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(Article begins on next page)

New Magnetic Resonance Imaging Series for Kidney Evaluation: Saving Time and Money

Renzulli M¹, Brocchi S¹, Pettinari I¹, Biselli M², Clemente A³, Corcioni B¹, Cappabianca S³,
Gaudiano C¹, Golfieri R¹.

¹ Department of Diagnostic Medicine and Prevention Radiology Unit, Sant'Orsola Hospital, University of Bologna, Via Albertoni , Bologna , Italy.

² Department of Medical and Surgical Sciences, Sant'Orsola Hospital, University of Bologna, Via Albertoni , Bologna , Italy.

³ Department of Precision Medicine Radiology and Radiotherapy Unit, University of Campania "L. Vanvitelli", Piazza Miraglia , Naples , Italy.

Short Title: New MRI series for kidney evaluation

16 **Abstract**

17
18 **Objectives:** This study investigates the diagnostic performance of a new T1 imaging series, generated
19 by the digital subtraction of the opposed phase from in phase T1-weighted images, in magnetic
20 resonance imaging (MRI) for renal angiomyolipoma (AML) evaluation.

21
22 **Methods:** This retrospective study involved 96 patients, sixty-three (65.6%) with at least one renal
23 AML and 33 (34.4%) healthy patients. Two radiologists having different experience retrospectively
24 reviewed two MR imaging series, starting with in and out-phase T1-weighted images and then the
25 new subtracted T1 images, in which AML appeared white on black background. The presence,
26 number, location, and dimensions of the AMLs, and reading time were collected separately for the
27 two kidneys. Statistical analysis was carried out using the appropriate tests.

28
29 **Results:** The number of lesions identified and the evaluation of lesion dimension did not statistically
30 differ between the different MR imaging series evaluated, without interobserver variability. Both
31 percentage agreement of the total number of observations and the κ coefficient showed very good
32 agreement between the radiologists. The median time for the diagnosis was statistically lower when
33 using the subtracted T1 imaging series for both observers with a median gain from 6.5 to 15 seconds
34 per identified lesion, resulting in a total time-saving of more than half (52.9%), in both patients with
35 and without AMLs, and in patients with a single or with more than one AML ($P < 0.001$).

36
37 **Conclusions:** The new subtracted T1 imaging series proved to be reliable in identifying fat-
38 containing renal lesions, by both expert and non-expert radiologists, resulting in a saving of both time
39 and money. Moreover, this new subtracted T1 imaging series could be an effective tool in non-
40 dedicated kidney examinations in which a faster reading is advisable.

41

42 **Advances in knowledge:** The opportunity of using a single set of MRI images in kidney evaluation
43 for identifying fat-containing lesions, considerably reducing reading time, resulting in cost-
44 effectiveness.

45

46 **Keywords**

47 Angiomyolipoma; Kidney Neoplasms; Magnetic Resonance Imaging; Chemical Shift Imaging;
48 Subtraction Technique.

49

50

51 **Introduction**

52

53 A renal Angiomyolipoma (AML) is a non-uncommonly found benign solid tumour¹ which represents
54 the second most frequent pathology (28.7%) after oncocytoma (51.2%) in kidneys.² The vast majority
55 of AMLs are incidentally identified because they are usually asymptomatic.³ However, more rarely,
56 AMLs can be associated with two hereditary symptomatic diseases: the tuberous sclerosis complex
57 and sporadic lymphangioleiomyomatosis.³ Incidental AMLs are smaller and usually unilateral as
58 compared with AMLs in a tuberous sclerosis complex.⁴ Solitary small AMLs (<20 mm) have a low
59 risk of growth and, if asymptomatic, do not warrant follow-up.^{5,6} Therefore, a correct imaging
60 diagnosis is mandatory in order to avoid unnecessary follow-up or non-appropriate treatment. A
61 classic AML is a benign, slow growing tumour composed of smooth muscle, adipose tissue and blood
62 vessels.³ The majority of AMLs contains fat that is clearly identifiable on imaging techniques, such
63 as Magnetic Resonance Imaging (MRI), so these tumours can be diagnosed without biopsy or surgery.
64 Approximately only 5% of renal AMLs have too little fat to be detected by imaging.⁷ An AML is the
65 only renal tumour which can be characterised based on its tissue composition in the vast majority of
66 cases. In fact, its diagnosis depends on the detection of the macroscopic fat within the lesions. On
67 MRI, the diagnosis of AMLs has traditionally been reached using T1-weighted sequences, comparing
68 the images with and without frequency-selective fat suppression.⁸ However, AMLs can be more
69 accurately diagnosed using the chemical shift in MRI.⁸⁻¹⁰ In fact, in chemical shift imaging, widely
70 used to identify microscopic amounts (intravoxel or intracellular) of fat, minimal fat AML shows a
71 significant signal-drop on opposed-phase images.^{6,11,12} Chemical shift imaging is an artefact due to
72 positional misregistration of the fat signal resulting from the different precessional frequencies of fat
73 and water protons, and manifests as alternating bands of bright and dark signals along the frequency-
74 encoding direction at fat–water interfaces.¹³ This artefact can be recognized on opposed-phase MR
75 images as a characteristic sharp black line at fat–water (fat–muscle or fat–solid organ) interfaces.¹⁴

76 Because the majority of AMLs contain macroscopic fat, this artefact will appear at the interface of
77 the AML with the kidney, or at the interface of the fatty and non-fatty portions of the mass. In small
78 AMLs, the signal void phase suppression artefact occupies the entire lesion. Consequently, small
79 AMLs, which will appear as a signal void on out-of phase images, may simulate cysts. For this reason,
80 comparison of in-phase and opposed phase images, generated from the same sequence, is always
81 required to identify fat components in small renal lesions.⁸

82 Subtraction imaging is a readily available technique which is routinely used in MRI, for example in
83 breast and liver imaging or in MR angiography to improve enhancing detection after the use of
84 contrast media.^{15,16} In fact, in liver MRI, the presence of arterial enhancement in some cases is not
85 easy to detect by visually comparing two image sets, such as those in arterial and unenhanced phases.
86 For example, some enhancing nodules can show the same relative signal intensity as the liver
87 parenchyma on arterial phase images and on unenhanced images, and this is also true for small
88 nodules. In these cases, dynamic subtraction of an unenhanced T1-weighted sequence from the
89 identical sequence carried out after gadolinium administration can be helpful.¹⁷⁻²⁰

90 The accurate identification of the chemical shift imaging is crucial in diagnosing AMLs. This is also
91 true in all the examinations carried out with different indications but always involving kidneys in
92 their field of view since AMLs are usually incidentally found. Furthermore, it would be useful to have
93 a single set of images in order to be able to evaluate the chemical shift imaging since this could reduce
94 reading time as compared to that involved in evaluating the two sets of standard T1-weighted images
95 (in-phase vs. out-phase). The chemical shift imaging can be overcome by Dixon sequences which
96 however are not available on all MR machines. Therefore, we decided to generate a new imaging
97 series by the digital subtraction of the opposed phase from in phase T1-weighted images. In these
98 subtracted T1 images, the remaining signal is only the eventual presence of chemical shift artefacts,
99 which appear strongly hyperintense on a “dark background”.

100 The purpose of this study was to investigate the diagnostic performance of our new subtracted T1
101 imaging series in kidney evaluation on MRI.

102

103 **Methods and Materials**

104 This single-centre retrospective study, carried out at our tertiary care centre, was approved by the
105 institutional review board, and the requirement for informed consent was waived.

106

107 *Study Patients*

108 The MRI database was reviewed from January 2012 to December 2017 to identify all patients in
109 which the word “Angiomyolipoma” was present in the final MRI report. The patients which satisfied
110 the following criteria were included in our study: (a) MRI performed in our Hospital, (b) good-quality
111 MRI examinations, in particular availability of opposed phase and in-phase T1-weighted images of
112 good quality and (c) a renal AML imaging diagnosis. During the study period, 64 consecutive patients
113 with at least one renal AML were identified. Only one patient was excluded due to inadequate
114 imaging examination (respiratory artefacts in the T1-weighted images), thus allowing analysis of 63
115 patients.

116 In order to evaluate the diagnostic performance of the new subtracted T1 imaging series, it was
117 decided to create an overall study population in which at least one third were healthy patients without
118 AML. In this way, the observer radiologists could analyse a patient population without knowing how
119 many patients were positive for AMLs. In the same study period (from January 2012 to December
120 2017), thirty-three healthy subjects with no renal AMLs were consecutively enrolled from the MRI
121 database by a radiologist who did not carried out the subsequent image analysis.

122 The final study population involved 96 patients, of whom thirty-three (34.4%) were healthy subjects
123 with no renal AMLs.

124

125 *MRI technique and image analysis*

126 In patients with AMLs, MRI examinations were performed following a previously described
127 protocol.²¹ In the healthy subjects, the MRI protocol was not dedicated to renal study in all cases and,
128 sometimes, the protocol was that of a study of the upper abdomen. In this latter case, the MRI
129 examination was performed following a previously described protocol.^{22,23} In particular, in all these
130 MRI examinations, the new imaging series was generated by the subtraction of the images obtained
131 from a breath-hold T1-weighted gradient-echo dual-echo “in and out of phase” sequence (TR/TE
132 150/4.6 ms and TR/TE 150/2.1 ms, respectively; 80° flip angle; 256 × 160 matrix; 62.50 Hz per pixel
133 bandwidth; one signal acquired; and 20–25-second acquisition time). In detail, for each of the 96
134 examinations, the new imaging series (subtracted T1 images) was created by a technologist
135 subtracting opposed phase T1-weighted images from in phase T1 weighted images using standard
136 software called Add/Sub on an independent console (Advantage Workstation, Release 4.4 Software,
137 General Electric Medical Systems, Milwaukee, WI, USA). This series generated a set of images with
138 a black background except for fat–water (fat–muscle or fat–solid organ) interfaces which appeared
139 white. Therefore, the chemical shift artefacts at the interface of the AML with the kidney, or at the
140 interface of the fatty and non-fatty components of the lesion, appeared white on black background.
141 All the images, standard T1 in phase and out of phase and subtracted T1 imaging series, were retrieved
142 from and evaluated on our institutional picture archiving and communication system (Carestream
143 PACS, version 1.4; Kodak, Rochester, NY).

144 The images were assessed by two radiologists, one senior radiologist with more than 10 years of
145 experience in abdominal MRI, and one junior with <3 years’ experience in abdominal MRI. They
146 were blinded to all of the information, including clinical history and imaging reports, especially those
147 concerning the presence of renal AMLs. The two observers independently reviewed all images,
148 starting with in and out of phase T1-weighted images, to evaluate the following features separately
149 for the two kidneys: presence, number, anatomic location and dimensions of the AMLs. The reading
150 time, in seconds, was also recorded beginning when the reader started to view the images and ending
151 once reaching the diagnosis (presence and number of AMLs), separately for each kidney. Reading

time did not include the time needed to measure and locate the lesion, since this time is the same independent of the different images used. All data were collected in a dedicated database for this series, one for each observer.

After at least 2 weeks, each observer independently evaluated the subtracted T1 imaging series of the entire study population. For this new imaging series, the two observers also independently reviewed all the radiologic images to evaluate the same features as for the standard T1 sequence, separately for the two kidneys. All data were collected by each observer in a new dedicated database, different from the first one.

160

161 *Statistical Analysis*

The distribution asymmetry of the quantitative data was assessed using the Skewness test. The quantitative variables were expressed as mean $\pm$ standard deviation, or median and interquartile range, as appropriate.

The systematic difference between the intra-observer and inter-observer results obtained from each MR images (T1 or subtracted T1 imaging series) was assessed using the Wilcoxon signed-rank test or the Mann-Whitney test, as appropriate. A statistically significant result showed that there was evidence of a systematic difference between the proportions of “positive” responses from the two MRI imaging series. The absence of a systematic difference implied that there was no bias. The degree of agreement between the observers was measured by both percentage agreement of the total number of observations, considering the total number of times in which the observers agreed which was divided by the total number of readings/classifications made, and by calculating Cohen's kappa (κ) coefficient. Perfect agreement was evident when Cohen's kappa equalled 1; a value of Cohen's kappa equal to zero suggested that the agreement was no better than that which would be obtained by chance alone. A *P* value of less than 0.05 was considered statistically significant. All the analyses were carried out using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA).

177

178 **Results**

179 The overall study population consisted of 96 patients evaluated by MRI from January 2012 to
180 December 2017. Mean age was 59 ± 9 years; 37.5% of the patients were male. Sixty-three patients
181 (65.6%) had at least one renal AML.

182 The number and dimensions of the lesions identified by the two observers using the T1 sequence as
183 a standard method and subtracted T1 images as an alternative method are shown in Table 1.

184 The overall number of lesions identified with the two imaging series by each observer did not
185 statistically differ. Moreover, a statistically significant difference between the observers in terms of
186 the number of lesions identified in both kidneys was not observed. When the size of the lesions was
187 considered, there were no significant differences between the imaging series (for either observer) and
188 between the observers (Table 1).

189 T1 subtracted imaging series showed good sensitivity and specificity for both the observers. In
190 particular, for the observer 1 the sensitivity and specificity in the evaluation of both the kidneys were
191 respectively 100% and 99.1% (CI95% 96.2-99.9%) [right kidney: sensitivity and specificity 100%;
192 left kidney: sensitivity 100% and specificity 98.2% (CI95% 92.4-99.8%)]. For the observer 2 the
193 sensitivity and specificity in the evaluation of both the kidneys were respectively 97.4% (CI95% 93.6-
194 99%) and 100% [right kidney: sensitivity 94.7% (CI95% 87.5-98.1%) and specificity 100%; left
195 kidney: sensitivity and specificity 100%].

196 The degree of agreement between the two observers is reported in Table 2. Both percentage
197 agreement of the total number of observations and the κ coefficient showed very good agreement
198 between the observers for each of the imaging series (Table 2).

199 The time needed by the two observers for kidney evaluation using both the standard T1 and the
200 subtracted T1 imaging series, are shown in Table 3. The median time for the diagnosis was
201 statistically lower in both observers, with a median gain of from 6.5 to 15 seconds per identified

202 lesion when using the subtracted T1 imaging series (Table 3). In both the patients with AMLs (Figure
203 1) and in those without AMLs (Figure 2), it was observed that the subtracted T1 imaging series
204 obtained a significant median time gain for the diagnosis for both observers (Table 3). Moreover, the
205 subtracted T1 imaging series allowed obtaining a significant median time gain in reaching a diagnosis
206 for both radiologists, even in the case of patients with a single AML or in those with more than one
207 lesion (Table 4). It is to note that regarding observer 1, when T1 sequence was utilized for right
208 kidney, only 3 out of 10 patients, who were identified by observer 2 with multiple lesions, were
209 detected. On the contrary, utilizing both T1 sequence in the left kidney and subtracted T1 imaging
210 series in both of kidneys, no substantial differences were detected between the two observers (right
211 kidney evaluated by T1 subtracted series: observer 1 six cases vs observer 2 eight cases; left kidney
212 evaluated by T1 sequence: observer 1 eight cases vs observer 2 eight cases; T1 subtracted series:
213 observer 1 ten cases vs observer 2 eleven cases).

214

215

216 **Discussion**

217 Solitary small AMLs (<20 mm) have a low risk of growth and, thus, do not require follow-up if
218 asymptomatic.⁵ Therefore, a correct imaging diagnosis is mandatory in order to carry out correct
219 management, such as the abstention from follow-up. An AML can be characterised based on its tissue
220 composition and depends on the detection of the fat within the lesions. On MRI, the diagnosis of
221 AMLs can be accurately carried out using chemical shift imaging which is also able to identify
222 microscopic amounts of fat as in case of a minimal fat AML.^{6,8-12}

223 Historically, MRI has an advantage as compared to Computed Tomography: the possibility of
224 carrying out image subtraction. For example, dynamic subtraction of an unenhanced T1-weighted
225 sequence from the identical sequence performed after gadolinium administration is helpful in liver
226 imaging,^{8,17,19,20} and it has become an integral part of radiological clinical practice. In fact, the

227 accurate detection of arterial enhancement is important for diagnosing small single HCCs,²⁴ and
228 enables more effective treatment.²⁵ Dynamic subtraction in MRI allows more accurate detection of
229 arterial enhancement leading to an earlier diagnosis of hepatocellular carcinoma.¹⁷ However, the
230 limits of this subtracted image series are well known in clinical practice. In fact, the subtraction is
231 obtained from two different acquisitions, the arterial phase and the unenhanced phase, which are
232 performed in two different breath-hold periods. Therefore, in case of different breaths, the subtracted
233 series results blurred due to the subtraction of images in different spatial levels. This problem, known
234 as misregistration artefact,¹⁷ is particularly relevant in cirrhotic patients with poor clinical condition
235 in whom the need to utilise these subtracted images exists.

236 In this study, the subtracted T1 imaging series is digitally generated in post-processing from two
237 identical imaging sets resulting from the same sequence, the dual T1-weighted in-phase and opposed-
238 phase sequences. This method allows having exact subtracted images acquired during the same
239 breath-hold period. Therefore, this is a “true” subtracted imaging series, different from subtraction
240 technique commonly used in the evaluation of contrast enhancement in which the unenhanced images
241 are subtracted from those performed after contrast injection, therefore in different breath-hold. Our
242 T1 subtracted imaging series is characterised by a black background on which the chemical shift
243 artefacts appear white.

244 In the present study, the new subtracted T1 imaging series for kidney evaluation was tested, in
245 particular for the identification of AMLs.

246 There is no evidence in the literature regarding this new imaging series, thus it is difficult to compare
247 these results to others. Therefore, the data of this study are critically discussed to highlight the
248 diagnostic utility of the new subtracted T1 images in kidney evaluation.

249 No significant differences were observed in the evaluation of the dimensions and number of AMLs
250 in either kidney when using the subtracted T1 imaging series with respect to the standard T1-weighted
251 sequence, with a good result in terms of sensitivity and specificity. Furthermore, there were no
252 differences in the evaluation of the dimensions and number of AMLs between the two observers,

253 even if, utilizing T1 sequence, observer 1 identified a lower number of patients with multiple lesions
254 in the right kidney. In particular, there was very good agreement between the two observers, despite
255 their different radiological skills.

256 This study was designed to calculate the time needed to evaluate the kidneys using the two different
257 imaging series, the standard T1-weighted and the subtracted T1 images. In the entire study
258 population, the reading times were markedly and statistically reduced using the new subtracted T1
259 imaging series for both observers, regardless of their different radiological skills. When evaluating
260 the total time spent on image reading by the two radiologists, the time saved is more than half (52.9%)
261 by using the new subtracted T1 images. This time saving was also achieved by dividing the study
262 population into different subgroups. In fact, in both patients with AMLs and in those without AMLs,
263 time saving was globally greater than 50% when using the subtracted T1 images, regardless of the
264 different experience of the two observers. A saving of more than 50% using the subtracted T1 imaging
265 series was also obtained when it was used in both patients with a single AML and in those with more
266 than one AML. Finally, the possibility of shortening reading times by analysing a single series rather
267 than two different sets of images yields very important saving in terms of time. This reduction in MRI
268 reading time is becoming increasingly important due to an increasing demand for cost-effectiveness
269 and efficiency in hospitals. Benjamin Franklin said: "time is money". Nevertheless, time is more
270 valuable than money: you can get more money, but you can't get more time.²⁶ This is not true when
271 using our new subtracted T1 imaging series which does not cost anything and is time saving.

272 More sophisticated 2D and 3D Dixon sequences are commercially available, which allow to obtain
273 qualitatively superior images by the use of techniques for phase correction and reduction of borders
274 artifact in chemical shift imaging.²⁷⁻²⁹ Unfortunately, the Dixon technique cannot be performed by all
275 MR machines; however, many recent papers were published without performing the Dixon
276 technique^{20,21,30} Therefore, in absence of Dixon sequence, our new subtracted T1 imaging series could
277 be an alternative tool to quickly and reliably detect renal fat-containing lesion because this imaging
278 series can be generated on any MR machine, regardless of the brand and technology.

279 The present study had a number of limitations, the first being its retrospective design. Another
280 limitation is that it is a single-centre study, which is a strong factor in interobserver coherence.
281 In conclusion, this new subtracted T1 imaging series not only proved to be reliable in the
282 identification of fat containing renal lesions but was also found to have zero cost. These advantages
283 were obtained by expert and non-expert radiologists. This new subtracted T1 imaging series could be
284 an effective tool in non-dedicated kidney examinations in which a faster reading is advisable.
285 Therefore, if our results are confirmed, the subtracted T1 imaging series could be used in radiological
286 practice in all hospitals and by all radiologists.

287

288

289

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- 362

363 TABLES

364

365 **Table 1** The dimensions and number of lesions identified by two observers using the standard T1
 366 sequence and the new subtracted T1 imaging series in abdominal MRI in patients with
 367 angiomyolipoma.

	Observer 1		<i>P</i>	Observer 2		<i>P</i>	Comparison Interobservers (<i>P</i>)	
	T1	Subtracted		T1	Subtracted		T1	Subtracted
Dimensions (mm)								
Right Kidney	7 (8.5)	7 (8)	.688	7 (8)	7 (7)	.676	.619	.64
Left Kidney	6.5 (6.5)	6 (7)	.816	8 (7.5)	8 (7)	.077	.188	.077
Number of lesions (N)								
Right Kidney	41	44	.87	51	47	.713	.598	.987
Left Kidney	54	60	.802	50	55	.862	.885	.824

368 Note: Values are expressed as medians (interquartile range) or numbers.

369

370

371

372

373 **Table 2** Degree of agreement between the two observers concerning the two MR imaging series

374 (T1 sequence or subtracted T1 imaging series).

Agreement	Right Kidney		Left Kidney	
	T1	Subtracted	T1	Subtracted
Percentage agreement (%)	88.5	92.7	88.5	87.5
Cohen's kappa (κ) coefficient	.759	.845	.762	.741

375

376

377

Table 3 Time needed for the diagnosis of an angiomyolipoma using a standard T1 sequence or the alternative subtracted T1 imaging series.

	Observer 1		<i>P</i>	Observer 2		<i>P</i>
All Patients	T1	Subtractive		T1	Subtractive	
Time (seconds)						
Right Kidney	15 (7)	7 (2)	<0.001	25 (13)	10 (3)	<0.001
Left Kidney	14.5 (9)	8 (4)	<0.001	23 (11)	10 (3)	<0.001
Patients <i>with</i> angiomyolipoma						
Time (seconds)						
Right Kidney	17 (11)	7 (4)	<0.001	25 (16)	10 (3)	<0.001
Left Kidney	15 (9)	9 (3)	<0.001	20.5 (10)	10 (3)	<0.001
Patients <i>without</i> angiomyolipoma						
Time (seconds)						
Right Kidney	15 (5)	7 (1)	<0.001	26.5 (12)	9 (3)	<0.001
Left Kidney	14 (7)	7 (3)	<0.001	25 (13)	9 (3)	<0.001

Note: Values are expressed as medians (interquartile range).

384 **Table 4** Time needed for the diagnosis of an angiomyolipoma using a T1 sequence or the alternative
385 subtracted T1 imaging series in patients with a single angiomyolipoma and in those with more than
386 one lesion.

387

	Observer 1		<i>P</i>	Observer 2		<i>P</i>
Patients <i>with</i> a Single Lesion	T1	Subtracted		T1	Subtracted	
Time (seconds)						
Right Kidney	16.5 (11)	7 (5)	<0.001	25 (18)	10 (4)	<0.001
Left Kidney	14 (7)	8 (3)	<0.001	20.5 (9)	10 (4)	<0.001
Patients <i>with more than one</i> Lesion						
Time (seconds)						
Right Kidney	18 (*)	9 (3)	.118	23 (7)	11.5 (3)	.002
Left Kidney	18 (11)	10 (3)	.016	21 (12)	11 (3)	<0.001

388 Note: Values are expressed as medians (interquartile range). *not computable because only 3 patients were detected with
389 multiple lesions.

390

Figure Legends

Figure 1. Magnetic resonance images in 64-year-old woman with renal angiomyolipoma. Axial T1 in phase image **(a)** shows a renal lesion with slightly hyperintense components (white arrow). In T1 out of phase image **(b)** is visible a loss of their signal intensity (white arrow). In the subtracted T1 image **(c)**, the intralesional fat appears strongly hyperintense (black arrow) in a dark background.

Figure 2. Axial magnetic resonance images in a healthy man, without angiomyolipoma. In and out of phase T1-weighted images **(a, b)** do not show any signal intensity abnormality and the renal parenchyma appears homogeneously black in the subtracted T1 sequence **(c)**.