Differential Diagnosis of Complex Cystic Renal Mass Using Multiphase Computerized Tomography

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Abbreviations and Acronyms
CMP = corticomedullary phase
CT = computerized tomography
EEP = early excretory phase
MCT = multiphase CT
PCP = precontrast phase
RCC = renal cell carcinoma

Purpose: We evaluated the additional usefulness of multiphase computerized tomography for improving the differential diagnosis of cystic renal masses by the Bosniak classification.

Materials and Methods: We reviewed the records of 104 patients with Bosniak class II (29 or 27.8%), III (38 or 36.5%) and IV (37 or 35.7%) cystic renal masses managed surgically between 1997 and 2007. On preoperative multiphase computerized tomography enhancement differences in HU between the precontrast and corticomedullary phases were measured at the highest enhancement area to correlate with pathological findings.

Results: Renal cell carcinoma was diagnosed in 56 patients (53.8%). Of the tumors 35 (62.5%) showed clear cell histology. According to Bosniak class 3 (11.5%), 21 (55.2%) and 32 (86.4%) class II to IV lesions, respectively, were diagnosed as renal cell carcinoma. For renal cell carcinoma and benign cysts mean HU at the precontrast phase was similar (31.5 and 32.4 HU, respectively), while renal cell carcinoma showed a significantly higher measurement at the corticomedullary phase (112.9 vs 59.8 HU, p <0.0001). To differentiate renal cell carcinoma a corticomedullary phase minus precontrast phase value of greater than 42 HU was predictive with 97.1% sensitivity and 85.7% specificity (area under the ROC curve 0.966). In a multiple regression model the corticomedullary phase minus precontrast phase value and the Bosniak classification independently determined malignant pathological findings (corticomedullary phase minus precontrast phase greater than 42 HU HR 31.541, 95% CI 8.320–119.563 and Bosniak class HR 5.545, 95% CI 2.153–14.279, each p <0.0001).

Conclusions: In cases of complex cystic renal masses diagnostic accuracy can be improved to differentiate renal cell carcinoma by combining Bosniak class and enhancement differences measured on multiphase computerized tomography between precontrast and maximal enhancement phases. This would help determine the need for and the method of surgical treatment.

Key Words: kidney; kidney neoplasms; tomography, emission-computed; cysts; carcinoma, renal cell

Cystic renal masses represent 6% of all asymptomatic renal masses¹ and it has been reported that radiographic cystic change is observed in 4% to 15% of RCC cases.² Unlike simple renal cysts, which can be managed expectantly, increasing complexity in terms of shape, nature of the cystic contents or radiographic enhancement patterns complicates therapeutic management.
In 1986 Bosniak introduced a new classification system for differentiating cystic renal masses using CT. The classification is generally accepted and its recent update is clinically used widely. However, CT along with other radiographic imaging modalities have dramatically advanced in the last decades. Section scanning intervals, image retrieval and processing, and contrast injection materials and methods have been transformed, which allows the clinicians to obtain more information about small cystic renal masses with tiny nodular lesions, and more objective and detailed visualization of fine structures and hairline thin septal enhancement changes than what the Bosniak categories could provide.

We investigated the efficacy of multiphase CT, especially in conjunction with the Bosniak classification, in the differential diagnosis of cystic renal masses in a group of patients with complicated renal cysts that were surgically managed.

MATERIALS AND METHODS

Between March 1997 and June 2007 cystic renal masses in 168 patients were surgically removed at our institution. Of the patients 32 were excluded from study due to Bosniak class I lesions and another 32 were excluded due to the lack of MCT imaging, leaving 104 available for final analysis. All preoperative CT examinations were performed using a 4-channel LightSpeed QX/i MDCT scanner (GE Medical Systems, Milwaukee, Wisconsin) or a 16-channel Sensation 16 MDCT scanner (Siemens Medical System, Erlangen, Germany). Briefly, PCP images were obtained first after the ingestion of E-Z-CAT® oral contrast agent (2% barium sulfate suspension) 30 minutes before examination. Subsequently CMP images were obtained 30 seconds after bolus injection of Ultravist® 300 (iopromide) or Iopamiro 300 (iopamidol) (Braco, Milano, Italy) intravenous contrast material into the antecubital vein with the aorta, renal artery and renal cortex highlighted. The dose was 2 ml/kg body weight at a rate of 3 ml per second to a maximum of 160 ml. EEP scans were obtained approximately 120 to 150 seconds after contrast injection when the vena cava and the renal vein were highlighted and the renal pelvis began contrast pooling. All scanning and image reconstruction were done at 2.5 mm increments.

Using MCT on CMP images a square region of interest was placed over the highest enhancing area to measure HU. The same HU measurement was repeated at exactly the same location in the mass at the same axial level using PCP and EEP images (fig. 1). The degree of enhancement was calculated from the difference in HU values between CMP and PCP scans (CMP minus PCP). In cases showing progressive enhancement into the excretory phase the difference between EEP and PCP (EEP minus PCP) was also tested.

All HU measurements were made by 2 independent readers (GEM and KS) blinded to pathological results. Mean values of the 2 measurements were used for analysis. Interobserver variability was reliably negligible for each variable (intraclass correlation coefficient 0.910, 95% CI 0.888–0.928, p <0.001). ANOVA and the chi-square test were used for comparative analysis between benign cysts and RCC as well as among Bosniak categories. Multiple linear regression analysis was used to test for significance for predicting malignancy. Statistical analysis was done using SPSS®, version 12.5 with p ≤0.05 considered significant.

RESULTS

According to the Bosniak classification cystic renal masses were class II in 29 cases (27.8%), including II-F in 3 (2.9%), III in 38 (36.5%) and IV in 37 (35.6%). There were 33 male patients (31.7%) with the cyst on the right side in 51 (49.0%). Mean patient age at pathological diagnosis was 51.0 years (range 25 to 75). The surgical procedure performed differed according to the Bosniak classification with the pro-

Figure 1. Bosniak category III lesion HU measurement in 41-year-old male. Of several most enhancing areas on CMP image area with highest value of 129.88 HU was selected. On PCP and EEP images corresponding area was 22.25 and 42.19 HU, respectively. Patient underwent open partial nephrectomy and pathological evaluation revealed cystic RCC.
portion of partial or radical nephrectomy increasing with increasing Bosniak category (Table 1). RCC was diagnosed in 56 patients (53.8%) and the incidence of this diagnosis also increased with increasing Bosniak category. Of the RCCs diagnosed clear cell histology was the most common type (35 men or 62.5%), followed by multilocular RCC (12 or 21.6%) and papillary RCC (7 or 12.5%). There was 1 case each of chromophobe and unclassified RCC.

Enhancement measurement using MCT showed significantly higher HU values in Bosniak III and IV lesions compared to those in Bosniak II lesions even before contrast enhancement (Fig. 2). In CMP all malignant lesions had significantly higher enhancement in all Bosniak categories and the degree of enhancement also increased with increasing Bosniak category (mean ± SD 48.4 ± 3.7, 92.3 ± 5.6 and 115.9 ± 7.6 for Bosniak classes II to IV, respectively). Progressive enhancement into the EEP was observed in 1 Bosniak II (3.4%), 19 Bosniak III (50%) and 14 Bosniak IV (37.8%) cases. In benign cyst vs malignant pathologies the percent of cases with a delayed enhancement pattern showed no difference (27.1% vs 37.5%, p = 0.179).

To predict malignant lesions a difference between PCP and CMP (CMP minus PCP) of greater than 45 HU differentiated the 2 diagnoses with 91.4% sensitivity and 88.6% specificity (area under the ROC curve 0.966). At this cutoff the false-negative and false-positive rates were 8.6% and 11.4%, respectively. At the cutoff of a CMP minus PCP value of greater than 42 HU the false-negative rate decreased to 2.9%, predicting with 97.1% sensitivity and 85.7% specificity. In masses with progressive enhancement into the EEP a value of EEP minus PCP of greater than 50 HU predicted with 85.7% sensitivity and 61.5% specificity (AUC 0.835), yielding a false-positive and a false-negative rate of 38.5% and 14.3%, respectively. When the cutoff was adjusted to 47 HU, the false-negative rate was decreased to 9.5%.

In the multiple regression model the CMP minus PCP variable and the Bosniak classification significantly and independently determined malignant pathological findings (CMP minus PCP greater than 42 HU, HR 31.541, 95% CI 8.320–119.563 and Bosniak class HR 5.545, 95% CI 2.153–14.279, each p <0.0001). Combining the 2 variables showed 100%, 90.5% and 90.6% sensitivity for discriminating RCC for Bosniak categories II to IV, which obviated the need for excision in 82.8%, 28.9% and 10.8% of patients, respectively (Table 2).

DISCUSSION

Through technical advancement in radiographic imaging and processing improved CT images have en-

Table 1. Patient characteristics by Bosniak classification

<table>
<thead>
<tr>
<th>Bosniak Class</th>
<th>No. Pts (%)</th>
<th>No. Surgical Procedures (%)</th>
<th>Cyst Excision</th>
<th>Partial/Radical Nephrectomy</th>
<th>No. Malignant Pathology (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>26 (25.0)</td>
<td>13 (48.3)</td>
<td>13 (51.7)</td>
<td>3 (10.3)</td>
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<tr>
<td>II–F</td>
<td>3 (2.9)</td>
<td>1 (33.3)</td>
<td>2 (66.7)</td>
<td>0</td>
<td></td>
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<tr>
<td>III</td>
<td>38 (36.5)</td>
<td>4 (10.5)</td>
<td>34 (89.5)</td>
<td>21 (55.3)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>37 (35.6)</td>
<td>1 (2.7)</td>
<td>36 (97.3)</td>
<td>32 (86.5)</td>
<td></td>
</tr>
<tr>
<td>Totals</td>
<td>104</td>
<td>19 (18.3)</td>
<td>85 (51.7)</td>
<td>56 (53.8)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Different enhancement in benign vs malignant cystic lesions stratified by Bosniak classification. A, PCP. B, CMP. C, EEP. Open bars indicate benign cyst. Black bars indicate RCC.
abled more accurate detection, diagnosis and differentiation of various renal lesions, especially small ones. Particularly more compact scanning with improved longitudinal spatial resolution synchronized to the contrast material flow in each patient generates more dynamic kidney images at 3 phases, making it possible to detect small or subtle differences that cannot be visualized by previous methodologies. Using thinner slices of dynamic CT images we sought to upgrade the Bosniak classification for differentiating benign cystic renal masses from malignant lesions, which would help avoid unnecessary surgery or change the surgical method to less invasive procedures.

The method we used to measure HU using CT is simple and results varied little, as shown by high interobserver agreement. In complicated cysts or cystic renal masses suspicious for RCC we search for nodular areas on the wall or a thickened septum that enhances after contrast injection because they are invariably where cancer is found. By locating the most enhancing area during CMP the HU value of the same area can be compared before contrast injection and after washout. Theoretically this simple method should be accurate since it detects and uses the archetypal RCC enhancement characteristic, that is early enhancement and early washout.

In our multivariate prediction model the enhancement difference variable was more predictive of malignant pathological findings than the Bosniak category (HR 31.541 vs 5.545). For Bosniak class II masses differentiation by the criterion of a CMP minus PCP value of greater than 42 HU demonstrated a 96.7% positive predictive value. All 3 patients with false-negative results had septal nodules that progressively enhanced into the EEP, of which 2 were papillary RCC. While clear cell histology is the most common RCC subtype, different enhancing patterns on CT among the different histological subtypes have been reported with the papillary and chromophobe types showing delayed enhancement. In our study no statistically significant differences in HU measurements using PCP, CMP and EEP images were observed between clear cell and nonclear cell subtypes, although the clear cell subtype showed stronger enhancement using CMP (116.8 vs 92.8 HU, p < 0.121), while the nonclear cell subtype showed a progressive HU increase into EEP from 92.8 to 95.3 HU. In such masses that show a delayed enhancement pattern with maximal enhancement at the excretory phase a value of EEP minus CMP of greater than 47 provided additional information with a 9.5% false-negative rate. Considering these intrinsic enhancing characteristic differences when the value of CMP minus PCP is 42 HU or less would help increase diagnostic accuracy.

Bosniak class III lesions are the most intricate subgroup. No uniformly distinguishing characteristic could be identified by inclusive and/or exclusive criteria. These lesions presented with the highest false-positive and false-negative rates. Similar difficulties have been addressed previously and some investigators have advocated biopsying suspicious lesions before determining surgical treatment. Lang et al performed core biopsies of 199 Bosniak II-F and III lesions, and reported a 95% positive predictive value for cancer and an 80% negative predictive value along with the possible benefits of decreased morbidity from cystic content/abscess drainage. In a smaller group of patients Harisinghani et al drew similar conclusions. However, the potential harm that biopsy can cause should not be neglected, including the morbidity and complications of the procedure, and the underestimated risk of needle track

<table>
<thead>
<tr>
<th>Bosniak Class (HU)</th>
<th>No. Pathological Results (%)</th>
<th>% Sensitivity</th>
<th>% Specificity</th>
<th>% Predictive Value</th>
<th>% False Results</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Benign Cyst</td>
<td>RCC</td>
<td></td>
<td>Pos</td>
<td>Neg</td>
</tr>
<tr>
<td>II: 42 or Less</td>
<td>24 (100)</td>
<td>0</td>
<td>100.0</td>
<td>92.3</td>
<td>60.0</td>
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<tr>
<td>Greater than 42</td>
<td>2 (40.0)</td>
<td>3 (60.0)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>III: 42 or Less</td>
<td>11 (84.6)</td>
<td>2 (15.4)*</td>
<td>90.5</td>
<td>64.7</td>
<td>76.0</td>
</tr>
<tr>
<td>Greater than 42</td>
<td>6 (24.0)</td>
<td>19 (76.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV: 42 or Less</td>
<td>4 (57.1)</td>
<td>3 (42.9)*</td>
<td>90.6</td>
<td>80.0</td>
<td>96.7</td>
</tr>
<tr>
<td>Greater than 42</td>
<td>1 (3.3)</td>
<td>29 (96.7)</td>
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* Lesions with progressive enhancement into the excretory phase could be additionally differentiated by an EEP minus PCP value of greater than 47 HU, which increased sensitivity up to 52 of 53 (98.1%).
spread, especially after rupturing the cystic wall with the fluid contents spilling into the intraperitoneal or retroperitoneal space. Questions on the quality of the biopsy core that is sufficient for confident pathological or differential diagnosis remain and they should be carefully considered. In the series by Lang et al biopsied tissue was insufficient in 10% of cases, while the initial cancer diagnosis was correct in 20 of 28 (71.4%), indeterminate in 6 (21.5%) and incorrect in 2 (7.1%).

It should also be noted that in the studies by Lang and Harisinghani et al not all lesions were surgically removed and pathologically confirmed. Therefore, the demonstrated results are in fact estimates of true false-negative findings. In the current study diagnostic accuracy was increased using enhancement difference variables according to enhancing patterns. In the 2 and 3 patients with false-negative results using a value of CMP minus PCP of greater than 42 HU in the Bosniak III and IV categories (table 2), adding the value of EEP minus PCP of greater than 47 HU discriminated 1 and 3 of the patients, increasing sensitivity to 95.2% and 100%, respectively.

Contrast enhanced ultrasonography and magnetic resonance imaging are another 2 radiographic modalities that have been actively investigated for use in cystic renal mass differentiation. The superior detectability of ultrasound using even a few small bubbles of contrast material to enhance a septum or cystic wall during real-time examination has been suggested as a valuable alternative to CT. Magnetic resonance imaging has also been suggested to better reveal more number and thickness of septa and/or their enhancement than CT. Unfortunately all of these studies have been underpowered due to the lack of accurate pathological diagnosis, which was mostly replaced by followup imaging for various periods. Pathological correlation was done in a minor subset of study participants and results should be interpreted accordingly as agreement between radiographic modalities instead of as diagnostic accuracy. Moreover, while there is general agreement when allocating class II and IV cysts, much discrepancy remains between the modalities for class III cysts.

However, as demonstrated in our study, no single criterion or combination of criteria using a single radiographic modality could sufficiently differentiate malignant Bosniak class III cystic lesions. Moreover, to our knowledge the cohort in the current study is the largest to date but it was still insufficient to be diagnostically definitive, so that our results are as yet preliminary. Thus, disregarding the advantages and disadvantages of each radiographic modality, we believe that all of these methods have complementary roles for increasing the accuracy of the diagnostic process and our results can be added for improvement.

CONCLUSIONS
In cases of complex cystic renal masses diagnostic accuracy can be improved for differentiating RCC by combining Bosniak class and enhancement differences measured on MCT between the precontrast and maximal enhancement phases. This would help determine the need for and the method of surgical treatment. We suggest a cutoff of 42 HU for complex cysts with maximal enhancement during CMP and 47 HU for those with areas with progressive enhancement into the excretory phase.

REFERENCES