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FULL PAPER

Use of an internal reference in semi-quantitative dynamic contrast-enhanced MRI (DCE MRI) of indeterminate adnexal masses

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Objective: Semi-quantitative dynamic contrast-enhanced MRI (DCE MRI) has proven useful in discriminating benign from borderline/malignant adnexal lesions. Our aim was to assess if the use of a lesion-to-internal-reference ratio improved the performance in characterizing adnexal masses and which internal reference was suitable.

Methods: Semi-quantitative DCE MRI images of 71 indeterminate adnexal lesions were retrospectively reviewed. A region of interest was manually drawn onto the enhancing solid component, psoas muscle and normal outer myometrium. The DCE parameters were evaluated, and the lesion-to-internal-reference ratios were calculated.

Results: When the wash in rate of the lesion was higher than that of the myometrium, 97% specificity and 12% sensitivity for borderline/malignancy was reached. When the maximum relative enhancement and maximum absolute enhancement (SI_{max}) of the lesion was less than those

of the psoas, 100% specificity for benignity was achieved. The highest area under the curve (AUC) (0.807) was achieved using a SI_{max} lesion-myometrium ratio. A slightly lower AUC (0.799) was achieved using a SI_{max} lesion-psoas ratio, but the psoas muscle was more frequently measurable in the same slice as the lesion ROI. Although the AUC was higher, when using ratios instead of individual DCE values, this was not significantly different.

Conclusion: DCE MRI has added diagnostic value in the assessment of adnexal lesions, and the use of internal references enables high specificity for malignancy and benignity. Lesion-internal-reference ratios have no added diagnostic value over DCE values alone.

Advances in knowledge: Both psoas muscle and myometrium are suitable internal references in the DCE assessment of adnexal lesions enabling high specificity for malignancy and benignity.

MRI has an excellent performance in characterizing adnexal masses. An overlap remains on conventional MRI as both benign and borderline/malignant pathologies can demonstrate wall thickening, septa and enhancing solid components. Therefore, a proportion of adnexal masses remains indeterminate after ultrasound and conventional MRI. Semi-quantitative dynamic contrast-enhanced MRI (DCE MRI) has previously been investigated in the assessment of indeterminate adnexal lesions. Time-intensity curves and descriptive DCE parameters of their enhancing solid components have aided differentiation of benign from borderline/malignant lesions.¹⁻⁶ However, semi-quantitative assessment of DCE, which is based on signal enhancement, is altered by cardiac flow rate, arterial blood pressure and contrast agent dose. To overcome this, internal references have been suggested to provide lesion-to-internal (lesion-internal

reference) ratios. A ratio adjusts for the above confounding factors allowing greater reproducibility. The myometrium and psoas muscles have previously been individually assessed in separate studies, including our own, as internal reference tissues.¹⁻³ Our study is the first to use both internal references in the same cohort and compare their efficacy.

A steep rise in a lesion time-intensity curve reflects its rate of enhancement. If the lesion curve is steeper than the myometrium curve, it is indicative of borderline/malignancy. Conversely, benign lesions are associated with a gradual increase in their time-intensity curve.^{1,3}

Thus, the myometrium has been proposed as an effective internal reference. However, there are certain pitfalls to this approach. These include post-hysterectomy patients, and

in the original system proposed by Thomassin-Naggara et al,¹ the myometrium must be at the same acquired slice as the enhancing component of the adnexal lesion, which is not always possible.

The primary aim of our study was to determine whether the myometrium or psoas muscle is the optimum internal reference.

The second aim of our study was to validate the use of comparing DCE parameters of the myometrium and adnexal lesions to differentiate benign from borderline/malignant tumours.^{1,3}

The third aim of our study was to determine if the use of reference ratios conferred added value over DCE parameters alone in distinguishing between benign and borderline/malignant adnexal lesions.

METHODS AND MATERIALS

Study approval was granted for retrospective review of anonymized images by the local clinical governance committee (071-11). Patient consent was obtained for the review of images. Patients who have pelvic MRI in our department routinely consent to future use of their imaging for research purposes.

Patients and lesions

From January 2007 to November 2011, 126 consecutive patients (132 lesions) who underwent pelvic MRI for the assessment of an indeterminate adnexal lesion were identified following screening with inclusion and exclusion criteria (see below). 71 lesions were included in the study. All images were reviewed by two radiologists in consensus, including a specialist radiologist with over 10 years' experience in gynaecological oncology imaging (YZT, AR), who were blinded to the final histological diagnosis.

Inclusion criteria for study entry were, a solid-enhancing component of at least 3 mm within the adnexal lesion (size required to draw a region of interest (ROI) with sufficient area to minimize error); multiphase DCE sequences for analysis; and histology or imaging follow-up (over 2 years) for lesions with benign features on MRI if surgery was not indicated or declined.

Cases were excluded if lesions were purely cystic ($n = 10$), had a solid component < 3 mm ($n = 3$) or if the solid component did not enhance ($n = 12$). Lesions lacking histology or follow-up imaging ($n = 16$), recurrent malignant lesions ($n = 1$) or patients with a hysterectomy ($n = 1$) were also excluded. One case was excluded owing to contrast extravasation resulting in incorrectly timed DCE sequences ($n = 1$). To achieve homogeneity, lesions imaged at 3 T ($n = 17$) were excluded.

Imaging technique

MRI was performed using 1.5 T MRI (Achieva®; Philips Healthcare, Eindhoven, Netherlands). A pelvic phased array coil was used in all patients. Prior to DCE MRI acquisition, the following sequences were obtained: sagittal T_2 weighted fast spin echo imaging from one femoral head to the other [repetition time (TR)/echo time (TE), 3300/100 ms; slice thickness, 6 mm; gap, 1 mm; number of signal acquisitions, six; field of view, 375–459 mm; matrix, 294×512 pixels]; axial T_1 weighted spin

echo from renal hilum to symphysis pubis (TR/TE, 500–600/18 ms; slice thickness, 6 mm; gap, 1 mm; number of signal acquisitions, three; field of view, 375–450 mm; matrix, 320×512 pixels); axial T_2 weighted fast spin echo MRI of the pelvis or beyond if necessary to cover the larger adnexal lesions (TR/TE, 3300/100 ms; slice thickness, 4 mm; gap, 1 mm; number of signal acquisitions, six; field of view, 240–300 mm; matrix, 256×512 pixels). Unenhanced and enhanced volume, fat-suppressed spoiled gradient-echo T_1 weighted imaging was performed in the sagittal or axial plane (TR/TE, 621/18 ms; slice thickness, 5 mm; gap, 0.5 mm; number of signal acquisitions, three; field of view, 240–320 mm; matrix, 205×512 pixels). DCE images were obtained before and after intravenous (IV) injection of 10 ml of 0.5 mmol ml⁻¹ of gadoteric acid (Dotarem®; Guerbet, Paris, France). The total acquisition time for this sequence was 22–30 s and was performed before and immediately after controlled pump IV injection of 3 ml s⁻¹ and then repeated at 30, 60, 90 and 120 s into the examination. Breath holding was not employed during the scan. The entire adnexal mass was covered by the dynamic acquisition. MRI was not imaged at specified points in the patients' menstrual cycle.

Dynamic contrast-enhanced semi-quantitative analysis

Multiphase dynamic contrast images were analysed by the specialist radiologist, blinded to diagnosis. The most avidly enhancing solid component in each adnexal mass was independently identified using coloured parametric maps generated on the MRI workstation. A circular ROI with a diameter > 3 mm was manually drawn. A ROI was also placed within the normal outer myometrium and psoas muscle on the exact same slice as the lesion ROI, as well as on an adjacent slice. The outer myometrium was defined as the outer 50% of myometrial thickness

Figure 1. A region of interest (ROI) was drawn on the enhancing solid component of the adnexal lesion (L7). A ROI was then drawn onto the normal outer myometrium (L5) and the psoas muscle (L8) on the same slice where possible.

(Figure 1). If the normal outer myometrium or psoas muscle was not measurable on the same slice, the myometrium or psoas muscle closest to the lesion ROI on an adjacent slice was measured. Even in cases with fibroids or adenomyosis, areas of the normal myometrium were always identifiable within the uterus. In 23 cases, the dynamic acquisition was acquired in the sagittal plane, for 45 cases in the axial plane, and for 4 cases in the coronal plane. A semi-quantitative analysis was performed using the MR breast imaging package of Philips Extended Workspace (R 2.6.3.2, 2009; Philips Medical Systems, Best, Netherlands) applied to the five-point dynamic run acquisitions. The following semi-quantitative enhancement parameters were then automatically calculated by the computer software:

- time to peak (TTP)
- maximum relative enhancement (SI_{rel}) = [maximum absolute enhancement (SI_{max}) – SI_0]/ $SI_0 \times 100$
- wash in rate (WIR) = $SI_{max} - SI_0$ /time (s)
- SI_{max} .

Where SI_0 is the tissue signal intensity on a non-enhanced T_1 weighted sequence.

DCE parameters of the lesions compared with those of the myometrium were compared to assess for differences between benign and borderline/malignant lesions. The ratios $SI_{max\ L}/SI_{max\ M}$, $SI_{rel\ L}/SI_{rel\ M}$ and WIR_L/WIR_M were calculated, where L denotes the solid component of the lesion and M denotes the myometrium.

DCE parameters of the lesions compared with those of the psoas were also calculated assessing for differences between benign and borderline/malignant lesions. The ratios $SI_{max\ L}/SI_{max\ P}$, $SI_{rel\ L}/SI_{rel\ P}$ and WIR_L/WIR_P were also calculated where L denotes the solid component of the lesion and P denotes psoas.

Statistics

Statistical analysis was performed using SPSS® v. 18 (SPSS Inc., Chicago, IL). The Student's *t*-test was utilized for parametric variables comparing benign and borderline/

Table 1. Histology of the adnexal lesions

Group	Number	Histopathology	Number
Benign	31	Mature cystic teratoma	9
		Benign mucinous cystadenoma	2
		Benign serous cystadenoma	4
		Cystadenofibroma	6
		Brenner tumour	3
		Struma ovarii	2
		Fibrothecoma	1
		Stromal luteoma	2
		Endometriosis	1
		Ovarian abscess	1
Malignant	40	Borderline mucinous tumour	2
		Borderline serous tumour	1
		Borderline serous cystadenoma	2
		Borderline seromucinous tumour	1
		Papillary cystadenocarcinoma	3
		Serous cystadenocarcinoma	8
		Mucinous cystadenocarcinoma	3
		Immature teratoma	1
		Granulosa cell tumour	3
		Ovarian-mixed Mullerian tumour	1
		Endometrioid ovarian adenocarcinoma	1
		Clear cell carcinoma	3
		Sertoli–Leydig tumour	2
		Metastasis	7
		Mesothelial cyst with foci of carcinoma	1
		Teratoma with squamous cell carcinoma	1

malignant adnexal lesions. The Mann–Whitney *U*-test was utilized for non-parametric variables. Adjustments for multiple tests were made with Holm's method. Receiver operating characteristic (ROC) curves and the area under the curve (AUC) were calculated as a descriptive tool to assess the overall discrimination of various ratios to predict borderline/malignancy.

RESULTS

Of the 126 patients identified, 71 lesions in 63 patients (8 were bilateral) met the inclusion criteria. 58 of these lesions were previously published at our institute (St Bartholomew's Hospital, London, UK), but their myometrium was not assessed.² The age range was 19–75 years with a mean age of 50.5 years. The size of the lesions ranged from 2 to 28 cm. The size of the solid components ranged from 0.7 to 14.0 cm. The histology of the adnexal lesions are listed in Table 1.

The normal myometrium was measurable in the same slice as the lesion ROI in 28 of 71 lesions. In the remaining 43 lesions, a ROI was placed on the closest normal myometrium on an adjacent slice. The psoas muscle was measurable at the same slice as the lesion ROI in 58 of 71 lesions. In the remaining 13 lesions, a ROI was placed on the closest psoas muscle on an adjacent slice.

Comparison of semi-quantitative parameters

Lesion and myometrium enhancement

Nine lesions had solid tissue with a $SI_{\max}$ value greater than that in the myometrium ($SI_{\max L} > SI_{\max M}$). Of these, six were borderline/malignant on histology. There were three benign lesions, a mucinous cystadenoma, abscess and struma ovarii. If the $SI_{\max L} > SI_{\max M}$, a sensitivity of 15% and specificity of 90% for borderline/malignancy could be reached.

Six lesions had solid tissue within the lesion with a WIR greater than that in the myometrium ($WIR_L > WIR_M$). Of these, five were borderline/malignant. One was a benign abscess. If the $WIR_L > WIR_M$, a sensitivity of 12% and specificity of 97% for borderline/malignancy could be reached.

15 lesions had a SI_{rel} within the solid component of the lesion greater than the myometrium ($SI_{\text{rel L}} > SI_{\text{rel M}}$). Of these, ten were borderline/malignant and five were benign. The histology of the benign cases were endometriosis, struma ovarii, an abscess, a mucinous cystadenoma and a cystadenofibroma. If the $SI_{\text{rel L}} > SI_{\text{rel M}}$, a sensitivity of 24% and specificity of 80% for borderline/malignancy could be reached.

Lesion and psoas enhancement

When the above DCE descriptive values of the lesions and psoas were compared, high specificity for benignity was reached. Five lesions had solid components with a $SI_{\max}$ less than that of the psoas ($SI_{\max L} < SI_{\max P}$). This was 100% specific for benignity with a sensitivity of 17%.

Nine lesions had solid components with a WIR less than that in the psoas ($WIR_L < WIR_P$), of which eight were benign giving a sensitivity of 26% and specificity of 98%. The ninth lesion was a borderline tumour.

Three lesions had a solid component with a SI_{rel} less than the psoas ($SI_{\text{rel L}} < SI_{\text{rel P}}$). This had 100% specificity for benignity, but a low sensitivity of 10%.

Analysis of ratios

A ROC curve was constructed to evaluate the AUC for each ratio and individual DCE values. Their ability to predict borderline/malignancy is listed in Table 2. $SI_{\max L}/SI_{\max M}$, with the myometrium measured on the same slice as the lesion, produced the greatest AUC (0.807) but was only measurable in 28 lesions. $SI_{\max L}/SI_{\max P}$ with psoas measured on the same slice produced the second highest AUC (0.799) but was feasible in 58 lesions. This indicated a better use of the psoas muscle as an internal reference in clinical practice. Both ratios had a higher AUC than using the $SI_{\max L}$ value alone (0.743).

Although ratios produced higher AUC than using individual values for $SI_{\max}$, SI_{rel} and TTP, this was not significantly different.

Table 2. Calculated lesion–internal reference ratios

DCE parameter	L-M ratio with L and M in same slice (<i>n</i> = 28)	L-M ratio with M in adjacent slice (<i>n</i> = 71)	L-P ratio with L and P in same slice (<i>n</i> = 58)	L-P ratio with P in adjacent slice (<i>n</i> = 71)	Individual DCE value (<i>n</i> = 71)
Maximum relative enhancement	0.682	0.727	0.762	0.701	0.748
Time to peak	0.521	0.441	0.419	0.337	0.389
Wash in rate	0.734	0.726	0.776	0.777	0.785
Maximum absolute enhancement	0.807	0.752	0.799	0.741	0.743

AUC, area under the curve; DCE, dynamic contrast enhanced; L, lesion; L-M ratio, lesion–myometrium ratio; L-P ratio, lesion–psoas ratio; M, myometrium; P, psoas muscle; ROC, receiver operating characteristic.

ROC AUC was then calculated for each ratio to assess the best discriminator for predicting borderline/malignancy. ROC AUC testing for borderline/malignancy is listed.

Table 3. *p*-values for the ability of dynamic contrast-enhanced (DCE) ratios in distinguishing benign from borderline/malignant lesions

DCE parameter	L-M ratio with L and M in same slice (<i>n</i> = 28)	L-M ratio with M in adjacent slice (<i>n</i> = 71)	L-P ratio with L and P in same slice (<i>n</i> = 58)	L-P ratio with P in adjacent slice (<i>n</i> = 71)	Individual DCE value (<i>n</i> = 71)
Maximum relative enhancement	0.100	0.359	0.001	0.004	<0.001
Time to peak	0.873	0.001	0.275	0.013	0.112
Wash in rate	0.037	0.001	<0.001	<0.001	<0.001
Maximum absolute enhancement	0.005	<0.001	<0.001	0.001	0.001

L, lesion; L-M ratio, lesion-myometrium ratio; L-P ratio, lesion-psoas ratio; M, myometrium; P, psoas muscle.

Bold *p*-values indicate significant *p*-values after Holm's test.

There was also no significant difference in using an internal reference measured in the same or adjacent slice to the lesion (*p* = 0.58–0.70 for myometrium, *p* = 0.24–0.49 for psoas).

Further analysis using the Youden index was carried out to establish the optimal threshold for the prediction of borderline/malignancy for the ratios with the greatest AUC. A $SI_{\max} L/SI_{\max} M$ ratio ≥ 0.3655 produced a sensitivity of 93.8% and specificity of 66.7% for borderline/malignancy when measured at the same slice as the adnexal lesion. A $SI_{\max} L/SI_{\max} P$ ratio ≥ 0.578 produced a sensitivity of 81.8% and specificity of 57.8% for borderline/malignancy when measured at the same slice as the adnexal lesion.

The performance of the ratios and individual DCE values in distinguishing benign from borderline/malignant lesions with their *p*-values is summarized in Table 3. The use of internal reference ratios mirrors the findings of DCE MRI. There is a significant difference in the enhancement of benign and malignant tumours on DCE MRI, but no statistical difference was seen with the addition of the internal reference ratios. There was a significant difference between several of the ratios and individual DCE values of benign and borderline/malignant lesions.

DISCUSSION

The myometrium was used as an internal reference by Thomassin-Naggara et al.¹ The following lesion/myometrium ratios were calculated: enhancement amplitude ratio, time of half rising ratio, maximal slope ratio and initial AUC for 60 s after injection (IAUC₆₀). The best ratio for the discrimination of benign and borderline/malignant lesions was the IAUC₆₀ with the largest area (0.93) under the ROC curve.

Like Thomassin-Naggara et al.¹ we found a significant difference in the DCE lesion–myometrium ratios of benign and borderline/malignant lesions. To the authors' knowledge, no other study has validated this finding. We are also the first study to compare different internal references (the psoas muscle and myometrium) to individual DCE values. It is often difficult to find the myometrium on the same slice as the tumour unless the specialist radiologist directs the angulation of the dynamic acquisition in

each patient or performs three-dimensional reformatting. As the psoas muscle extends over a far greater distance, we postulated the psoas muscle could be used as an alternative internal reference. In our study, ratios with the psoas muscle gave similar AUCs when testing for borderline/malignancy.

Figure 2. A suggested algorithm in the assessment of indeterminate adnexal lesions. DCE, dynamic contrast enhanced; L, lesion; M, myometrium; P, psoas muscle; ROI, region of interest; $SI_{\max}$, maximum absolute enhancement; SI_{rel} , maximum relative enhancement; WIR, wash in rate.

Thomassin-Naggara et al¹ compared the time–intensity curves of the adnexal lesions solid components and their myometrium. Lesion time–intensity “curve Type 3”, with an initial rise steeper than that of the myometrium, had 100% specificity but 37% sensitive for borderline/malignancy. Lesion time–intensity “curve Type 1”, with a gradual increase, with no well-defined shoulder, was 89% specific and 70% sensitive for benignity. A “curve Type 2” with a moderate initial rise in the signal of solid tissue relative to that of the myometrium, followed by a plateau, demonstrated no significant difference between the benign and malignant groups. In our cohort, the imaging was obtained at 30-s intervals with five time points. This is significantly less frequent than Thomassin-Naggara et al,¹ where imaging was obtained every 2.4 s and only three slices were obtained. We could not assess the time–intensity curves of the lesion and the myometrium, as there were insufficient time points to create an accurate curve. However, the trade-off of fewer time points was being able to image the entire adnexal mass with DCE MRI within a reasonable time frame.

Our equivalent to the time–intensity curve was comparing the individual values of the adnexal lesion DCE parameters to that of the references. If the DCE parameters (SI_{max} , SI_{rel} or WIR) of the lesion were greater than that of the myometrium, it is highly specific for malignancy. If the DCE parameters (SI_{max} , SI_{rel}) of the lesion were less than the psoas, 100% specificity for benignity could be reached (Figure 2).

Our results suggest that the psoas is a suitable internal reference, more readily obtainable than the myometrium and with only a slightly smaller AUC. The highest psoas ratio AUC was 0.799, compared with the highest myometrial ratio AUC of 0.807. An

internal reference may not be necessary from our results, as no statistical significance in the AUC between the individual DCE value and their respective ratios was found. However, apart from the WIR, ratios did have a higher AUC than that of their corresponding individual DCE values.

When comparing the individual DCE values, if the $SI_{max\ L}$ or $SI_{rel\ L}$ was less than the $SI_{max\ P}$ or $SI_{rel\ P}$, 100% specificity for benignity was achieved. Conversely, if the DCE values of the lesion were greater than the myometrium, 97% specificity could be reached for borderline/malignancy. These last two findings apply to a minority of adnexal lesions owing to their low sensitivity, however, when present would enable great confidence in differentiating benign from borderline/malignant lesions.

A limitation of our retrospective study was that our patient selection may have a bias towards malignancy as the selection criteria favours a malignant mass. However, this does not impact the clinical value of our findings.

CONCLUSION

In evaluation of complex adnexal lesions, DCE MRI provides added value in the differentiation of benign and malignant lesions. Within the DCE parameters, if the absolute or relative enhancement of the solid component is greater than the myometrium, this confers high specificity for malignancy. If the solid component enhances less than the psoas, this confers high specificity for benignity. Our study has established that using the psoas as an internal reference is comparable to using the outer myometrium. However, the use of internal reference ratios does not significantly improve performance of DCE MRI.

REFERENCES

1. Thomassin-Naggara I, Darai E, Cuenod CA, Rouzier R, Callard P, Bazot M. Dynamic contrast-enhanced magnetic resonance imaging: a useful tool for characterizing ovarian epithelial tumors. *J Magn Reson Imaging* 2008; **28**: 111–20. doi: [10.1002/jmri.21377](https://doi.org/10.1002/jmri.21377)
2. Bernardin L, Dilks P, Liyanage S, Miquel ME, Sahdev A, Rockall A. Effectiveness of semi-quantitative multiphase dynamic contrast-enhanced MRI as a predictor of malignancy in complex adnexal masses: radiological and pathological correlation. *Eur Radiol* 2011; **22**: 880–90. doi: [10.1007/s00330-011-2331-z](https://doi.org/10.1007/s00330-011-2331-z)
3. Thomassin-Naggara I, Toussaint I, Perrot N, Rouzier R, Cuenod CA, Bazot M, et al. Characterization of complex adnexal masses: value of adding perfusion- and diffusion-weighted MR imaging to conventional MR imaging. *Radiology* 2010; **258**: 793–803. doi: [10.1148/radiol.10100751](https://doi.org/10.1148/radiol.10100751)
4. Dilks P, Narayanan P, Reznick R, Sahdev A, Rockall A. Can quantitative dynamic contrast-enhanced MRI independently characterize an ovarian mass? *Eur Radiol* 2010; **20**: 2176–83. doi: [10.1007/s00330-010-1795-6](https://doi.org/10.1007/s00330-010-1795-6)
5. Sohaib SA, Sahdev A, Van Trappen P, Jacobs IJ, Reznick RH. Characterization of adnexal mass lesions on MR imaging. *AJR Am J Roentgenol* 2003; **180**: 1297–304.
6. Van Vierzen PB, Massuger LF, Ruys SH, Barentsz JO. Borderline ovarian malignancy: ultrasound and fast dynamic MR findings. *Eur J Radiol* 1998; **28**: 136–42.