RESEARCH
www.commprac.com
ISSN 1462 2815

PERFUSION PARAMETERS OF RENAL LESIONS - AN OVERLOOKED TOOL IN CHARECTERIZATION OF RENAL NEOPLASMS

Dr. V.R. Meenu [1], Dr. G. Yuvabalakumaran [2]*, Dr. Sindhu Bairavi Moongilmadai Rajoo [3], Dr. R.M. Sidhesh [4], Dr. Sathiya Narayanan [5] and Dr. Senthil Kumar [6]

[1] Post Graduate Resident, Department of Radiology, Vinayaka Mission's Kirupananda Variyar Medical College and Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Salem, Tamilnadu. Email: meenurajendran9@gmail.com
[2] Professor and Head, Department of Radiology, Vinayaka Mission's Kirupananda Variyar Medical College and Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Salem, Tamilnadu. *Corresponding Author Email: Yuvabalakumaran@yahoo.com
[3] Specialist Radiologist, Al Qassimi Hospital, Sharjah, UAE. Email: dr.sindhubairavi@yahoo.com
[4] Associate Professor, Department of Radiology, Vinayaka Mission's Kirupananda Variyar Medical College and Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Salem, Tamilnadu. Email: dr.sidhesh@gmail.com
[5] Assistant Professor, Department of Radiology, Vinayaka Mission's Kirupananda Variyar Medical College and Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Salem, Tamilnadu. Email: drsathi101@gmail.com
[6] Associate Professor, Department of Anatomy, Vinayaka Mission's Kirupananda Variyar Medical College and Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Salem, Tamilnadu. Email: skdrchinu88@gmail.com

DOI: 10.5281/zenodo.11195570

Abstract

The prime objective of this study is to evaluate CT perfusion parameters of various renal neoplasm in a study group of 40 patients, using a 16 slice CT. The principle of CTperfusion depends upon the attenuation changes in the tissue over time, after the administration of intravenous iodinated contrast media. The concentration of iodine in the tissues determines the degree of enhancement. It is measured by CT as attenuation, which indirectly reflects the tissue vascularity. In our study, using perfusion parameters, 4,6,30 cases were diagnosed to be Angiomyolipoma, Oncocytoma and RCC, respectively. Conclusion - CT perfusion study can be added as a routine CT protocol during the evaluation of renal lesions along with the conventional CT which helps in differentiation between benign and malignant lesions, thus aiding in prompt diagnosis and treatment.

Keywords: Renal Neoplasms, CT Perfusion, Radiological Investigations, RenalLesions.

INTRODUCTION

The extensive use of cross- sectional imaging such as computed tomography and magnetic resonance imaging has improved the incidental and early detection of renal lesions. The renal lesions could be either benign or malignant. Benign lesions such as simple cysts need no intervention whereas complex cysts, malignant lesions like renal cell carcinoma require surgical intervention. Early diagnosis aids in proper management and improves the prognosis. Renal tumours have variable characteristic histology and clinic-biological profile and each differ in their response to the available treatment modalities. Around ninety per cent of all renal tumours come under five histological types. The two frequent benign tumours are angiomyolipoma and oncocytoma and the three subtypes of RCC which are clear cell carcinoma, chromophobe carcinoma and papillary carcinoma [1]. Angiomyolipoma being the commonest benign tumour that can be identified accurately by the presence of intra-

tumoural fat in cross sectional images. But 5% of AMLs (lipid- poor AMLs and AMLs that completely lack fat) have an insufficient amount of fat to be perceived on cross-sectional imaging modalities [2]. Hence differentiating them from the RCC especially the clear cell type remains a diagnostic challenge. Further the imaging and histological findings of Oncocytoma and Chromophobe RCC overlap [3, 4] making their differentiation difficult.

Renal cell carcinoma is the most common malignant tumour, accounting for 86% of all primary malignant renal tumours [5]. The most common histological subtypes of RCC include clear cell, papillary and chromophobe types, accounting for 70%, 10%-15%, and 5%, respectively [6]. The different subtypes of RCC are associated with distinctively different disease progression and metastatic potential [7]. Hence accurate subtyping of RCC by imaging becomes important for optimizing treatment protocols and also for predicting the prognosis. Apart from detecting the lesion, the Radiological investigations play a vital role not incharacterizing the renal masses, which helps in deciding the appropriate treatment plan. There are various studies which distinguishes benign from malignant renal lesions based on imaging features & degree of enhancement on multiphasic multidetector computed tomography & magnetic resonance imaging [8]. There arealso reports on subtype differentiation of renal cell carcinoma by computed tomography or magnetic resonance imaging [9, 10]. Although the value of cross- sectional imaging in detection of renal lesions have increased in recent years, their accuracy in characterizing their nature remains low [11]. Percutaneous biopsy could help in such cases but it is an invasive procedure [12, 13]. In recent years a functional imaging technique, perfusion CT allows quantitative evaluation of tissue perfusion after the administration of intravenous contrast. It has shown promising results in the field of oncology by characterization of renal lesions [14] and thus aiding subtype differentiation of renal cell carcinomas. CT perfusion is based on the changes in the tissue attenuation over time after administration of iodinated contrast media intravenously. Concentration of iodine in the tissues determines their degree of enhancement and indirectly reflects the tissue vascularity and vascular physiology [15, 16]. These are predicted based on the following parameters of perfusion like blood flow (BF), blood volume (BV), mean transit time (MTT) and permeability (PS). CT perfusion depicts the regional perfusion of the tumour and their vascular permeability thereby giving indirect evidence of the tumour angiogenesis. Moreover different histologic subtypes of renal neoplasms have been shown to have different perfusion parameters, which will have an impact on the prognosis [17-20]. By examiningthe previous consideration, the aim of our study was to prospectively evaluate if CTp could be a useful tool in addition to multiphasic CT in characterization of renal neoplasms.

Objectives

- Obtaining the perfusion parameters i.e. blood flow, blood volume, permeability by CT in patients with renal neoplasms.
- Comparing the CT perfusion parameters in the renal neoplasms & normal renal parenchyma.
- Analyzing the differences in CT perfusion parameters of various benign and malignant renal tumours and to correlate with the histopathological examination.
- Calculation of the sensitivity & specificity of CT perfusion parametersin differentiating benign and malignant renal neoplasms.

MATERIAL AND METHODOLOGY

Materials:

CT perfusion study was done by SIEMENS 16 SLICE CT scanner.

The images were obtained with the following imaging parameters: 110 kVp tube voltage, 120 mAs tube current, 0.5 s gantry revolution time, 512 x 512 pixel (spatial resolution) and 1.2 mm slice thickness of reconstructed images.

Scanning protocol:

A baseline non-contrast image of the upper abdomen was obtained to cover both the kidneys completely in the imaging field to locate the tumour. After identification of the tumour, a pre-defined scan volume of the tumour predominantly including the solid areas was determined in the z axis for CTp study. After which a bolus of 50 mlof low osmolar non-ionic contrast agent Iohexol (Omnipaque) 350 was administered intravenously through 18-gauge cannula, using a power injector at a flow rate of 5 ml/ sec, followed by 30 ml saline solution at the same flow rate. After a time delay of 6 seconds from the commencement of the contrastadministration, the dynamic volume acquisition using CT was started. This delay in the scan time was to ensure that there is little acquisition of unenhanced baseline data allowing both the software to plot the enhancement change over time and to allow evaluation of the lesion's attenuation over unenhanced study. The dynamic cine-modeacquisition consisted of 4 contiguous sections, collimated to 5mm, with temporal resolution of 1 second without table movement and using appropriate scanning parameters. The total time duration was approximately 60 seconds including the first- pass enhancement and delayed phase.

Post processing analysis of the acquired images:

All the acquired CT perfusion images were analyzed using commercial perfusion software, syngo® Body tumour perfusion CT. A processing threshold (CT value range) of between -30 and 150 Hounsfield units (HU) was used in order to optimize the visualization of soft tissue. On axial CT images, the slice showing the maximal transverse diameter of the tumour was chosen for further analysis. After initiating motion correction and automatic segmentation, the arterial input function was determined by placing a circular region of interest (ROI) in the proximal segment of abdominal aorta. In the same selected image, exclusive ROI were drawn manually (maximum 1 cm^2) for the renal tumour and normal renal cortex, after carefully excluding areas of necrosis, calcifications, cystic change and hemorrhage. For each patient reference ROIs were also drawn on the healthy normal renal cortex of the same and contralateral kidneys and mean perfusion parameters were obtained and kept as control values. The obtained ROI were then automatically copied onto the perfusion maps. Time-density curves were obtained and the quantitative perfusion parameters were calculated by using body perfusion software Patlak analysis.

Four different perfusion parametric maps were generated for every patient.

1. Temporal maximum intensity projection (MIP) in Hounsfield unit (HU).
2. Blood volume (BV) in ml/1000 ml.
3. Blood flow (BF) in ml/100ml/min.
4. Permeability (PS) in 0.5 ml/100 ml/min.

Histopathology:

The patients were followed up after surgery and HPE reports were collected. Out of the 40 patients, 32 underwent radical nephrectomy and 8 were partial nephrectomies. The specimens that were subjected to histopathological analysis were staged based on TNM classification and their types and subtypes determined. The Fuhrman grading system (I-IV) was used to grade clear cell RCC. Grades I and II were considered low-grade clear cell carcinoma and grades III and IV were considered high-grade clear cell carcinoma.

METHODOLOGY

This prospective study on CT perfusion on various renal neoplasms was conducted in Vinayaka Mission's Kirupananda Variyar Medical College & Hospitals. A total number of 40 patients between the age of 25 to 85 years with renal lesions which were detected by ultrasound & conventional computed tomography were included in this study. The data collected from the patients in our study group were analyzed with SPSS software version 21.0.

OBSERVATION AND RESULTS

Table 1: Age Distribution of various renal tumours in the study group

AGE GROUP in years	AML		ONCOCYTOMA		RCC	
	N	PERCENTAGE	N	PERCENTAGE	N	PERCENTAGE
30-39	1	25	0	0	1	3.33
40-49	3	75	1	16.67	2	6.67
50-59	0	0	3	50	14	46.67
60-69	0	0	2	33.33	11	36.67
70-79	0	0	0	0	2	6.67

Table 2: Sex Distribution of various renal tumours in the study group

TUMOURS	NO OF CASES	SEX DISTRIBUTION			
		MALE	%	FEMALE	%
AML	4	0	0	4	100
ONCOCYTOMA	6	5	83	1	17
RCC	30	20	67	10	33
Total	40	25	62	15	38

Table 3: Distribution of renal lesions based on the size of the tumour

Renal lesion	MEAN TRANSVERSEDIAMETER		TOTAL
	<40 mm	>40 mm	
AML	**2**	**2**	**4**
ONCOCYTOMA	**2**	**4**	**6**
RCC	**10**	**20**	**30**
Total	**14**	**26**	**40**

Table 4: Frequency distribution of histopathological types and subtypes of renal tumour in our study group

HISTOPATHOLOGICAL DIAGNOSIS	Frequency	Percentage
Angiomyolipoma with minimal fat	4	10
Oncocytoma	6	15
Chromophobe Renal cell carcinoma	7	17.5
Papillary Renal cell carcinoma	5	12.5
Clear cell Renal cell carcinoma - Low grade	10	25
Clear cell Renal cell carcinoma - High grade	8	20
Total	**40**	**100**

Table 5: Comparison of CT Perfusion Parameters between Various Renal Tumours in the Study Group

ANOVA TEST						
RENAL LESION		Sum ofSquares	df	Mean Square	F	Sig. P-value
BF-RL	Between Groups	124335.64	2	62167.82	9.347	0.001
	Within Groups	246080.26	37	6650.818		
	Total	370415.9	39			
BV-RL	Between Groups	96181.053	2	48090.526	12.147	0.000
	Within Groups	146489.07	37	3959.164		
	Total	242670.12	39			
PS-RL	Between Groups	61885.418	2	30942.709	20.783	0.000
	Within Groups	55088.066	37	1488.867		
	Total	116973.48	39			

Table 6: Comparison of intra-lesional mean values of Blood Flow, Blood Volume and Permeability in the study group.

TUKEY HSD POST HOC TEST					
Dependent Variable			Mean Difference (I-J)	Std. Error	Sig.P- value
BF-RL	AML	ONCO	-154.55000*	52.6419	0.017
	AML	RCC	1.79333	43.4097	1.000
	ONCO	RCC	156.34333*	36.4714	0.000
BV-RL	AML	ONCO	-175.38333*	40.6159	0.000
	AML	RCC	-50.63	33.4927	0.417
	ONCO	RCC	124.75333*	28.1395	0.000
PS-RL	AML	ONCO	-122.69167*	24.9071	0.000
	AML	RCC	-15.01167	20.5389	1.000
	ONCO	RCC	107.68000*	17.2561	0.000

Table 7: Comparision of Mean Perfusion Parameters between Angiomyolipoma & Subtypes of Rcc

GROUP STATISTICS									
RENAL LESION		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
BF-RL	AML	4	243.350	8.7256	4.3628	229.466	257.234	234.2	252.7
	NON CCRCC	12	139.742	29.1178	8.4056	121.241	158.242	91.3	166.3
	CCRCC	18	309.433	39.2282	9.2462	289.926	328.941	249.4	381.5
	Total	34	241.768	85.8209	14.7182	211.823	271.712	91.3	381.5
BV-RL	AML	4	130.850	6.3511	3.1756	120.744	140.956	121.7	135.9
	NON CCRCC	12	102.925	17.7265	5.1172	91.662	114.188	79.2	140.1
	CCRCC	18	233.850	31.0572	7.3202	218.406	249.294	196.8	286.5
	Total	34	175.524	67.9661	11.6561	151.809	199.238	79.2	286.5
PS-RL	AML	4	85.225	4.5294	2.2647	78.018	92.432	79.1	89.7
	NON CCRCC	12	60.8412	11.7751	3.3992	53.360	68.323	46.7	87.1
	CCRCC	18	126.500	35.2707	8.3134	108.960	144.040	83.1	175.4
	Total	34	98.471	40.6649	6.9740	84.282	112.660	46.7	175.4

Table 8: Mean values of intratumoural CT perfusion parameters in AML, Non clear cell and clear cell RCC.

TUKEY HSD POST HOC TEST					
Dependent Variable			Mean Difference(I-J)	Std.Error	Sig. P- value
BF-RL	AML	NON CCRCC	103.60833*	19.5968	0.000
		CCRCC	-66.08333*	18.76251	0.004
BV-RL	AML	NON CCRCC	27.925	14.65548	0.198
		CCRCC	-103.00000*	14.03155	0.000
PS-RL	AML	NON CCRCC	24.38333	15.63533	0.387
		CCRCC	-41.27500*	14.96969	0.029

Table 9: Mean values of perfusion parameters within the lesion among various subtypes of RCC in our study group

GROUP STATISTICS									
RENAL LESION		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
BF	CCRCC	18	309.433	39.2282	9.2462	289.926	328.941	249.4	381.5
	CMRCC	7	159.929	5.3624	2.0268	154.970	164.888	149.7	166.3
	PAPRCC	5	111.480	24.0187	10.7415	81.657	141.303	91.3	151.2
	Total	30	241.557	91.5033	16.7061	207.388	275.725	91.3	381.5
BV	CCRCC	18	233.850	31.0572	7.3202	218.406	249.294	196.8	286.5
	CMRCC	7	112.557	13.3270	5.0371	100.232	124.883	99.2	140.1
	PAPRCC	5	89.440	14.4237	6.4505	71.530	107.349	79.2	114.7
	Total	30	181.480	70.2880	12.8328	155.234	207.726	79.2	286.5
PS	CCRCC	18	126.500	35.2707	8.3134	108.960	144.039	83.1	175.4
	CMRCC	7	60.814	14.3885	5.4383	47.507	74.121	46.7	87.1
	PAPRCC	5	60.880	8.4111	3.7616	50.436	71.324	49.2	69.6
	Total	30	100.237	43.0369	7.8574	84.167	116.307	46.7	175.4

Table 10: Comparison of mean values of intralesional Blood Flow, Blood Volume & Permeability among the various subtypes of RCC.

TUKEY HSD POST HOC TEST					
Dependent Variable			Mean Difference(I-J)	Std.Error	Sig. P-value
BF-RL	CCRCC	CMRCC	149.50476*	14.50755	0.000
	CCRCC	PAPRCC	197.95333*	16.46463	0.000
	CMRCC	PAPRCC	48.44857	19.07067	0.051
BV-RL	CCRCC	CMRCC	121.29286*	11.595	0.000
	CCRCC	PAPRCC	144.41000*	13.15917	0.000
	CMRCC	PAPRCC	23.11714	15.24202	0.423
PS-RL	CCRCC	CMRCC	65.68571*	12.90811	0.000
	CCRCC	PAPRCC	65.62000*	14.64943	0.000
	CMRCC	PAPRCC	-0.06571	16.96815	1.000

DISCUSSION

This study including 40 patients with renal lesions revealed, the following incidence of thetumours:

- 4 cases of Angiomyolipoma with minimal fat accounting for 10%
- 6 cases of Oncocytoma accounting for 15%
- 30 cases of Renal cell carcinoma accounting for 75%. Out of the 30 RCCs, Clear cell type, Papillary and Chromophobe subtypes accounted for 60%, 17%and 23% respectively.

Amidst all the renal tumours, RCC had a higher incidence in our study which was almost similar to the data provided in literature. In the subtypes of RCC, clear cell type RCC had higher prevalence. The renal masses were commonly seen after 4th decade of life, of which Oncocytoma and RCC had a higher incidence between 50-59 years of age (in 6th decade), whereas AML was commonly seen in the 4th and 5th decade. Our findings correlated with the study done by **Chow, Wong-Ho et al**. AML has female predilection whereas RCC and Oncocytoma had a male predilection with male to female ratio of 1.6:1 for renal tumours. This is consistent with the study done by **Motzer RJ et al** in the year 2011. CT perfusion parameters provides valuable information in differentiation of benign and malignant renal lesions. The perfusion parameters were evaluated by placing Region of Interest (ROI) manually by avoiding necrotic areas. In this study the following perfusion parameters: blood flow of 241.56 ml/min/100ml, 181.48 ml/1000ml and 100.24 (0.5ml/min/100ml) in Renal Cell Carcinoma were significantly decreased when compared to normal renal cortex (P- value<0.01). This is in concordance with the study done by **Chen Y, Zhang J et al**.

CONCLUSION

CT perfusion is a non-invasive and cost-effective method that can be used to evaluate the hemodynamic variation of renal lesions. The CT perfusion parameters blood flow, blood volume and permeability had been a highly sensitive tool in the diagnosis, differentiation of benign and malignant renal lesions and further providing details about the histological subtypes. Hence, CT perfusion study could be added in routine CT protocols during the evaluation of renal lesions, along with the conventional CT. This will aid in the differentiation of benign and malignant lesions. Thus, avoiding invasive procedures in benign lesions and needless surgeries in indolent tumours.

Acknowledgments:

The authors would like to thank all of the study participants and the administration of Department of Radiology Vinayaka Mission's Kirupananda Variyar Medical College & Hospital, Vinayaka Missions Research Foundation (DU), Salem, Tamilnadu, India for granting permission to carry out the research work.

Conflicts of interest: There are no conflicts of interest**.**

Ethical statement:

Institutional ethical committee accepted this study. The study was approved by the institutional human ethics committee, Vinayaka Mission's Kirupananda Variyar Medical College & Hospital, Vinayaka Missions Research Foundation (DU), Salem. Informed written consent was obtained from all the study participants and only those participants willing to sign the informed consent were included in the study. The risks and benefits involved in the study and the voluntary nature of participation were explained to the participants before obtaining consent. The confidentiality of the study participants was maintained.

Funding: Nil.

Authors' contributions:

Dr.G. Yuvabalakumaran & Dr.V.R. Meenu- conceptualization, data curation, investigation, methodology, project administration, visualization, writing—original draft, writing—review and editing; ***Dr. Dr. Sindhu Bairavi Moongilmadai Rajoo & Dr. R.M. Sidhesh***-conceptualization, methodology, writing—original draft, writing—review and editing; ***Dr Sathiya Narayanan & Dr. Senthil Kumar*** - methodology, writing—original draft, writing, review and editing. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript**.**

Data Availability:

All datasets generated or analyzed during this study are included in the manuscript.

References

1) Hélénon, O., Eiss, D., Debrito, P., Merran, S., & Correas, J.-M. (2012). How to characterise a solid renal mass: A new classification proposal for a simplified approach. Diagnostic and Interventional Imaging, 93(4), 232–245.

2) Katabathina VS, Vikram R, Nagar AM, Tamboli P, Menias CO, Prasad SR. Mesenchymal neoplasms of the kidney in adults: imaging spectrum with radiologic-pathologic correlation. Radiographics. 2010;30:1525–1540.

3) Davidson AJ, Hayes WS, Hartman DS, McCarthy WF, Davis CJ. Renal oncocytoma and carcinoma: failure of differentiation with CT. Radiology. 1993;186:693–696.

4) Wu J, Zhu Q, Zhu W, Chen W, Wang S. Comparative study of CT appearances in renal oncocytoma and chromophobe renal cell carcinoma. Acta Radiol. 2016;57:500–506.

5) R. Siegel, D. Naishadham, and A. Jemal, “Cancer statistics, 2013,” CA Cancer Journal for Clinicians, vol. 63, no. 1, pp. 11–30, 2013.

6) Eble JN, Sauter G, Epstein JI, Sesterhenn IA. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Urinary System and Male Genital Organs. Lyon: IARC Press; 2004.

7) Zhang, J., Lefkowitz, R. A., & Bach, A. (2007). Imaging of Kidney Cancer.Radiologic Clinics of North America, 45(1), 119–147.

8) Garant M Bonaldi VM,Taourel P, Pinsky MF, Bret PM, Enhancement patterns of renal masses during multiphase helical CT acquisitions. Abdominal Imaging 1998;23: 431-436.

9) Kim JK, Kim TK, Ahn HJ, Kim CS, Kim KR, Cho KS: Differentiation of subtypesof renal cell carcinoma on helical CT scans. AJR Am J Roentgenoly. 2002; 178: 1499-1506.

10) Sun, M.R., Ngo, L., Genega, E.M., Atkins, M.B., Finn, M.E., Rofsky, N.M. etal, Renal cell carcinoma: dynamic contrast-enhanced MR imaging for differentiation of tumor subtypes--correlation with pathologicfindings. Radiology. 2009;250:793–80.

11) S. Choudhary, A. Rajesh, N. J. Mayer, K. A. Mulcahy, and A. Haroon, “Renal oncocytoma: CT features cannot reliably distinguish oncocytoma from other renal neoplasms,” Clinical Radiology, vol. 64, no. 5, pp. 517–522, 2009.

12) Silverman SG, Gan YU, Mortele KJ, Tuncali K, Cibas ES. Renal masses in the adult patient: the role of percutaneous biopsy. Radiology 2006; 240:6–22.

13) Maturen KE, Nghiem HV, Caoili EM, Higgins EG, Wolf JS, Jr, Wood DP., Jr. Renal mass core biopsy: accuracy and impact on clinical management. AJR Am J Roentgenol. 2007;188:563–70.

14) C. Chen, Q. Liu, Q. Hao et al., “Study of 320-slice dynamic volume CT perfusionin different pathologic types of kidney tumor: preliminary results,” PLoS ONE, vol.9, no. 1, Article ID e85522, 2014.

15) Miles KA. Tumour angiogenesis and its relation to contrast enhancement on computed tomography: a review. Eur J Radiol. 1999;30:198–205.

16) Das CJ, Thingujam U, Panda A, Sharma S, Gupta AK. Perfusion computed tomography in renal cell carcinoma. World J Radiol. 2015;7:170–179.

17) Gigli F, Zattoni F, Zamboni G, Valotto C, Bernardin L, Mucelli RP, Zattoni F. [Correlation between pathologic features and perfusion CT of renal cancer: a feasibility study]. Urologia 2010; 77: 223-231 [PMID: 21234864].

18) Lindblad, P. (2004). Epidemiology of Renal Cell Carcinoma. Scandinavian Journalof Surgery, 93(2), 88–96.

19) Chow, Wong-Ho; Dong, Linda; Devesa, Susan (May 2010). "Epidemiology and Risk Factors of Kidney Cancer". Nature Reviews Urology. **7** (5): 245–257.

20) D. Pascual and A. Borque, “Epidemiology of Kidney Cancer,” Advances in Urology, vol. 2008, Article ID 782381, 7 pages, 2008.