Adrenal Adenoma and Metastasis from Clear Cell Renal Cell Carcinoma: Can They Be Differentiated Using Standard MR Techniques?

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Aims and objectives

When an incidental adrenal mass is detected in patients with a known extraadrenal primary malignancy, it is crucial to differentiate between an adrenal adenoma and metastasis. Depending on whether the mass is an adenoma or metastasis, staging and the treatment strategy of the primary tumor may be significantly different.

Opposed-phase and in-phase gradient-echo (GRE) imaging has been proposed as a method that could successfully differentiate adenomas from metastases [1-3]. This has been explained to be due to the abundant intracellular lipid content in adrenal adenomas [4]. Reinig et al. [1] reported that chemical shift-induced signal change of the adrenal masses enabled differentiation between adenomas, metastasis, and pheochromocytomas. Mayo-Smith et al. [2] suggested that both quantitative and qualitative chemical-shift MR imaging were able to differentiate adrenal adenomas from metastases. However, there has been concern that metastasis from extraadrenal primary malignancies which contain high lipid content such as clear cell renal cell carcinoma (RCC) could mimic adrenal adenomas in chemical-shift MR imaging [5]. Shinozaki et al. [5] reported a case of adrenal metastasis from clear cell RCC showing significant signal drop from in- to opposed-phased images. To the best of our knowledge, the diagnostic value of chemical-shift imaging in differentiating between adrenal adenomas and metastasis from clear cell RCCs has not been previously tested. Furthermore, the imaging features using standard MR techniques that may be helpful in differentiating adrenal adenoma and metastasis from clear cell RCC have not been well described in the literature.

Therefore, the purpose of our study was to evaluate the ability of MR to differentiate adrenal adenoma from metastasis using chemical-shift imaging and MR feature analysis in patients with clear cell RCC.

Methods and materials

Patients

Institutional Review Board approval was obtained for this retrospective study; requirement for informed consent was waived. Through a computerized search of our medical database from January 2002 to December 2012, we identified 29 patients with pathologically proven clear cell RCC who underwent MR for the evaluation of adrenal masses at our institution. Inclusion criteria were availability of MR images that included in- and opposed-phase sequences and proof of diagnosis. Proof of diagnosis required either
histopathological evaluation or imaging and clinical follow-up. The criteria for imaging and clinical follow-up were as follows: (a) if the mass was stable in size for at least 6 months, it was considered an adenoma [6]; (b) with evidence of underlying widespread metastatic disease, if the mass displayed an increase in size (> 2 mm/year), was newly appeared during follow-up, or showed interval regression in size following targeted chemotherapy, the mass was accepted as metastasis [7-9]; (c) for these cases in which pathologic confirmation was absent, a consensus was reached among the departments of radiology, surgery, radiation oncology and medical oncology. However, masses smaller than 8 mm were excluded, because obtaining accurate measurements of chemical-shift MR may be difficult in smaller masses in that they are prone to volume averaging with the SI of the adrenal margin, rendering spurious reduction of the SI of the adrenal mass in the opposed phase [10]. Therefore, among the 29 patients, we excluded four patients with pathology other than adenoma or metastasis. In addition, one patient was excluded because of insufficient proof of diagnosis. There were no adrenal masses excluded due to small size. Ultimately, twenty-four patients (18 men and 6 women) with a mean age of 57.7 years (range, 31-77 years) comprised our study population. Of the 24 patients, 11 had 13 metastases (surgically confirmed in 7 and based on follow-up imaging in 6 tumors), and the remaining 13 patients had 15 adenomas (surgically confirmed in 7 and based on follow-up imaging in 8 tumors). A total of 28 adrenal masses in 24 patients (four patients with two tumors) were evaluated.

**MR Protocol**

The patients underwent MR examinations using 1.5-T systems (Magnetom Vision [in 19 patients] or Magnetom Sonata [in 5 patients], Siemens Medical Solutions, Erlangen, Germany). The following sequences were acquired in the axial or coronal plane (chemical shift MR imaging was acquired in the coronal plane for the following reasons: i) lesser number of images for coverage of both the kidney and adrenal glands; ii) easier comparison of the signal intensity of the adrenal and renal lesion with that of the liver and spleen) as follows: (a) coronal T1-weighted opposed- and in-phase GRE imaging with a TR of 100 msec, and a TE of 2.4 and 5.0 msec for in- and opposed-phase imaging, respectively; flip angle of 70°; field of view of 30-35 cm; 4-mm slice thickness; intersection gap of 0.8 mm; 256 x 179 matrix; and one signal acquisition; (b) axial T2-weighted turbo spin echo without fat saturation with a TR of 3500 msec, and a TE of 98 msec; flip angle of 150°; field of view of 30-35 cm; 4-mm slice thickness; intersection gap of 0.8 mm; 320 x 205 matrix; and one signal acquisition; (c) coronal T1-weighted 3D FLASH breath hold technique with fat selective prepulse (VIBE) using a TR of 4.8 msec, and a TE of 2.3 msec; flip angle of 10°; field of view of 30-35 cm; 2.5-mm slice thickness; 256 x 145 matrix; and one signal acquisition obtained before and after intravenous bolus administration of 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) at a rate of 2 mL/sec, and followed by a 20-mL saline flush by a power injector. Scanning delay times for dynamic contrast-enhanced images determined by real-time MRI fluoroscopic monitoring were 7 seconds after contrast media arrival at a
distal thoracic aorta (immediate), and then 1, 3, and 5 minutes after contrast medium injection.

**Quantitative Image Analysis for Chemical-shift Imaging**

All images were reviewed by two radiologists (S.W. and J.Y.C.) blinded to the final diagnosis. First, the maximal diameter of the mass was measured as the greater of the longest diameters in the axial and coronal planes. Then, a free-drawn region of interest (ROI) was placed on solid portion of the tumor referencing T2-weighted and contrast-enhanced VIBE images, and avoiding the peripheral areas to avoid causing partial volume effect from phase cancellation artifacts at the interface between fatty tissue [11]. The area, location, and size of the ROI were constant between in- and opposed-phase images. The signal intensity index (SII), a quantitative measure of signal intensity change between in- and opposed-phases was calculated using the following equation [12, 13]:

\[ \text{SII} = \frac{(\text{SI}_{\text{in adrenal}} - \text{SI}_{\text{opp adrenal}})}{\text{SI}_{\text{in adrenal}}} \times 100. \]

A SII of 16.5% or greater was considered a diagnostic of adenoma [12]. Furthermore, in the patients in the adenoma group who had also underwent CT scans including a precontrast phase, a separate ROI was placed on the tumor in the same manner as on MR in order to determine if the adenoma was lipid-rich (< 10 HU) or not [14]. The CT measurement was performed by another radiologist (S.Y.K.) unaware of the chemical shift MR findings.

**Qualitative Image Analysis**

The opposed- and in-phase, T2-weighted, T2 star-weighted, and pre- and post-contrast VIBE images were analyzed by the same radiologists (S.W. and J.Y.C.) to assess the following characteristics of the adrenal mass [15-18]: (a) SI of the tumor on T2-weighted images as compared with that of the liver as definitely or slightly hyperintense, isointense, or hypointense; (b) the presence of cystic change or necrosis, defined as a region within the tumor with SI identical to that of cerebrospinal fluid on T2-weighted images, low SI on T1-weighted images, without enhancement, and lobulating shape for cystic change, and as a region with high SI but with a lesser degree than that of the cerebrospinal fluid on T2-weighted images, low SI on T1-weighted images, absence of enhancement, and with a central location within the tumor for necrosis; (c) hemorrhage, defined as a nonenhancing region of high SI on T1-weighted images, variable SI on T2-weighted images, and without suppression on fat-saturated sequences; and (d) lateralization of the adrenal mass with regard to the primary clear cell RCC.

**Statistical Analysis**
All statistical analyses were done with PASW statistical software (version 18.0; SPSS, Chicago, IL, USA). A two-tailed P value of < .05 was considered to indicate a statistically significant difference. The Student $t$ test was used to compare the quantitative variables between the two groups. For the qualitative variables, the Fisher exact test was used to compare the proportions between the adenomas and metastases. The Pearson correlation coefficient was used to assess the relationship between precontrast CT attenuation and SII. In addition, a subgroup analysis for SII was done in small (< 3 cm) and homogeneous (without qualitative features of cystic change, necrosis, or hemorrhage) tumors.

**Results**

**Patient Characteristics**

The mean patient age was 57.4 years ± 10.8 in the adenoma group and 58 years ± 12.2 in the metastasis group ($P = .90$). The ratio of men to women was 1.6:1 in the adenoma group and 10:1 in the metastasis group ($P = .166$).

**Quantitative Image Analysis**

The results of the quantitative image analysis are summarized in Table 1. The mean tumor size of metastases was significantly greater than that of adenomas. The mean size of adenomas and metastases were 19.9 mm ± 8.7 and 41.7 mm ± 18.2, respectively ($P = .001$).

The mean SII of adenomas was significantly greater than that of metastases (Figs. 1 and 2). The mean SII of the adenomas and metastases were 45.0% ± 24.6 and 6.6% ± 4.7, respectively ($P < .001$). Using the diagnostic criteria of SII > 16.5%, the sensitivity, specificity, and accuracy in determining adenomas were 80% (12/15), 100% (13/13), and 89.3% (25/28).

Fourteen of the 15 adrenal adenomas had available precontrast CT scans. The mean precontrast attenuation was 14.9 HU ± 14.2 (range, -9 to 37 HU). Among them six adenomas were lipid-rich (mean, 1.5 HU ± 6.9, range, -9 to 9 HU) and 8 were lipid-poor (mean, 24.9 HU ± 8.5, range, 12 to 37 HU). All six lipid-rich adenomas demonstrated a SII greater than 16.5%, therefore resulting in 100% sensitivity for the diagnostic criterion. Regarding the lipid-poor adenomas, it was observed that 62.5% (5/8) had a SII greater than 16.5%. Therefore these three adenomas were misclassified as metastases (Fig. 3). There was a significant negative correlation between precontrast CT attenuation and SII (Fig. 4): rho ($r$) = -0.8099 ($P = .0004$).
Qualitative Image Analysis

The results of the qualitative image analysis are summarized in Table 2. All adenomas were slightly higher (40%, 6/15) or similar (60%, 9/15) in SI to the liver, whereas the metastases showed definitely higher SI (46.2%, 6/13), slightly higher SI (46.2%, 6/13), and lower SI (7.7%, 1/13) compared with the liver ($P = 0.001$). The metastases (46.2%, 6/13) had a significantly greater proportion of masses with a SI definitely higher than the liver compared with adenomas (0%, 0/0; $P = 0.005$). Up to 53.8% (7/13) of the metastases demonstrated cystic change, necrosis, or hemorrhage (Fig. 5). On the other hand none of the adenomas demonstrated such MR features ($P < 0.05$ for all features) except for one (6.7%) of the 15 adenomas, which demonstrated cystic change or necrosis. There was no significant difference in the lateralization of the adrenal masses with regard to the primary clear cell RCC ($P = 1.000$).

Subgroup Analysis of Small (< 3cm) and Homogeneous Adrenal Tumors

There were a total of 11 adenomas and 4 metastases that met the criteria of small and homogeneous adrenal tumors. Within this subgroup, the mean SII of adenomas were significantly larger than that of metastases. The mean SII of the adenomas and metastases were 41.7% ± 27.0 and 5.1% ± 6.0, respectively ($P = .001$). Using the criteria of SII > 16.5%, the sensitivity, specificity, and accuracy in determining adenomas were 72.7% (8/11), 100% (4/4), and 80% (12/15).

Images for this section:

<p>| Table 1: Analyses of Quantitative Characteristics of Adenomas and Metastases |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adenomas ($n = 15$)</th>
<th>Metastases ($n = 13$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (mm)</td>
<td>19.9 ± 8.7 (10.3, 34.9)</td>
<td>41.7 ± 18.2 (16.3, 72.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>In-phase SI</td>
<td>233.5 ± 87.1 (137, 382)</td>
<td>218.6 ± 57.2 (124, 323)</td>
<td>0.593</td>
</tr>
<tr>
<td>Opposed-phase SI</td>
<td>124.7 ± 74.1 (55, 355)</td>
<td>204.4 ± 52.2 (116, 289)</td>
<td>0.004</td>
</tr>
<tr>
<td>Signal intensity index</td>
<td>45.0 ± 24.6 (4.7, 71.5)</td>
<td>6.6 ± 4.7 (0.6, 13.7)</td>
<td>$&lt; 0.001$</td>
</tr>
</tbody>
</table>

Note.— Data are means ± standard deviations, and ranges are in parentheses.
Fig. 1: Scatterplots of signal intensity index (SII) of adrenal adenomas and metastases.
Fig. 2: Chemical-shift MR and precontrast CT scans of right lipid-rich adrenal adenoma in 56-year-old woman with clear cell RCC. (a, b) Adrenal mass (arrow) shows overt signal intensity (SI) loss between in-phase (a) and opposed-phase (b) gradient-echo coronal MR images with a calculated SII of 71.48. (repetition time msec/echo time msec, 100/5.0 and 100/2.4 for in- and opposed -phases, respectively) (c) Coronal T2-weighted image shows adrenal mass (arrow) demonstrating slightly higher signal intensity than the liver without hemorrhage, cystic change, or necrosis. (repetition time msec/echo time msec, 3500/98) (d) Transverse precontrast CT image shows hypoattenuating (7-HU) adrenal mass (arrow).

Fig. 3: Chemical-shift MR and precontrast CT scans of right lipid-poor adrenal adenoma in 31-year-old woman with clear cell RCC. (a, b) Adrenal mass (arrow) shows no overt
signal intensity loss between in-phase (a) and opposed-phase (b) gradient-echo coronal MR images with a calculated SII of 5.84. (repetition time msec/echo time msec, 100/5.0 and 100/2.4 for in- and opposed-phases, respectively) (c) Transverse precontrast CT image shows hyperattenuating (37-HU) adrenal mass (arrow).

**Fig. 4:** Scatter plot of signal intensity index versus precontrast CT attenuation values of adrenal adenomas. Vertical reference line indicates the 10-HU cutoff value used for determining lipid-rich (< 10 HU) and lipid-poor (# 10 HU). Horizontal reference line indicates the 16.5%-cutoff value used in the diagnostic criteria for determining adenomas.
Table 2: Analyses of Qualitative Characteristics of Adenomas and Metastases

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Adenomas (n = 15)</th>
<th>Metastases (n = 13)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2-weighted SI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;&gt; Liver</td>
<td>0 (0.0%)</td>
<td>6 (46.2%)</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt; Liver</td>
<td>6 (40.0%)</td>
<td>6 (46.2%)</td>
<td>(0.005)*</td>
</tr>
<tr>
<td>= Liver</td>
<td>9 (60.0%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>&lt; Liver</td>
<td>0 (0.0%)</td>
<td>1 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>Cysts or necrosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (6.7%)</td>
<td>7 (53.8%)</td>
<td>0.011</td>
</tr>
<tr>
<td>No</td>
<td>14 (93.3%)</td>
<td>6 (46.2%)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0 (0.0%)</td>
<td>5 (38.5%)</td>
<td>0.013</td>
</tr>
<tr>
<td>No</td>
<td>15 (100%)</td>
<td>8 (61.5%)</td>
<td></td>
</tr>
<tr>
<td>Laterализация</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ipsilateral</td>
<td>7 (46.7%)</td>
<td>7 (53.8%)</td>
<td>1.000</td>
</tr>
<tr>
<td>contralateral</td>
<td>8 (53.3%)</td>
<td>6 (46.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Note.— Data are number of lesions, and percentages are in parentheses
*P values calculated by comparing the ratio of definitely higher than liver with the rest

Table 2: Analyses of Qualitative Characteristics of Adenomas and Metastases

Fig. 5: MRscans in 68-year-old man with 4.7-cm sized right adrenal metastasis from clear cell RCC. (a) Coronal T2-weighted image shows adrenal mass (arrow) with multiple
areas of cystic change and necrosis. (repetition time msec/echo time msec, 3500/98)
(b, c) Adrenal mass (arrow) shows no overt signal intensity loss between in-phase (b) and opposed-phase (c) gradient-echo coronal MR images with a calculated SII of 1.18. (repetition time msec/echo time msec, 100/5.0 and 100/2.4 for in- and opposed-phases, respectively)
Conclusion

In this retrospective study, the mean SII values of adrenal metastases were significantly higher than that of adenomas in the patients with clear cell RCC. By using a diagnostic criterion of SII > 16.5% adenomas could be differentiated from metastases with a sensitivity, specificity, and accuracy. Therefore, unlike the concern that metastases from clear cell carcinoma may occasionally mimic adenomas, the SII of adrenal masses may be helpful in differentiating adenomas from metastases. Accurate characterization of the adrenal mass in this clinical setting is critical for staging and therapeutic planning and with our study results, unnecessary invasive procedures such as percutaneous biopsy or surgery may be avoided in selected patients.

However, our study results demonstrated that chemical-shift imaging had limited value in the subgroup of lipid-poor adenomas with a sensitivity of 62.5%. Furthermore, there was a significant negative correlation between the precontrast CT attenuation and SII. This is in agreement with previous studies that have reported that the role of MR for characterizing hyperattenuating adrenal masses is limited owing to a strong correlation between decrease in SI on the opposed phase and CT attenuation [10, 13, 19]. Taking this into consideration, it has been proposed that dedicated adrenal CT including a delayed washout phase may be the modality of choice in diagnosing adrenal adenomas, since the excellent diagnostic performance of the relative percentage washout in adrenal adenomas are maintained at all attenuation values [6, 20]. However, recently Choi et al. [8] observed that metastases from hypervascular tumors such as RCC may exhibit similar percentage of enhancement washout to that of lipid-poor adrenal adenomas. In their study, 95% of metastases from RCC were falsely diagnosed as lipid-poor adenomas when the threshold of 60% for absolute percentage washout or 40% for relative percentage washout was used. Therefore, our study results along with that of Choi et al. [8] suggest that if a lipid-poor adrenal mass is detected using chemical-shift MR in patients with underlying clear cell RCC, dedicated adrenal CT may not be helpful as the next diagnostic test. In this clinical setting either biopsy or close follow-up may be recommended.

In our study, certain MR imaging features were helpful in the differentiation between adenomas and metastases. While metastases mostly exhibited T2 SI that was definitely or slightly hyperintense to the liver, adenomas were mostly isointense or slightly hyperintense to the liver. This is concordant with previous reports which observed that the SI of metastases tended to be higher than adenomas [21, 22]. However, they also acknowledged that the overlap between the two entities were substantial. Furthermore, the liver as a reference value for T2 SI may not be accurate, because of the large SI changes that can be seen with fatty infiltration or iron overload [2]. The presence of necrosis, cystic change, and hemorrhage was also significantly predictive for metastases. Of note, in our study we did not separately evaluate cystic change and necrosis,
because it sometimes may be difficult to exactly distinguish the two imaging features. A comprehensive analysis of these features and their prevalence in the adenomas or metastases has not been well defined in the literature. Yet, several investigators have reported that compared to adenomas, metastases tend to be more heterogeneous on CT and MR [7, 8, 23]. We speculate that due to the higher prevalence of cystic change, necrosis, and hemorrhage, the metastases may demonstrate a heterogeneous appearance. However, we must note that the higher prevalence of these MR findings in metastases may have been partly attributed to their larger size compared with adenomas. It is well known that as a mass increases in size, large necrotic areas within the mass may indicate malignancy [8]. Subsequently, small adrenal metastases may often exhibit homogeneous appearance [24, 25]. A larger study including a subgroup analysis of small adrenal masses would provide a more definitive conclusion regarding the diagnostic value of cystic change, necrosis, and hemorrhage.

In conclusion, quantitative analysis of chemical-shift MR imaging using the signal intensity index was useful for differentiating between adenomas and metastases from clear cell RCCs. In addition, MR imaging features such as cystic change, necrosis and hemorrhage favored the diagnosis of metastasis from clear cell RCC over that of adenoma.

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References


