DIFFERENTIATION OF RENAL CELL CARCINOMA SUBTYPES BY MULTISLICE COMPUTERIZED TOMOGRAPHY

KHALED Z. SHEIR, MOHAMED EL-AZAB, AHMED MOSBAH, MAHMoud EL-BAZ AND ATALLAH A. SHAABAN

From the Urology (KZS, AM, AAS), Radiology (ME-A) and Pathology (ME-B) Departments, Urology and Nephrology Center, Mansoura University, Mansoura, Egypt

ABSTRACT

Purpose: We differentiated renal cell carcinoma subtypes using multislice computerized tomography (CT).

Materials and Methods: We reviewed the CT images of 87 patients with renal cell carcinoma. Three subtypes of renal cell carcinoma were noted, including clear cell in 37 cases, papillary in 26 and chromophobe in 24. Biphasic CT (unenhanced, corticomedullary and excretory phases) was done in all patients. We compared patient age and sex, tumor size, enhancement degree and pattern (homogeneous, heterogeneous and predominantly peripheral), the presence or absence of calcification or cystic degeneration (necrotic or hemorrhagic areas within the tumor) and tumor spreading patterns, including perinephric change, venous invasion and lymphadenopathy, in the 3 subtypes.

Results: The degree of enhancement was significantly different among the 3 subtypes in the corticomedullary and excretory phases (p < 0.001). Cystic degeneration was more evident in the clear cell subtype than in the other subtypes regardless of tumor size (p < 0.001). A hypervascular pattern (higher tumor enhancement after contrast material injection due to higher vascularity) was noted in 48.6% of clear cell subtype in comparison to 15.4% of papillary and 4.2% of chromophobe subtypes (p < 0.001). The chromophobe subtype showed homogeneous enhancement in 75% of cases in comparison to 45% and 65% of clear cell and papillary subtypes (p > 0.05). Calcification was evident in 21.6%, 23.1% and 25% of clear cell, papillary and chromophobe subtypes, respectively (p > 0.05).

Conclusions: To differentiate the subtypes of renal cell carcinoma the degree of enhancement is the most valuable parameter. The presence or absence of cystic degeneration, vascularity and enhancement patterns can serve supplemental role in differentiating renal cell carcinoma subtypes.

KEY WORDS: kidney; carcinoma, renal cell; tomography, x-ray computed

Malignant tumors of the kidney represent 2% to 3% of all human neoplasia. Renal cell carcinoma accounts for 85% to 90% of all kidney tumors. The classification of renal cell carcinoma into subtypes has become of interest because of the association with prognosis. Renal cell carcinoma represents a heterogeneous group of tumors with distinct histopathological, genetic and clinical features ranging from benign to high grade malignant. It can be classified into clear cell, papillary, chromophobe, collecting duct and unclassified subtypes. The clear cell subtype is the most common (approximately 70% of renal cell carcinomas) with an overall 5-year survival rate of 55% to 60%. The papillary subtype represents 15% to 20% of cases and it associated with a high 5-year survival rate of 80% to 90% The chromophobe subtype accounts for 6% to 11% of cases and has the worst prognosis with a 5-year survival rate of approximately 90%. Collecting duct carcinoma is a rare subtype, accounting for less than 1% of renal cell carcinomas, although patients with this subtype have the worst prognosis with a 5-year survival rate of less than 5%. The behavior of renal cell carcinoma depends on its subtype and accordingly precise prediction of the subtype may be helpful for treatment planning, such as determining the degree of preoperative evaluation and extent of surgery.

Computerized tomography (CT) is considered the modality of choice for the diagnosis of renal cell carcinoma. Recently multislice CT has provided many advantages in the diagnosis of such cases due to its rapid acquisition and high spatial resolution, especially for determining tumor vascularity, and the extension and assessment of renal vasculature, giving an advantage for selecting cases suitable for nephron sparing surgery. Furthermore, with helical CT it is possible to analyze the tumor dynamic enhancement pattern, which is generally affected by its size. The differentiation of renal cell carcinoma subtypes by imaging modalities is still a well-known challenge. We compared CT findings in different subtypes of renal cell carcinoma and investigated its role in differentiating subtypes.

MATERIALS AND METHODS

Patients. Between January 2001 and March 2004, 98 patients underwent radical nephrectomy for renal cell carcinoma, of whom 11 were excluded because they did not undergo the same CT protocol. Therefore, 87 patients, including 46 men and 41 women with a mean age of 55 years (range 22 to 75), of whom each had 1 tumor, were included in this study. Of these patients 37 had the clear cell subtype, 26 had the papillary subtype and 24 had the chromophobe subtype. CT examination. All CT examinations were performed us-
ing a multislice CT scanner (LightSpeed Plus, General Electric Medical Systems, Milwaukee, Wisconsin). Scans were obtained with certain parameters for imaging acquisition, including scan type helical/full/0.8 seconds, gantry tilt 0 degrees, 120 kV, 220 mA, slice thickness 2.5 mm, table speed 7.5 mm per rotation, reconstruction interval 2.5 mm and large field of view. Images were reconstructed on a 512 × 512 matrix. All patients received 500 to 1,000 ml oral contrast material 30 minutes before CT and 120 ml contrast material (iopamidol) injected intravenously into the antecubital vein using a mechanical injector at a rate of 3.0 ml per second.

All patients underwent biphasic CT, including unenhanced, corticomedullary phase (CMP) and excretory phase (EP) scanning. CT of the entire kidney was performed in every phase during approximately 20 to 23 seconds of patient breath holding. Scanning for the corticomedullary and excretory phases was started 30 and 300 seconds after contrast injection, respectively. Immediately after scanning for the excretory phase scanning covering the lower abdomen and pelvis was performed.

Image analysis. An experienced radiologist blinded to renal cell carcinoma subtype reviewed CT images at a special workstation (Advantage Window 4.1, GE Medical Systems). The length and CT number of the lesion in a particular region of interest were measured. We assessed tumor size, enhancement degree and pattern (homogenous, heterogenous and predominantly peripheral), the presence or absence of calcification or cystic degeneration (necrotic or hemorrhagic areas within the tumor) and tumor spreading patterns (perinephric change, venous invasion and lymphphadenopathy).

To evaluate the degree of tumor enhancement we measured the attenuation of 3 separate regions of interest and calculated the mean of these 3 values. One location for measuring the attenuation value was the solid enhancing area in the excretory phase. A region of interest cursor was placed over an enhanced area, which was consistent in location during all CT phases. We tried to exclude areas of calcification from the region of interest. The tumor enhancement pattern was classified as homogenous when most tumor areas showed a uniform degree of enhancement, predominantly peripheral when most tumor portions were not enhanced and only the peripheral rim or septa showed enhancement. The pattern was classified as heterogenous in the remaining cases. To eliminate the effect of tumor size on enhancement pattern and cystic degeneration we classified tumors into 2 groups according to maximum diameter, namely 5 cm or less and greater than 5 cm.

Perinephric changes were indicated when there was evidence of strands of soft tissue attenuation or parasitized vessels in the perinephric area and thickening of Gerota’s fascia. Venous invasion was indicated when the lumen of the renal vein or inferior vena cava was replaced by tumor. Lymphphadenopathy was defined as a lymph node enlarged to more than 1 cm.

Statistical analysis. Statistical comparisons were performed for various CT findings of different renal cell carcinoma subtypes. Group comparison was done with the Kruskal-Wallis test for CT attenuation values at different phases, patient age and tumor size. When ANOVA was statistically significant, pairwise comparisons were made with the Mann-Whitney U test. The distribution of patient sex, enhancement pattern frequency, presence of calcification or cystic degeneration, tumor spreading patterns and tumor vascularity were compared using the chi-square test. Test results were considered significant at p < 0.05. An investigator blinded to cohort identity performed the statistical analysis. To evaluate the diagnostic validity of the attenuation value in different subtypes of renal cell carcinoma we generated ROC curves and analyzed them to determine the cutoff value for the differentiation with the highest accuracy.

### RESULTS

Mean age ± SD was 54 ± 7 years (range 37 to 75) in patients with the clear cell subtype, 52 ± 10 years (range 37 to 71) in those with the papillary subtype and 47 ± 9 (range 22 to 66) in those with the chromophobe subtype (p = 0.03). Pairwise analysis revealed a statistically significant difference between the clear cell and chromophobe subtypes only (p = 0.005). The male-to-female ratio was 0.5:1 for the clear cell, 1.6:1 for the papillary and 1:2:1 for the chromophobe subtype (p = 0.09).

Mean tumor diameter was 9 ± 3.8 cm (range 3.5 to 20) for the clear cell subtype, 7.9 ± 2.8 cm (range 3 to 15) for the papillary subtype and 8.1 ± 3.6 cm (range 3 to 14) for the chromophobe subtype (p = 0.3). There were 6 clear cell, 4 papillary and 6 chromophobe cases with a tumor of 5 cm or less (p = 0.6).

The table lists attenuation values of the 3 subtypes. Clear cell, chromophobe and papillary subtype pre-enhancement attenuation values did not differ (p = 0.07, fig. 1, IA, IIA and IIIA). On CMP and EP images attenuation values were higher for the clear cell subtype than for the chromophobe and papillary subtypes (p < 0.001, fig. 1, IB, IC, IIIB, IIC, IIIB and IIC). Pairwise comparisons showed significantly different attenuation values for the clear cell and papillary subtypes on CMP only (p < 0.001). Significant differences in attenuation values were seen on CMP and EP between the clear cell or papillary and chromophobe subtypes (p < 0.001).

Figure 2 shows ROC curves for CMP and EP attenuation values of different subtypes for differentiating the clear cell subtype from the other subtypes. Area under the curve (Az value) for CMP enhancement was 0.94 (95% CI 0.887 to 0.993) with high statistical significance (p < 0.001). The cutoff value with highest accuracy was 83.5 HU. The area under the curve (Az value) for EP enhancement was 0.74 (95% CI 0.635 to 0.841) with high statistical significance (p < 0.001). The cutoff value with the highest accuracy was 64.5 HU.

The table shows the enhancement patterns of the 3 subtypes. There were no statistically significant differences among all subtypes even when classified according to tumor size. Calcification within the tumor was noted in 8 patients (21.6%) with clear cell renal carcinoma, in 6 (23.1%) with papillary renal carcinoma and in 6 (25%) with chromophobe renal carcinoma (p > 0.05). Cystic degeneration (necrotic or hemorrhagic areas within the tumor) was more evident in the clear cell subtype than in the other subtypes regardless of

<table>
<thead>
<tr>
<th>CT attenuation and tumor enhancement pattern of 3 renal cell carcinoma subtypes</th>
<th>Conventional</th>
<th>Papillary</th>
<th>Chromophobe</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. tumors</td>
<td>37</td>
<td>26</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Mean CT attenuation ± SD:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before enhancement</td>
<td>29.9 ± 7.0</td>
<td>32.9 ± 3.0</td>
<td>33.6 ± 3.7</td>
<td>0.07 (Kruskal-Wallis test)</td>
</tr>
<tr>
<td>CMP</td>
<td>138.2 ± 38.0</td>
<td>89.2 ± 31.4</td>
<td>55.17 ± 24.0</td>
<td>0.000 (Kruskal-Wallis test)</td>
</tr>
<tr>
<td>EP</td>
<td>73.0 ± 17.6</td>
<td>70.0 ± 10.4</td>
<td>33.9 ± 12.1</td>
<td>0.000 (Kruskal-Wallis test)</td>
</tr>
<tr>
<td>No. enhancement pattern (%):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homogeneous</td>
<td>17 (45.9)</td>
<td>17 (65.4)</td>
<td>18 (75)</td>
<td></td>
</tr>
<tr>
<td>Heterogeneous</td>
<td>17 (45.9)</td>
<td>8 (30.8)</td>
<td>4 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Peripheral</td>
<td>3 (8.1)</td>
<td>1 (3.8)</td>
<td>2 (8.3)</td>
<td></td>
</tr>
</tbody>
</table>
tumor size (p <0.001). A hypervascular pattern (higher tumor enhancement after contrast medium injection due to higher vascularity) was observed in 48.6% of the clear cell subtype in comparison to 15.4% of the papillary and 4.2% of the chromophobe subtypes (p <0.001).

When evaluating tumor spreading patterns, we observed perinephric changes in 15 clear cell (40.5%), 5 papillary (19.2%) and 7 chromophobe (29.2%) cases. Venous invasion was noted in 10 clear cell (27%), 4 papillary (15.4%) and 2 chromophobe (8.3%) cases. These cases were also confirmed at pathological examination. Lymphadenopathy was noted in 7 clear cell (18.9%), 5 papillary (19.2%) and 5 chromophobe (20.8%) cases. Statistical analysis revealed that the frequency of perinephric changes, venous invasion and lymphadenopathy in the different subtypes did not differ significantly (p >0.05). CT stage according to the American Joint Committee on Cancer system was I (T1 N0 M0) in 71 patients (clear cell in 29, papillary in 21 and chromophobe in 21), II (T2 N0 M0) in 15 (clear cell in 7, papillary in 5 and chromophobe in 3) and IV (T1–3b N2 M0) in only 1 with the clear cell subtype.

DISCUSSION

The classification of renal cell carcinoma is based mainly on tumor histopathological appearance and genetic abnormalities. Each subtype is associated with a different prognosis and tumor behavior. Precise preoperative identification of the renal cell carcinoma subtype may influence the degree of preoperative evaluation and the determination of the appropriate extent of surgery. A patient with a subtype that tends to not metastasize or recur, such as the chromophobe subtype, may not need to undergo a complex metastasis survey and unnecessarily wide resection may be avoided, thereby, decreasing postoperative morbidity and mortality.

Until recently the differentiation of renal cell carcinoma subtypes has been attempted on CT in only 3 series. Fujimoto et al analyzed the enhancement pattern of renal cell carcinoma greater than 5 cm on contrast enhanced helical CT. They reported that strong enhancement equal to the renal cortex was noted only in the clear cell subtype (75% of cases) and not in the other subtypes. Wildberger et al evaluated CT findings, including tumor nodule, margin, shape and enhancement, to differentiate various subtypes. They found that the sensitivity for differentiating the clear cell subtype was approximately 72%. Kim et al observed that the sensitivity and specificity for differentiating the clear cell subtype from the other subtypes were 74% and 100% at a cutoff of 84 HU on CMP, and 84% and 91% at a cutoff of 44 HU for EP, respectively. However, in all of these studies the nonclear cell subtypes could not be predicted by CT criteria.

In our study we found that the attenuation value is the most useful parameter for differentiating renal cell carcinoma subtypes, especially the clear cell vs the other subtypes, with high validity (Az value greater than 0.94 on CMP and 0.74 on EP). The clear cell subtype showed stronger enhancement than the other subtypes on CMP and EP, and
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A. ROC curve for corticomedullary phase attenuation

B. ROC Curve for excretory phase attenuation

FIG. 2. ROC curves. A, CMP. B, EP

tumors with attenuation values more than approximately 83.5 HU on CMP and 64.5 HU on EP were likely to be clear cell renal carcinoma. Although strong enhancement of the clear cell subtype has been observed in previous reports,\textsuperscript{13-15} the actual enhancement values for differentiating it from nonconventional subtypes have only been reported by Kim et al.\textsuperscript{13} Strong enhancement of the clear cell subtype is caused by its rich vascular network and alveolar architecture on histological examination.\textsuperscript{2,17}

Our study revealed that the enhancement pattern, the presence or absence of calcification and the tumor spreading pattern overlap among renal cell carcinoma subtypes. There were no statistically significant differences among all subtypes, even when further classified according to tumor size. However, the clear cell (70.3\%) and papillary (69.2\%) subtypes tended to show heterogeneous or predominantly peripheral enhancement, whereas the chromophobe subtype (75\%) usually showed homogeneous enhancement. These findings are in agreement with those reported by Kim et al.\textsuperscript{13} Different enhancement patterns of renal cell carcinoma subtypes is supported by findings on pathological examination. The chromophobe subtype, which tends to demonstrate homogeneous enhancement on CT, shows a homogeneous cut surface without hemorrhage or necrosis and a solid growth pattern on pathological examination. In contrast, the clear cell subtype, which usually shows heterogeneous or predominantly peripheral enhancement on CT, commonly has hemorrhage or necrosis within the tumor on pathological examination.\textsuperscript{2,19}

In our study the overall frequency of perinephric changes, venous invasion and lymphadenopathy were lower than those documented in previous reports.\textsuperscript{1,4} This might be attributable to the fact that the increased use of CT has resulted in the earlier detection of renal cell carcinoma than in the past and the use of contrast enhanced multislice CT has been beneficial for differentiating malignant tumors from unenhanced benign cysts.

Renal cell carcinoma enhancement may be variable according to the contrast injection parameter and scan delay time. In a study of Birnbaum et al using a different contrast injection protocol the degree of enhancement was stronger on EP than on CMP,\textsuperscript{20} which was dramatically different from our results. Therefore, our tumor enhancement pattern criterion is applicable only to cases in which the contrast injection protocol and scan time are similar to those in our study.

CONCLUSIONS

The degree of enhancement is the most valuable parameter for differentiating among renal cell carcinoma subtypes. The presence or absence of cystic degeneration, tumor vascularity and enhancement patterns can serve supplemental role in the differentiation of renal cell carcinoma subtypes.

CT findings could help in preoperative identification of the renal cell carcinoma subtype and influence the degree of preoperative evaluation and extent of surgery, resulting in less aggressive surgery in patients with a subtype that tends not to metastasize or recur, such as chromophobe subtype. Thus, postoperative morbidity and mortality would be decreased, particularly in elderly patients or patients with significant comorbidities.

REFERENCES


EDITORIAL COMMENT

Tissue characterization with CT began with the demonstration of fat in angiomyolipomas. This has resulted in avoiding surgery in many patients with this benign lesion. Advances in CT, PETCT, and MRI are providing more precise assessment of the extent of disease. It is not surprising that preoperative imaging will have an ever important role in defining the histological nature of a lesion. These authors provide examples of imaging as a tool for diagnosis and treatment planning.

Harold A. Mitty
Vascular and Interventional Radiology
Mt. Sinai School of Medicine
New York, New York