar, Chairman and Professor Kalyan Kumar Sen, Principal of Gupta College of Technological Sciences for their kind help and inspiration for writting this review.

REFERENCE

1. Rang HP, Dale MM, Ritter JM, Moore PK. Pharmacology. 5th Edn, Elservier: 693, (2006).
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics 2002. CA Cancer J Clin, 55: 74-108, (2005).
3. Jamel A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin, 57: 43-66, (2007).
4. Vogelzang NJ, Stadler WM. Kidney cancer Lancet.352: 1691-1696, (1998).
5. Hock LM, Lynch J, Balaji KC. Increasing incidence of all stages of kidney cancer v in last 2 decades in United States: an analysis of surveillance, epidemiology and end result program data. J Urol, 167: 57-60, (2002).
6. Lam JS, Shavarts O, Leppert JT, Figlin RA, Belldegrun AS. Renal cell carcinoma 2005: New frontiers on staging, prognostication and targeted molecular therapy. J Urol, 1673: 1853-1858, (2005).
7. Lohse CM, Chevile. A review of prognostic pathologic features and algorithms for patients treated surgically for renal cell carcinoma. Clin Lab Med, 25:433-446, (2005).
8. Lam JS, Leppert JT, Figlin RA, Belldegrun AS. Surveillance following radical or partial nephrectomy for renal cell carcinoma. Curr Urol. Rep, 6: 7-18, (2005).
9. Kitamura H, Hoxma I, Torigoe T, Asanuma H. Sato N, Tsukamato T. Down regulation of class 1 antigen is a prognostic factor for clear cell carcinoma. . J Urol, 177: 1269-1272, (2007).
10. Panuck AJ, Zisman A, Belldegrun AS. The changing natural history of renal cell carcinoma. J Urol, 166: 1611-1623, (2001).
11. Lam JS, Breda A, Belldegrun AS, Figlin RA. Evolving principle of surgical management and prognostic factor for outcome in renal cell carcinoma. J Clin Oncol, 24: 5565-5575, (2006).
12. Latif F, Tory K, Gnarra J, *et al*. Identification of the von Hippel-Lindau disease tumor suppressor gene. Science, 260: 1317-1320, (1993).
13. Kim WY, Kaelin WG. Role of VHL gene mutation in human cancer. J Clin Oncol, 22: 4991-5004, (2004).
14. Iliopoulos O, Kibel A, Gray S, Kaelin WG Jr. Tumour suppression by the human von Hippel-Lindau gene product. Nat Med, 1: 822-826, (1995).
15. Chen F, Kishida T, Duh FM, *et al*. Suppression of growth of renal carcinoma cells by the von Hippel-Lindau tumor suppressor gene. Cancer Res, 55: 4804-4807, (1995).
16. Iliopoulos O, Levy AP, Jiang C, Kaelin WG Jr, Goldberg MA. Negative regulation of hypoxia-inducible genes by the von Hippel-Lindau protein. Proc Natl Acad Sci USA,93:10595-10599, (1996).
17. Cohen AJ, Li FP, Berg S, et al. Hereditary renal-cell carcinoma associated with a chromosomal translocation. N Engl J Med, 301:592, (1979).
18. Cohen HT, McGovern FJ. Renal-Cell Carcinoma. N Engl J Med, 353:2477-24790, (2005).
19. Motzer RJ, Bacik J, Mariani T, Russo P, Mazumdar M, Reuter V. Treatment outcome and survival associated with metastatic renal cell carcinoma of non-clear-cell histology. J Clin Oncol, 20:2376-23781, (2002).
20. Delahunt B, Eble JN. Papillary renal cell carcinoma: a clinicopathologic and

immunohistochemical study of 105 tumors. Mod Pathol, 10:537-544, (1997).
21. Gunawan B, von Heydebreck A, Fritsch T, et al. Cytogenetic and morphologic typing of 58 papillary renal cell carcinomas: evidence for a cytogenetic evolution of type 2 from type 1 tumors. Cancer Res, 63:6200-6205, (2003).
22. Zbar B, Glenn G, Lubensky I, et al. Hereditary papillary renal cell carcinoma: clinical studies in 10 families. J Urol, 153: 907-912, (1995).
23. Schmidt L, Duh FM, Chen F, et al. Germline and somatic mutations in the tyrosine kinase domain of the MET protooncogene in papillary renal carcinomas. Nat Genet, 16: 68-73, (1997).
24. Jeffers M, Schmidt L, Nakaigawa N, et al. Activating mutations for the met tyrosine kinase receptor in human cancer. Proc Natl Acad Sci USA, 94:11445-11450, (1997).
25. Fischer J, Palmedo G, von Knobloch R, et al. Duplication and over expression of the mutant allele of the MET proto-oncogene in multiple hereditary papillary renal cell tumors. Oncogene, 17:733-739, (1998).
26. Zhuang Z, Park WS, Pack S, et al. Trisomy 7-harbouring non-random duplication of the mutant MET allele in hereditary papillary renal carcinomas. Nat Genet, 20:66-69, (1998).
27. Cheville JC, Lohse CM, Zincke H, Weaver AL, Blute ML. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. Am J Surg Pathol, 27:612-624, (2003).
28. Peyromaure M, Misrai V, Thiounn N, *et al*. Chromophobe renal cell carcinoma: analysis of 61 cases. Cancer, 100:1406-1410, (2004).
29. Toro JR, Glenn G, Duray P, *et al*. Birt-Hogg-Dube syndrome: a novel marker of kidney neoplasia. Arch Dermato, 135:1195-1202, (1999).
30. Birt AR, Hogg GR, Dube WJ. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. Arch Dermatoi, 113:1674-1677, (1977).
31. Zbar B, Alvord WG, Glenn G, *et al*. Riskof renal and colonic neoplasms and spontaneous pneumothorax in the Birt-Hogg- Dube syndrome. Cancer Epidemiol Biomarkers Prev, 11:393-400, (2002).
32. Weirich G, Glenn G, Junker K, *et al*. Familial renal oncocytoma: clinicopathological study of 5 families. J Urol, 160:335-340, (1998).
33. Nickerson ML, Warren MB, Toro JR, *et al*. Mutations in a novel gene lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with the Birt- Hogg-Dube syndrome. Cancer Cell, 2: 157-164, (2002).
34. Da Silva NF, Gentle D, Hesson LB, Morton DG, Latif F, Maher ER. Analysis of the Birt-Hogg-Dube (BHD) tumour suppressor gene in sporadic renal cell carcinoma and colorectal cancer. J Med Genet, 40:820-824, (2003).
35. Khoo SK, Kahnoski K, Sugimura J, *et al*. Inactivation of BHD in sporadic renal tumors. Cancer Res, 63:4583-4587, (2003).
36. Cohen HT, McGovern FJ. Renal-Cell Carcinoma. N Engl J Med, 353(23): 2477-2490, (2005).
37. Ramon Peces. Malignancy and Chronic Renal Failure, Saudi J Kidney Dis Transpl, 14(1) .5-14, (2003).
38. Ishikawa I. Uremic acquired renal cystic disease: Natural history and complications. Nephron, 58:257-567, (1991).
39. Hoshida Y, Nakanishi H, Shin M, Satoh T, Hanai J, Aozasa K. Renal neoplasias in patients receiving dialysis and renal transplantation: Clinico-pathological features and P53 gene mutations. Transplantation, 68:385-390, (1999).

40. Doublet JD, Peraldi MN, Gattegno B, Thibault P, Sraer JD. Renal cell carcinoma of native kidneys: prospective study of 129 renal transplant patients. J Urol, 158:42-44, (1997).
41. Peces R, Alvarez-Navascues R. Unilateral renal cell carcinoma with coexistent renal disease: a rare cause of end-stage renal disease. Nephrol Dial Transplant, 16:291-4, (2001).
42. Birkeland SA, Lokkegaard H, Storm HH. Cancer risk in patients on dialysis and after renal transplantation. Lancet, 355: 1886-1887, (2000).
43. Birkeland SA. De novo cancers compli-cating renal transplantation: Experience in the Nordic countries. Ann Transplant, 2:22-26, (1997).
44. Hoshida Y, Tsukuma H, Yasunaga Y, *et al*. Cancer after renal transplantation in Japan. Int J Cancer, 71:517-529, (1997).
45. Peto J. Cancer epidemiology in the last century and the next decade. Nature, 411:390-305, (2001).
46. Pommer W, Bronder E, Klimpel A, Helmert U, Greiser E, Molzahn M. Urothelial cancer at different tumour sites: Role of smoking and habitual intake of analgesics and laxatives. Results of the Berlin Urothelial Cancer Study. Nephrol Dial Transplant, 14:2892-2897, (1999).
47. Indolfi P, Terenziani M, Casale F, *et al*. Renal cell carcinoma in children: a clinicopathologic study. J Clin Oncol, 21(3):530-535, (2003).
48. Asanuma H, Nakai H, Takeda M, *et al*. Renal cell carcinoma in children: Experience at a single institution in Japan. J Urol, 162 (4):1402-1405, (1999).
49. Selle B, Furtwangler R, Graf N, *et al*. population based study of renal cell carcinoma in children in Germany, 1980-1995. Cancer; 107(12):2906-14, (2006).
50. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. J Clin Oncol, 17:2530-2540, (1999).
51. Motzer RJ, Bacik J, Schwartz LH, *et al*. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol, 22:454-463, (2004).
52. Hiroshi takamura, taiga tsukamoto. Prognostic biomarker of renal cell carcinoma: Recent advances.Indian J Urol. 2008, 24(1): 10-15, (2008).
53. Flanigan RC, Salmon SE, Blumenstein BA, *et al*. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med, 345:1655-1659, (2001).
54. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomized trial, Lancet, 358:966-970, (2001).
55. Novick AC. Nephron-sparing surgery for renal cell carcinoma. Annu Rev Med, 53:393-407, (2002).
56. Gill IS, Matin SF, Desai MM, *et al*. Comparative analysis of laparoscopic versus open partial nephrectomy for renal tumors in 200 patients. J Urol, 170:64-68, (2003).
57. Patel, M. N. *et al.* Robotic partial nephrectomy for renal tumors larger than 4 cm. *Eur. Urol.* 57, 310–316, (2010).
58. Patel MN, Bhanddari M, Menon M, Rogers CG. Robotic assisted partial nephrectomy: Has it come of age?. Indian J Urol, 25.523-528, (2009).
59. Zlotta AR, Wildschutz T, Raviv G, *et al*. Radiofrequency interstitial tumor ablation (RITA) is a possible new modality for

treatment of renal cancer: ex vivo and in vivo experience. J Endourol, 11:251-258, (1997).
60. Uchida M, Imaide Y, Sugimoto K, Uehara H, Watanabe H. Percutaneous cryosurgery for renal tumours. Br J Urol. 75: 132-136, (1995).
61. Gollob JA, Upton MP, DeWolf WC, Atkins MB. Long-term remission in a patient with metastatic collecting duct carcinoma treated with taxol/carboplatin and surgery. J Urol, 58:1058, (2001).
62. Peyromaure M, Thiounn N, Scotte F, Vieillefond A, Debre B, Oudard S. Collecting duct carcinoma of the kidney: a clinicopathological study of 9 cases. J Urol, 170: 1138-1140, (2003).
63. Yagoda A, Abi-Rached B, Petrylak D. Chemotherapy for advanced renal-cell carcinoma: 1983-1993. Semin Oncol, 22: 42-60, (1995).
64. Hanada K, Yewdell JW, Yang JC. Immune recognition of a human renal cancer antigen through post-translational protein splicing. Nature, 427:252-256, (2004).
65. Small EJ, Motzer RJ. Interferon for renal cell carcinoma. In: Belldegrun A, Ritchie AWS, Figlin RA, Oliver RTD, Vaughan ED, eds. Renal and adrenal tumors. New York: Oxford University Press, 381-387, (2003).
66. Stefan O, Walter R. Encyclopedia of Molecular Pharmacology. 5th Edn, Springer: 411, (2008).
67. Yang JC, Sherry RM, Steinberg SM, *et al*. Randomized study of high-dose and lowdose interleukin-2 in patients with metastatic renal cancer. J Clin Oncol, 21:3127-3132, (2003).
68. Childs R, Chernoff A, Contentin N, *et al*. Regression of metastatic renal-cell carcinoma after nonmyeloablative allogeneic peripheral- blood stem-cell transplantation. N Engl J Med, 343:750-758, (2000).
69. Holtl L, Zelle-Rieser C, Gander H, *et al*. Immunotherapy of metastatic renal cell carcinoma with tumor lysate-pulsed autologous dendritic cells. Clin Cancer Res, 8:3369-3376, (2002).
70. Su Z, Dannull J, Heiser A, *et al*. Immunological and clinical responses in metastatic renal cancer patients vaccinated with tumor RNA-transfected dendritic cells. Cancer Res, 63:2127-2133, (2003).
71. Marten A, Renoth S, Heinicke T, *et al*. Allogeneic dendritic cells fused with tumor cells: preclinical results and outcome of a clinical phase I/II trial in patients with metastatic renal cell carcinoma. Hum Gene Ther, 14:483-494, (2003).
72. Avigan D, Vasir B, Gong J, et al. Fusion cell vaccination of patients with metastatic breast and renal cancer induces immunological and clinical responses. Clin Cancer Res, 10:4699-4708, (2004).
73. Escudin B, Eison T, Stadler WM, Szczylik C *et al*. Sorafenib in advanced cl;ear renal cell carcinoma. N Engl J Med, 356: 125-134, (2007).
74. Yang JC, Haworth L, Sherry RM *et al*. A randomized trial of bevacizumab, an anti vascular endothelial growth factor antibody, for metastatic renal cell. N Engl J Med, 349: 427-434, (2003).
75. Motzer RJ, Hutson TE, Tomezak P, Michaelson MD *et al*. Suniximab versus interferon alpha or both for advanced renal cell carcinoma. N Engl J Med, 356: 2271-2281, (2007).
76. Hudes G, Carducii M, Tomczak P, Dutcher J *et al*. Temsirolimus, interferon alpha or both for advanced renal cell carcinoma. N Engl J Med, 356:2271-2281, (2007).
77. Yuen JSP. Molecular targated therapy in advanced renal cell carcinoma: A review of recent past and glimpse into near future. Indian J Urol, 25:427-436, (2009).

78. Lindblad P, Chow WH, Chan J, *et al*. The role of diabetes mellitus in the etiology of renal cell cancer. Diabetologia, 42:107-112, (1999).
79. Orth SR, Ritz E, Schrier RW. The renal risks of smoking. Kidney Int, 51:1669-1677, (1997).
80. Danpanich E, Kasiske BC. Risk factors for cancer in renal transplant recipients. Transplantation, 27:1859-1864, (1999).
81. WCRF and AICR. Food nutrition and prevention of cancer: A global perspective, World cancer research fund and American institute of cancer research, Washington DC: 1997.
82. Weikert S, Boeing H, PIschon T, Olsen A *et al*. Fruits and vegetable and renal cell carcinoma. Finding from European Prospective Investigation into caner and Nutrition (EPIC). Int J Cancer. 118:3133-3139, (2006).
83. Rashidkhani b, Lindblad P, Wolk A. Fruits, vegetables and risk of renal cell carcinoma: A prospective study on Swidish women. Int J Cancer, 113,541-5, (2005).
84. Hu J, Mao Y, White K. Canadian cancer registries. Epidemiology re4search group. Diet and vitamin or mineral supplement and risk of renal cell carcinoma in Canada. Cancer Causes Control, 14: 705-714, (2003).
85. Galeone C, Peluccie C, Talamini R, Negri E, et al Fibre intake and of renal cell carcinoma: A case control study from Italy. Int J Cancer, 121.1867-1872, (2007).
86. Murthy NS, Mukherjee S, Ray G, Ray A. J Postgrad Med, 55(1): 454-54, (2009).