Accuracy of Multi-Detector CT Scan in Pre-operative Staging of Renal Cell Carcinoma: Comparison of Radiological and Histopathological Findings

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ABSTRACT

Objective: To evaluate the accuracy of pre-operative multi-detector CT scan (MDCT) compared to histopathology findings in tumor staging of renal cell carcinoma.

Methods: Retrospective review of 29 renal cell carcinomas at Siriraj Hospital from 2004-2007. Two blinded radiologists evaluated the pre-operative MDCT images independently. Imaging findings were compared with surgical specimens and pathological findings.

Results: A total of 29 renal cell carcinomas were proven on histopathology. The respective accuracy for overall staging of reader 1 and 2 were 0.75 and 0.65. The reader 1 and 2 reached a sensitivity of 75% and 87%, a specificity of 70% and 50% for perinephric involvement, and a sensitivity of 100% and 100%, a specificity of 63% and 54% for renal pelvis involvement. The kappa interobserver agreements for perinephric involvement and renal pelvis involvement were 0.67 and 0.83, respectively.

Conclusion: False positive finding of perinephric involvement causes overstaging of Robson stage I disease or in T1-T2 disease of TNM classification. Perinephric stranding may not be reliable or specific findings, and a result of perinephric involvement in CT scan is still limited. MDCT is accurate in the pre-operative evaluation of renal cell carcinoma in Robson stage II-IV disease.

Keywords: Renal cell carcinoma, multi-detector CT, pre-operative staging

Siriraj Med J 2010;62:18-22

E-journal: http://www.sirirajmedj.com

Renal cell carcinoma (RCC) represents 85-90% of all malignant renal tumors in adults and is the most lethal of the urological cancers.[1] Surgery provides the only effective therapy for renal cell carcinoma. Radical nephrectomy, including ipsilateral adrenalectomy, as established by Robson, became the therapeutic standard in 1969. This was challenged in the 1980s by favorable results with open nephron-sparing surgery. During the past decade, nephron-sparing surgery has been accepted as a safe and effective treatment in selective cases. Before conservative surgery is performed, an accurate pre-operative imaging is required to obtain anatomic information, vascular and collecting system structures and neoplasm staging. Also survival depends on the local and distant extent of each tumor, and precise staging is critical for pre-operative planning and prognosis.[2,3]

Multi-detector CT (MDCT) with very thin-slice collimation allows the reformatting of images in any plane without significant artifact. The high spatial resolution makes it suitable for the assessment of most vascular and abdominal abnormalities and for the evaluation of renal neoplasms.

The purpose of this study was to evaluate the accuracy of MDCT with the aim of providing all anatomic and pathologic information necessary to correctly stage and to adequately plan treatment.

MATERIALS AND METHODS

1. Patients:

A retrospective study was approved by the Ethics Committee (Si 287/2007). The study included patients who were diagnosed renal cell carcinoma at Siriraj

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Hospital, by ICD 10 coding C64, from June 2004 to May 2007. By these criteria, there were 79 patients. The patients were excluded from the study if their pre-operative CT scan and operative record were not available to evaluate tumor staging.

Finally, there were 29 patients (20 men and 9 women) aged 14-79 years (mean age 48 years) with histological diagnosis of renal cell carcinoma who had pre-operative CT images. The presenting symptoms of patients were recorded.

2. Examination technique:

CT image was performed by using MDCT scanner (16-slice MDCT: GE light speed; medical system or 64-slice MDCT: GE light speed; VCT). The images included unenhanced CT and contrast enhanced CT. Time interval between pre-operative CT imaging study and operation date ranged from 9 days to 95 days.

3. Image evaluation:

Axial and additional reformatted images were evaluated by two independent radiologists who were unaware of the result. This study was a retrospective review, so the results did not effect to operative planning. Radiologists evaluated tumor characterization: size, border, density and pattern of enhancement, area of hemorrhage or necrosis and calcification and other parameters for tumor staging according to criteria based on either the Robson or the TNM classification system. (Table 1)

- Renal pelvis involvement: determined by demonstrable infiltration of the tumor in the renal pelvis, filling defect or amputation of the pelvocalyceal system on the excretory phase CT images.

- Perinephric involvement was determined by the presence of streaks or nodules in the perinephric space surrounding the lesion.

- Renal vein or inferior vena cava (IVC) involvement was determined by a low-attenuation filling defect within vein.

- Adrenal glands involvement was defined by abnormal enlargement and enhancement of the adrenal gland or the non-visualized adrenal gland by an infiltrative renal mass.

- Lymph node involvement was determined by nodal enlargement of greater than 1.0 cm in the short-axis diameter with loss of hilar fat or presence of necrosis.

The results of the interpretations were entered in a database and were evaluated for strength of agreement using the Cohen kappa statistics. These were interpreted as follows; 0-0.20 = slightly agreement, 0.20-0.40 = fair agreement, 0.40-0.60 = moderate agreement, 0.60-0.80 = substantial agreement and 0.80-1.00 = almost perfect agreement.

Imaging findings were compared with operative findings and pathological reports by one of two expert pathologists in renal pathology. Sensitivity, specificity and accuracy were calculated to determine MDCT interpretation for preoperative staging.

RESULTS

In the 29 cases of RCC, the most common presenting symptom was hematuria in 15 cases (50%). The other symptoms were palpable loin mass (2 cases), back pain (1 case) and weight loss (1 case). Ten patients (34%) had incidental renal masses discovered with tumors diagnosed during health screening or work-up for other symptoms not related to the genitourinary tract.

- Surgical findings

Surgery confirmed the presence of renal cell carcinoma in all 29 patients. Twenty-two patients underwent radical nephrectomy. Five patients underwent nephron-sparing surgery (4 cases from the incidentally, asymptomatic patients and only one symptomatic patient) described as follows: 1 patient underwent enucleation, 3 patients underwent partial nephrectomy, and 1 patient underwent wedge resection.

Tumor removal was not performed in 2 patients due to advanced disease. One had severe adhesion of the tumor to adjacent organs, and only incisional biopsy was performed. The surgeon recorded the local extension of the tumor in the operative notes. In another patient, percutaneous ultrasound-guided biopsy was performed due to advanced disease with multiple organ metastases (stage IV) and was excluded from analysis. Finally, 28 patients were included for analysis of tumor staging by MDCT images compared to operative and histopathological findings. One patient who underwent only the percutaneous ultrasound-guided biopsy was included in the accuracy analysis of tumor staging, but was not included in the CT evaluation of tumor extension.

A total number of 29 renal cell carcinomas were found: and measurement of tumor sizes by MDCT images ranged form 2.0 to 21.5 cm (mean size, 6.8 cm). The tumor size of incidental RCC ranged from 2.0 to 4.5 cm.

- MDCT findings

The presence, location, size and border of all lesions were correctly shown in all patients. Twenty-two tumors (75%) were well-defined and seven (24%) were ill-defined borders. Twenty-three tumors (80%) showed heterogeneous density on the unenhanced phase (13 of 23 tumors also revealed necrotic area). Four tumors (13%) showed homogeneous isodensity. Two tumors (6%) showed homogeneous hypodensity. All tumors revealed significantly inhomogeneous enhancement which indicated a rich vascular supply (Fig 1). The attenuation values on the unenhanced phase ranged from 26 to 54 HU (mean attenuation value, 35 HU). Enhancement values ranged from 13 to 110 HU (mean attenuation value 61 HU).

Eight tumors (27%) revealed internal calcification. Three tumors (10%) showed intratumoral hemorrhage. No demonstrable intratumoral fat was detected.

Pelvocalyceal system involvement: Only 28 patients were included for analysis of tumor staging. Six of 28 patients had a diagnosis of invasion of the pelvocalyceal system on CT, and these were confirmed surgically. All 6 cases showed intraluminal filling defect on the excretory phase (Fig 2). Sensitivity was 100% and specificity 63% for reader 1. Sensitivity was 100% and specificity 54% for reader 2.

Perinephric involvement: There were 8 of 28 patients with perinephric involvement in comparison with operative findings and histological findings. All 8 patients also had capsular involvement. There was good correlation between perinephric involvement and capsular involvement. The sensitivity was 75% and specificity 70% for reader 1. The sensitivity was 87% and specificity 50 % for reader 2.

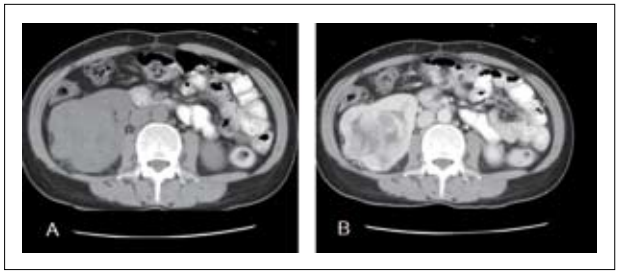

Fig 1. A: Unenhanced CT and B: Contrast enhanced CT show typical renal cell carcinoma: large enhancing mass with necrosis confined to right kidney. CT and histopathology reveal stage I by Robson classification and T2 by TNM classification.

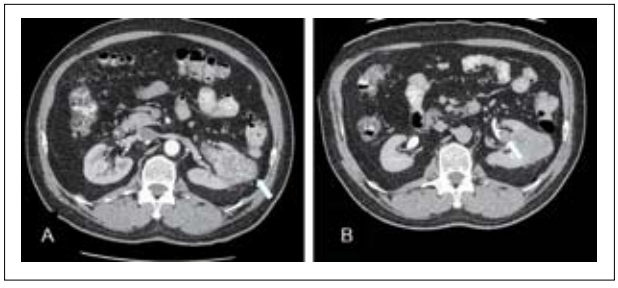

Fig 2. A: Arterial phase CT shows enhancing mass at left renal hilum (arrow). B: Excretory phase CT demonstrates tumor infiltrated in left pelvocalyceal system (arrow) and it is confirmed on histopathologic study.

Renal vein and IVC involvement: There were 2 of 29 patients with renal vein and infradiaphragmatic part of the IVC involvement. One case showed only renal vein involvement. Vascular invasion was correctly diagnosed with MDCT by both readers.

Adrenal gland involvement: Both readers interpreted a normal ipsilateral adrenal gland correctly which correlated with surgery and pathology.

Regional lymph node involvement: There was no significant lymph node involvement by CT criteria, that was greater than 1 cm in the short axis or in presence with necrosis and also there was no report of any metastatic node from histopathology.

Distant metastasis: Four cases with distant metastasis were diagnosed with MDCT by both readers, 1 case had liver metastasis, 2 cases had pulmonary metastasis and 1 case had multiple metastases (lung, bone and liver metastasis).

The interobserver agreement (kappa-value) for perinephric fat involvement was kappa = 0.67 (95% CI: 0.38-0.96), pelvocalyceal system involvement was kappa = 0.83 (95% CI: 0.61-1.05), adrenal glands, lymph node, renal vein and distant metastasis were kappa = 1.

The respective overall accuracies of reader 1 and 2 were 0.75 and 0.65 (Table 2 and 3). Surgical pathological examination of the surgical specimen revealed the stage according to Robson classification. According to the cell type in our study: 25 cases (86%) were clear cell or conventional cell type (1 of 25 cases with sarcomatoid), 2 cases were papillary type, 1 case was clear cell and papillary type and 1 case was chromophrobe type.

The gross specimens revealed hemorrhagic area in 16 cases and necrotic area in 14 cases. The gross specimen revealed multilocular cystic mass in 1 case which appeared as homogeneous hypodensity mass on CT. CT images failed to demonstrate fine septa in the cystic mass.

TABLE 1. Staging criteria for renal cell carcinoma.

Robson classification[4]	
Stage I	Confine to kidney
Stage II	Perirenal fat involvement but confined to Gerota's fascia
Stage IIIa	Gross renal vein and IVC involvement
Stage IIIb	Lymphatic involvement
Stage IIIc	Vascular and lymphatic involvement
Stage IVa	Adjacent organs other than adrenal involved
Stage IVb	Distant metastasis

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Definition of primary tumor (T) of TNM classification[5]	
Tx	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
T1	Tumor 7 cm or less in greatest dimension, limited to the kidney.
T1a	Tumor 4 cm or less in greatest dimension, limited to the kidney.
T1b	Tumor more than but not more than 7 cm in greatest dimension, limited to the kidney.
T2	Tumor more than 7 cm in greatest dimension, limited to the kidney.
T3	Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia.
T3a	Tumor directly invades adrenal gland or perinephric tissues but not beyond Gerota's fascia.
T3b	Tumor grossly extends into renal vein or vena cava below the diaphragm.
T3c	Tumor grossly extends into vena cava above diaphragm or invades the wall of vana cava.
T4	Tumor invades beyond Gerota's fascia.

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TABLE 2. Comparison between MDCT interpretation of tumor extension by reader 1, 2 and operative or histopathological findings in 28 cases.

Histopathology		MDCT interpretation by Reader 1,2							
		Perinephric involvement		Renal pelvis involvement		Renal vein involvement		Adrenal involvement	
		+	-	+	-	+	-	+	-
Perinephric	+	6,7	2,1						
involvement	-	6,10	14,10						
Renal pelvis	+			6,6	0,0				
	-			8,10	14,12				
Renal vein	+					3,3	0,0		
	-					0,0	25,25		
Adrenal	+							0,0	0,0
involvement	-							0,0	28,28

DISCUSSION

Regarding renal cell carcinoma, the advantage of multi-detector CT is that it is a high accuracy technique for tumor characterization, local extension including collection system, vascular or perinephric involvement, as well as lymph node and visceral metastasis.[3,6,7] These help for pre-operative staging and treatment planning. It is also accepted as the preferred imaging technique because of low cost and ready accessibility. However, some limitations of false positive and false negative from MDCT have been present.

For tumor characterization, most renal cell carcinomas in our study were well-defined solid lesions with attenuation values of 30 or greater on unenhanced CT. The small (<3 cm diameter) tumors usually have a homogeneous appearance, while larger lesions tend to be more heterogeneous with hemorrhage or necrosis. Two tumors mimicked a high-attenuation renal cyst on unenhanced CT scan which revealed homogeneous hypodensity lesions after pathological evaluation. The pattern of enhancement is important in distinguishing hyperdense cysts from solid tumors. Enhancement values of more than 12 HU are considered as significant enhancement and suspicious for tumor more than cyst with high protein content or hemorrhagic cyst.[8]

Pelvocalyxeal system:

The relation ship of the tumor to the collecting system is critical in planning nephron-sparing surgery. The findings of collecting system involvement of this study were intraluminal filling defect or mass replaced calyceal system. Central location of mass and surrounding the calyces is not sufficient to interprete collecting system involvement.[3] False positive was found in cases with no excretory phase CT images. The use of the excretory phase improves determination of tumor invasion of the collecting system.

Perinephric space:

Involvement of perinephric fat is a key point in planning nephron-sparing surgery. Diagnosed infiltration of the perinephric fat makes radical nephrectomy necessary. Perineprhic spreading of a tumor is the most difficult point in staging renal cell carcinoma by CT, leading to reduced CT accuracy in staging renal cell carcinoma.[3,6] The spread of tumoral tissue within the perinephric fat changes the stage of the tumor from stage I to stage II or from T1/T2 to T3a and upstage of the tumor may affect the surgical procedure. The most specific finding perinephric involvement is the presence of an enhancing nodule in the perinephric space. It is highly specific, but low sensitivity (46%).[1] Only perinephric stranding is not sufficient to diagnose perinephric invasion and it is found in about half of patients with a localized T1 and T2 tumor. A retrospective analysis showed that the probable cause of perinephric stranding is tissue edema related to previous inflammatory processes, and vascular engorgement.[6] False positive in our study was misinterpretation of perinephric stranding as perinephric involvement (Fig 3). False positive of perinephric involvement causes overstaging of the Robson stage I disease or T1 and T2 disease of the TNM classification. False negative occurred from microinvasion by histopathology or subtle finding on CT. Perinephric involvement from CT interpretation is still limited. CT evaluation using axial images with additional multiplanar images and specific signs may decrease these misinterpretations.

Renal vein and IVC involvement:

The evaluation of renal vein and IVC thrombosis is crucial for treatment planning. If tumor thrombus spreads into the IVC, the exact extension of the thrombus is essential for planning the correct surgical approach. An abdominal incision is performed if the thrombus is infrahepatic, whereas a thoracoabdominal incision is needed if the thrombus extends above the diaphragm (suprahepatic IVC).[9,10] Multiplanar imaging may add a benefit in the evaluation of the extension of the thrombus.

Renal vein and IVC was correctly diagnosed by MDCT. All these cases revealed heterogeneous enhancement of the thrombus which indicated neovascularity and tumoral thrombus. Streaming of unopacified blood as it returns from the lower extremities can mimic a

TABLE 3. The results of overall staging from MDCT diagnosis by 2 readers.

Robson criteria	Stage I (reader 1,2)	Stage II (reader 1,2)	Stage III (reader 1,2)	Stage IV (reader 1, 2)
Correct staging	14,10	2,3	2,2	4,4
Understaging	0,0	1,0	0,0	0,0
Overstaging	6,10	0,0	0,0	0,0

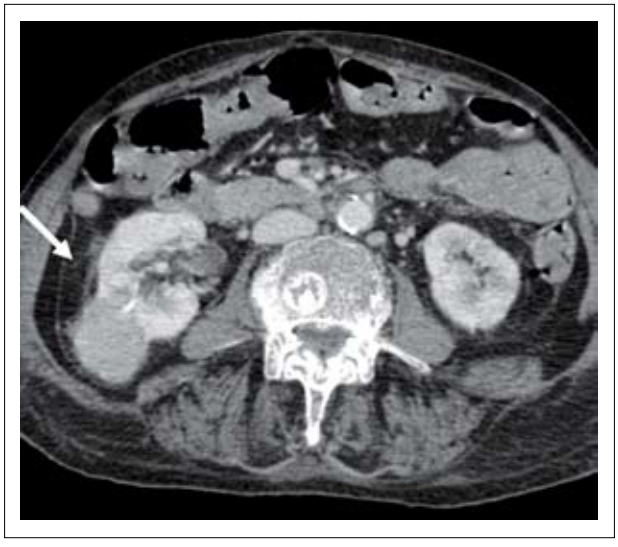

Fig 3. Contrast CT scan shows enhancing mass at right kidney with streak of density in perinephric space (white arrow), false positive for perinephric involvement by 2 readers.

small clot and is a potential cause of false-positive diagnosis (pseudothrombosis). Delayed images to show resolution of the filling defect are usually sufficient to confirm the artifactual nature of such pseudothrombosis.[1,2] The MDCT appearance of the thrombus enabled the differentiation between bland thrombus and tumor thrombus. Direct continuity of the thrombus with the primary tumor and heterogeneous contrast enhancement of the thrombus suggests tumoral thrombus.[2]

Adrenal gland involvement:

There was no patient in this study with adrenal gland involvement. The current surgical trend is to spare adrenal glands that appear normal on CT. This is based on a previous study that showed a 100% negative predictive value for tumor spreading at histopathological examination.[11] By contrast, adrenal enlargement, displacement, or nonvisualization was associated with malignant spread in 24% of cases. The risk of adrenal spread is higher among patients with large or advanced-stage renal cell carcinoma, multifocal, presence of renal vein thrombus, and tumors that involved the upper pole of the kidney.[1-3,6]

Lymph node involvement

The diagnosis of lymph node involvement from CT is still based on size criteria. With 10 mm as the limiting size for normal nodes, 4% of lymph nodes have a false negative finding because micrometastasis cannot be identified. False-positive can be between 3% and 43%, because nodal enlargement may be determined by reactive hyperplasia.[11] An ill-defined border of the lymph node, or enhancement or necrosis of the lymph node may help differentiate metastatic nodes from reactive hyperplasia. In our study, we used size and density of the lymph node to predict metastasis. No metastatic node was detected based on our CT criteria in this study and also by histopathology. We had two cases of para-aortic lymph nodes, about 1 cm and smooth border with homogenous density and the result was reactive hyperplasia on histopathological examination. This observation confirmed the limit of size criteria to evaluate nodal metastasis.

There were limitations of this study that the numbers of patients were small and the variable of pre-operative CT protocol. These limitations affect the accuracy, sensitivity and specificity of MDCT for renal cell carcinoma evaluation.

CONCLUSION

MDCT represents a reliable diagnostic method for pre-operative planning. A false positive finding of perinephric involvement causes over staging of Robson stage I disease or T1-T2 disease of TNM classification. In our study, MDCT is accurate in the pre-operative evaluation of renal cell carcinoma in Robson stage II-IV disease.

ACKNOWLEDGMENTS

The authors thank Dr.Akarin Nimmannit M.D. for very kind assistance in the statistical analysis. This work was supported by a grant by the Siriraj Research and Medical Education.

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