Contrast-Enhanced MRI in Women with Endometrial Cancer: Dynamic Versus Single-Phase Acquisitions

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ABSTRACT

BACKGROUND: The 2019 European Society of Urogenital Radiology (ESUR) guidelines for endometrial cancer recommend performing either dynamic contrast-enhanced magnetic resonance imaging (CE MRI) or single-phase CE MRI. However, no study has directly compared these options. Therefore, this study compared dynamic versus single-phase CE MRI for the evaluation of myometrial invasion in women with endometrial cancer.

METHODS: This retrospective, single-institution comparative study was conducted among women with surgically proven endometrial cancer, including 30 consecutive women with single-phase CE MRI and 30 age- and pathologic stage-matched women with dynamic CE MRI. Three readers independently compared dynamic and single-phase CE MRI in terms of the tumor-myometrium signal intensity (SI) difference ratio, depth of myometrial invasion, image quality, and image number. Pathologic findings served as a reference standard for the depth of myometrial invasion.

RESULTS: The estimated mean SI difference ratios of dynamic CE MRI and single-phase CE MRI fell within an equivalence margin of 0.05 (90% confidence intervals [CIs] = [−0.0497 to −0.0165], [−0.0226 to −0.0403], and [−0.0429 to −0.0433], respectively, for readers A, B, and C). The area under the receiver operating characteristic curve for the detection of deep myometrial invasion was not significantly different between the acquisitions ($P = .3315$, $P = .3345$, and $P = .8593$, respectively). Single-phase CE MRI showed significantly better image quality than dynamic CE MRI ($P = .0143$, $P = .0042$, and $P = .0066$, respectively), while the median number of images for dynamic CE MRI was 2.4 times higher than that for single-phase CE MRI.

CONCLUSION: Single-phase acquisition may be a better option for CE MRI in women with endometrial cancer than dynamic acquisition.

KEYWORDS: Magnetic resonance imaging, contrast media, endometrial neoplasms, myometrial invasion, uterus

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Introduction

Endometrial cancer, the most common gynecologic malignancy in developed countries,[1] is surgically staged according to the 2009 Federation of Gynecology and Obstetrics (FIGO) system, which includes evaluations of metastasis to the pelvic and paraaortic lymph nodes.[2] Lymphadenectomy has been considered part of the surgical staging procedure; however, most surgeons believe that lymphadenectomy is not necessary for women at a low risk of lymph node metastasis, and not performing lymphadenectomy avoids its concomitant risks and complications.[3] The European Society for Medical Oncology (ESMO) recently recommended that the surgical staging of endometrial cancer should be tailored based on the risk of lymph node metastasis.[4] According to the ESMO guidelines, lymphadenectomy is not recommended in low-risk patients with grade 1 or 2 endometrioid adenocarcinoma without deep myometrial invasion.

Magnetic resonance imaging (MRI) is the most preferred imaging modality used to stratify women with endometrial cancer into low-risk versus intermediate- to high-risk groups because it is the modality that best determines the depth of myometrial invasion.[2,5-12] T2-weighted imaging (T2WI), contrast-enhanced imaging, and diffusion-weighted imaging (DWI) are key MRI sequences to assess myometrial invasion of endometrial cancer. Of these, CE MRI is mostly performed as high temporal resolution, dynamic CE MRI.[6,13-17] However, high-spatial-resolution, single-phase CE MRI is also an option. In the 2019 ESUR guidelines for endometrial cancer, it is also recommended that CE MRI can be performed using both dynamic CE MRI and single-phase CE MRI.[10] Our prior experience with dynamic CE MRI suggested that the temporal window for tumor-myometrium contrast in endometrial cancer is not narrow enough to require dynamic CE

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Table 1. Imaging parameters of standardized MRI protocols for endometrial cancer.

SEQUENCE	T2 TSE	T1 TSE	DWI	DYNAMIC CE MRI	SINGLE-PHASE CE MRI
Plane	Sagittal Axial Obl[a] axial	Axial	(Obl[a]) axial	Obl[a] axial	Coronal
Bandwidth (Hz)	250	250	32	190	189.9
Repetition time (ms)	6000	620	2420	5-6	8.1
Echo time (ms)	100	10	70	2-3	3.7
Flip angle (°)	90	90	90	10	12
Sense factor	1	1	2	2/1	2/1
Echo train length	17	3	53	54	26
Slice thickness (mm)	5	5	5	4	1
space (mm)	6	6	6	6	0.5
Number of signal average	2	2	4	2	2
Field of view (cm)	25	25	25	25	25
Matrix	256 × 256	256 × 256	100 × 100	356 × 356	252 × 250
Scan time (min: s)	3:10	3:30	3:00	4:6	4:40

Abbreviations: TSE, turbo spin-echo; DWI, diffusion-weighted imaging; CE MRI, contrast-enhanced magnetic resonance imaging.
[a]Obl indicates oblique, and oblique axial images were obtained perpendicular to the endometrial cavity.

MRI.[16] Given that radiologists invest substantial time and effort into reviewing hundreds of dynamic CE MRI images, it might be necessary to compare dynamic CE MRI with single-phase CE MRI. However, to the best of our knowledge, no studies have compared dynamic CE MRI with single-phase CE MRI in women with endometrial cancer. Therefore, our study was conducted to compare dynamic CE MRI with single-phase CE MRI in the evaluation of myometrial invasion in women with endometrial cancer.

Materials and Methods

Ethics approval and consent to participate

This retrospective, single-institutional comparative study was approved by the institutional review board of Seoul Metropolitan Government Seoul National University (SMG-SNU) Boramae Medical Center (institutional review board [IRB] No. 16-2017-27), and the requirement for informed consent was waived due to the retrospective nature of the study.

Study population

Before May 2014, our institution conducted dynamic CE MRI as a standard part of preoperative MRI for endometrial cancer. Based on scientific evidence,[16] we adopted single-phase CE MRI instead of dynamic CE MRI in May 2014. We retrospectively searched our database for women who underwent single-phase CE MRI and surgically proven endometrial cancer, and the last 30 consecutive women were selected as the single-phase CE MRI group. Among women who underwent dynamic CE MRI and had surgically proven endometrial cancer, 30 age- and surgicopathologic stage-matched women were chosen for comparison as the dynamic CE MRI group. A deviation of ±3 years was allowed for age matching.

Image acquisition

The MRI studies were performed with a 1.5 T MRI unit (Achieva and Intera; Philips Medical Systems, Best, the Netherlands) using a phased-array torso coil. The patients were asked to fast for 4 to 6 hours and empty the bladder before MRI to reduce motion artifacts.[18] In addition, half an hour before MRI, the patients received an intramuscular injection of 20 mg of scopolamine butylbromide (Buscopan; Boehringer Ingelheim Korea, Seoul, Korea) as an antiperistaltic agent.

Our MRI protocol for endometrial cancer is summarized in Table 1. A fat-saturated T1-weighted 3-dimensional fast field echo sequence was used for both dynamic CE MRI and single-phase CE MRI. For dynamic CE MRI (Figure 1), oblique axial images were obtained perpendicular to the endometrial cavity, and the scan percentage was reduced to 60% to allow a temporal resolution of 25 to 40 seconds depending on the uterine size. The loss of image resolution from the reduced scan percentage was compensated with the peripheral part of the k-space of the last dynamic reference scan.[19] Imaging began simultaneously with the administration of 0.1 mmol gadolinium/kg body weight, injected at a rate of 2 mL/second through an antecubital vein, and approximately 7 to 12 continuous sets of image

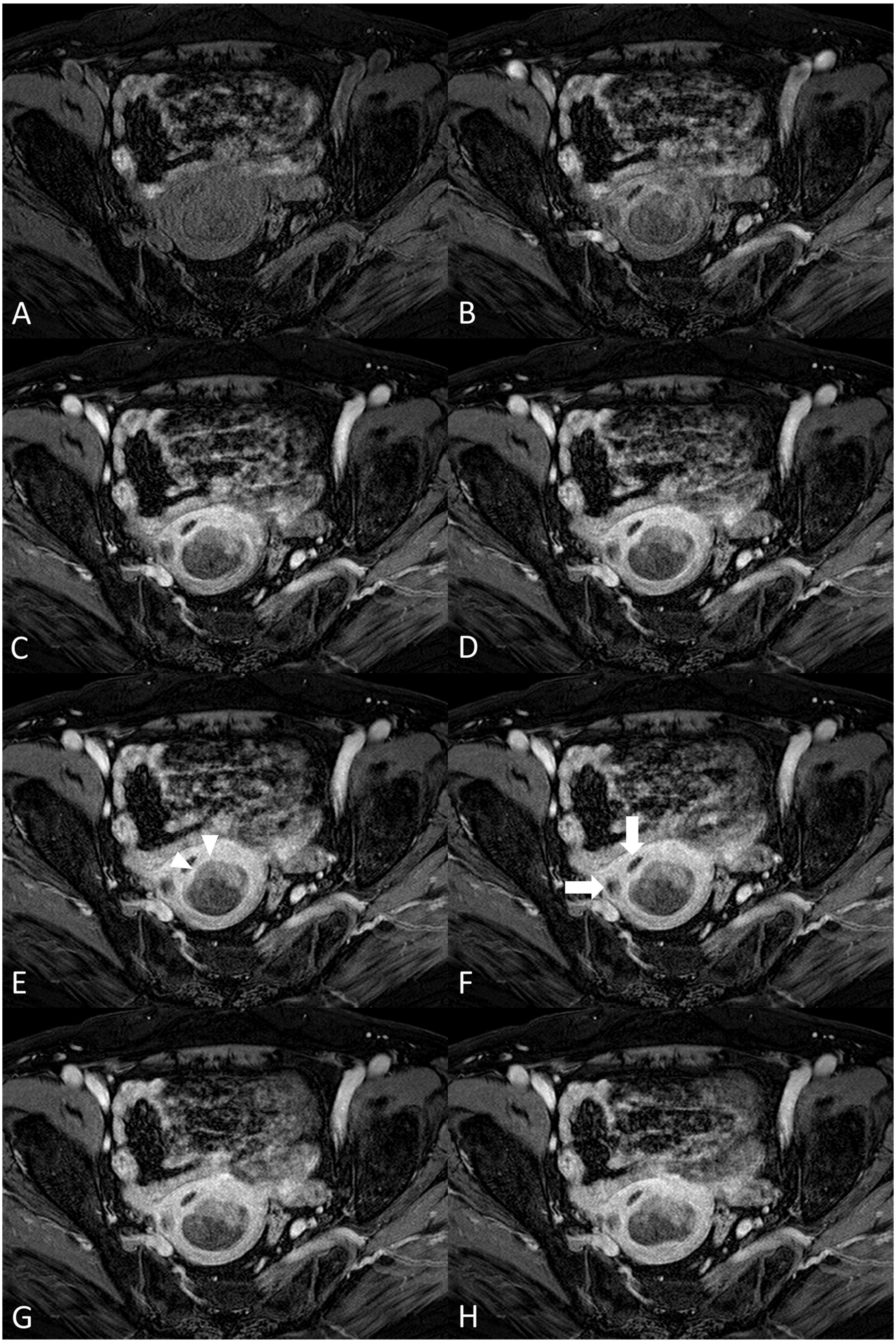

Figure 1. Sequential dynamic CE MRI images from A to H. A was obtained simultaneously with the administration of contrast material, and subsequent sequential dynamic CE MRI images were obtained with a time resolution of 38 seconds. An endometrial mass invading less than half of the myometrium is shown in the right anterior uterine corpus (arrowheads in E). The SI difference ratio calculated from E was 0.20. Two intramural myomas are shown in the right anterior uterine corpus (arrows in F). CE MRI, contrast-enhanced magnetic resonance imaging; SI, signal intensity.

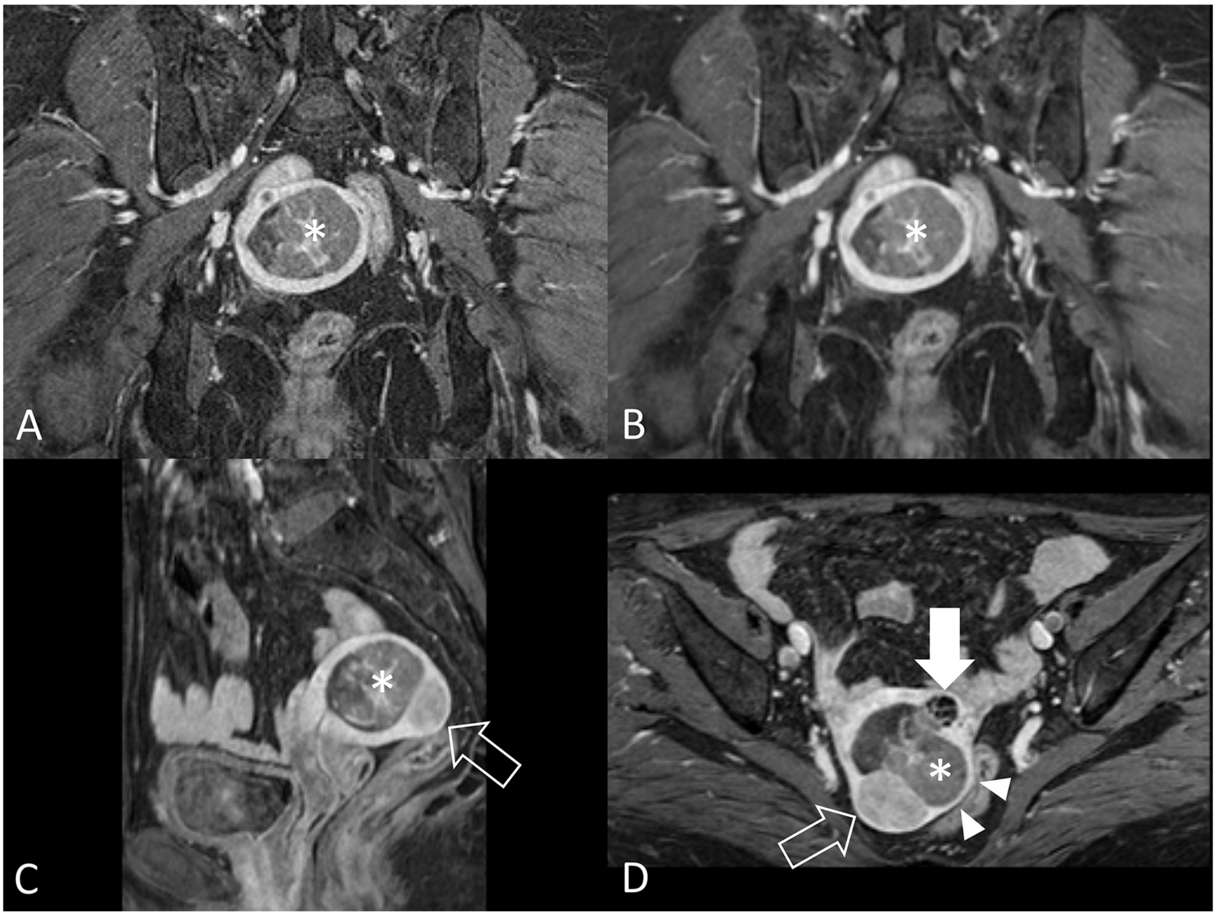

Figure 2. Single-phase CE MRI data (A) reconstructed into coronal (B), sagittal (C), and oblique axial (D) images. On the oblique axial image (D), invasion of more than half of the myometrium is shown in the left posterior uterine corpus (arrowheads). Intramural myomas are seen in the uterine fundus (open arrows in C and D) and anterior uterine corpus (arrow in D). * = endometrial cancer. CE MRI, contrast-enhanced magnetic resonance imaging.

series were acquired during 4 to 6 minutes of examination. For single-phase CE MRI (Figure 2), coronal images were obtained with a slice thickness of 1 mm and a space of 0.5 mm. Because single-phase CE MRI required an average of 4 minutes and 40 seconds, a linear profile order was used to fill the central k-space with an appropriate imaging delay.[16] The obtained coronal data were immediately reconstructed into sagittal, coronal, and oblique axial planes by the technologists at the console and then transferred to the picture archiving and communication system (PACS: Marosis M-view, Infinitt, Seoul, Korea). A 2-mm thickness and no interslice gap were chosen to facilitate comparison with the standard anatomic sequences. The average time for image reconstruction was approximately 1 minute.

Image analysis

For each woman included in this study, the MR images were loaded to a dedicated study worklist on the PACS after the removal of personal identifying information by an author (***) who did not participate in subsequent image interpretation. Two genitourinary radiologists (*** [reader 1] and *** [reader 2] with 4 and 15 years of experience in genitourinary imaging, respectively) and 1/4-year resident (*** [reader 3]), who were informed of the primary aim of the study but blinded to the surgicopathologic results of each patient, independently evaluated the dynamic CE MRI and single-phase CE MRI in a random order, with reference to the T2WI and DWI sequences, for the following: (a) the tumor-myometrium SI difference ratio, (b) the depth of myometrial invasion (superficial vs deep),[20] and (c) image quality. Image quality was scored according to a 4-point grading system (Table 2), and the SI difference ratio was calculated as follows: SI difference ratio = $(SI_m - SI_c)$ / $(SI_m + SI_c)$, where SI_m is the SI of the myometrium, and SI_c is the SI of the endometrial cancer. This formula provides a unitless parameter between 0 and 1, with 1 representing the greatest relative contrast. For dynamic CE MRI, the SI difference ratio was calculated from the images that showed the largest subjective contrast difference between the tumor and the myometrium. Myometrial invasion was scored as superficial if the tumor showed no invasion or invasion of less than half of the myometrium, while deep myometrial invasion was defined as invasion of at least half of the myometrium.[20] In addition, subendometrial enhancement (SEE) on dynamic CE MRI was

Table 2. Grading of diagnostic image quality.

SCORE	DIAGNOSTIC QUALITY	DESCRIPTION
4	Excellent	Clear depiction of the uterus
3	Adequate	Minor artifact that did not interfere with image interpretation
2	Questionable	Impaired depiction of the uterus
1	Nondiagnostic	Insufficient image quality

assessed by consensus between readers 1 and 2 with the following classification: (a) no demonstrable SEE, (b) disrupted SEE, and (c) intact SEE.[15,21] The number of images was counted by reader 2 for subsequent analysis.

Histopathologic analysis

Most of the study participants (n = 57) underwent standard operations consistent with the current International FIGO surgicopathologic staging and guidelines (pelvic washing for cytologic analysis, total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy with or without paraaortic lymphadenectomy).[20] Lymphadenectomy was omitted in the remaining 3 women according to the clinicians' discretion. Surgicopathologic reports were prospectively provided as part of daily practice by 1 of 4 staff pathologists who were blinded to the results of the MRI studies, with a prescribed form that included the depth of myometrial invasion.

Statistical analysis

Statistical analyses were performed with MedCalc (version 18.6, MedCalc Software, Mariakerke, Belgium). To test the equivalence of the tumor-myometrium SI difference ratio between single-phase CE MRI and dynamic CE MRI, 2 one-sided tests for independent means were used with a margin of 0.05,[22,23] which was inferred from the interquartile range of the SI difference ratio in a previous study.[16] The diagnostic performance in the assessment of deep myometrial invasion was compared using the area under the receiver operating characteristic curve (AUC). The image quality and the number of images were compared using the Wilcoxon rank-sum test. A *P* value of less than 0.05 was considered to indicate a statistically significant difference. Interobserver agreement was assessed using the weighted kappa (κ) statistic with the following categories for κ values: 0.00 to 0.20, slight; 0.21 to 0.40, fair; 0.41 to 0.60, moderate; 0.61 to 0.80, substantial; and 0.81 to 1.0, near perfect.

Results

In all 60 women (mean age: 56 ± 10 years in the dynamic CE MRI group and 57 ± 9 years in the single-phase CE MRI group), pathologic confirmation of endometrial cancer was obtained following hysterectomy. The specimens showed no invasion or invasion of less than half of the myometrium in 42 women and invasion of half or more of the myometrium in 18 women. The surgicopathologic characteristics of the study

Table 3. Surgicopathologic characteristics of the study participants.

VARIABLE	DYNAMIC CE MRI	SINGLE-PHASE CE MRI
Histologic subtype		
Endometrioid	24 (80.0)	26 (86.7)
Serous papillary	2 (6.7)	—
Mucinous	—	—
Clear cell	—	1 (3.3)
Squamous	—	—
Undifferentiated	1 (3.3)	—
Mixed	3 (1.0)	3 (1.0)
Histologic grade		
Well differentiated	11 (36.7)	16 (53.3)
Moderately differentiated	12 (40.0)	10 (33.3)
Poorly differentiated	6 (20.0)	2 (6.7)
Not determined	1 (3.3)	2 (6.7)
Myometrial invasion		
No or less than half	21 (70.0)	21 (70.0)
Equal to or more than half	9 (30.0)	9 (30.0)
Surgical stage		
IA	15 (50.0)	18 (60.0)
IB	2 (6.7)	4 (13.3)
II	4 (13.3)	4 (13.3)
IIIA	4 (13.3)	1 (3.3)
IIIB	1 (3.3)	—
IIIC	4 (13.3)	3 (10.0)
IVA	—	—
IVB	—	—

Data represent numbers of women, with percentages in parentheses.
Abbreviation: CE MRI, contrast-enhanced magnetic resonance imaging.

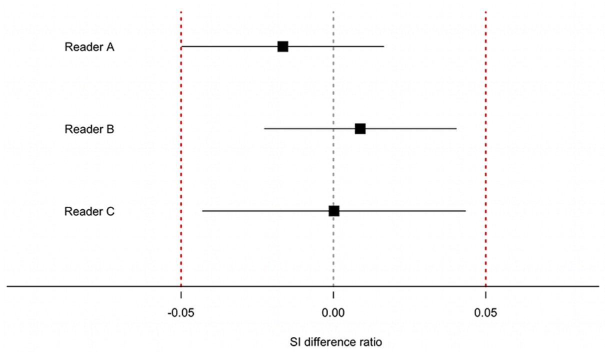

Figure 3. Plots of the 2 one-sided test results showing the absolute differences in the tumor-myometrium SI difference ratios between single-phase CE MRI and dynamic CE MRI. The mean differences (squares) and their 90% CIs (horizontal lines) are within the equivalence margin of 0.05 (vertical dashed lines) for all readers. CE MRI, contrast-enhanced magnetic resonance imaging; SI, signal intensity; CI, confidence intervals.

participants are summarized in Table 3. The median interval between MRI and surgery was 11 days (95% CI: 7-76 days) in the dynamic CE MRI group and 10 days (95% CI: 7-11 days) in the single-phase CE MRI group.

SI difference ratio

For reader A, the SI difference ratio of dynamic CE MRI ranged from 0.03 to 0.42, with a median value of 0.18, while that of single-phase CE MRI ranged from 0.04 to 0.33, with a median value of 0.20. For reader B, the SI difference ratio of dynamic CE MRI ranged from 0.04 to 0.42, with a median value of 0.22, while that of single-phase CE MRI ranged from 0.06 to 0.36, with a median value of 0.21. For reader C, the SI difference ratio of dynamic CE MRI ranged from 0.06 to 0.45, with a median value of 0.22, while that of single-phase CE MRI ranged from 0.07 to 0.31, with a median value of 0.22. The dynamic and single-phase CE MRI SI difference ratios were found to be equivalent for all readers with a margin of equivalence of 0.05 (90% CI of the mean difference = [−0.0497 to −0.0165], [−0.0226 to −0.0403], and [−0.0429 to −0.0433], respectively, for readers A, B, and C) (Figure 3).

Diagnostic performance

The sensitivity and specificity of dynamic and single-phase CE MRI in the detection of deep myometrial invasion are summarized in Table 4, and the AUCs in the detection of deep myometrial invasion are presented in Table 5. For all readers, the difference in the AUC between dynamic CE MRI and single-phase CE MRI was not significant (P = .3315, P = .3345, and P = .8593, respectively, for readers A, B, and C). The interobserver agreement in the diagnosis of deep myometrial invasion was substantial for dynamic CE MRI and moderate to substantial for single-phase CE MRI (Table 6).

SEE

SEE was depicted in only 30.0% (9/30) of women who underwent dynamic CE MRI, and SEE was demonstrated in 17.7% (1/6) of premenopausal women who were eligible for fertility-sparing management. In all cases, SEE was disrupted and no women showed intact SEE.

Image quality

For reader A, the image quality of dynamic CE MRI ranged from 1 to 4, with a median score of 3, while that of single-phase CE MRI ranged from 2 to 4, with a median score of 3. For reader B, the image quality of dynamic CE MRI ranged from 1 to 4, with a median score of 3, while that of single-phase CE MRI ranged from 2 to 4, with a median score of 3. For reader C, the image quality of dynamic CE MRI ranged from 1 to 3, with a median score of 3, while that of single-phase CE MRI ranged from 2 to 4, with a median score of 3. For all readers, image quality was significantly better for single-phase CE MRI than for dynamic CE MRI (P = .0143, P = .0042, and P = .0066, respectively, for readers A, B, and C).

Number of images

The number of images for dynamic CE MRI ranged from 350 to 880, with a median of 640, while that for single-phase CE MRI ranged from 112 to 300, with a median of 270. The median number of images was 2.4 times higher for dynamic CE MRI than for single-phase CE MRI, and the difference was statistically significant (P < .0001).

Discussion

Moon et al reported that an imaging delay of approximately 90 seconds after contrast material injection may be optimal to obtain appropriate tumor-myometrium contrast in women with endometrial cancer. In their study, the appropriate tumor-myometrium contrast tended to continue or increase over time and not be instantaneous.[16] Therefore, as long as the central *k*-space data for tumor-myometrium contrast are obtained after an appropriate imaging delay, single-phase CE MRI can be performed without losing tumor-myometrium contrast, compared with dynamic CE MRI. In this study, the *k*-space profile order was set to be linear and the central lines were acquired halfway through the acquisition. By doing so, we could fill the central k-space data 2 or 3 minutes after contrast material injection because the acquisition of single-phase CE MRI took approximately 4 to 6 minutes. As expected, the tumor-myometrium SI difference ratio was not significantly different between dynamic CE MRI and single-phase CE MRI (P = .2342, P = .7553, and P = .9410, respectively, for readers A, B, and C).

The volume data for single-phase CE MRI can be reconstructed into multiple imaging planes (Figure 2). Using several

Table 4. Sensitivity and specificity of dynamic CE MRI and single-phase CE MRI in the detection of deep myometrial invasion in women with endometrial cancer.

READER	SENSITIVITY (%)		SPECIFICITY (%)	
	DYNAMIC CE MRI	SINGLE-PHASE CE MRI	DYNAMIC CE MRI	SINGLE-PHASE CE MRI
A	67 (6/9)	89 (8/9)	86 (18/21)	86 (18/21)
B	44 (4/9)	78 (7/9)	95 (20/21)	86 (18/21)
C	44 (4/9)	44 (4/9)	86 (18/21)	90 (19/21)

Abbreviation: CE MRI, contrast-enhanced magnetic resonance imaging.

Table 5. AUC values for dynamic CE MRI and single-phase CE MRI in the detection of deep myometrial invasion in women with endometrial cancer.

READER	DYNAMIC CE MRI	SINGLE-PHASE CE MRI	*P*
A	0.762 (0.572-0.897)*	0.873 (0.701-0.966)*	.3315
B	0.698 (0.504-0.851)*	0.817 (0.634-0.934)*	.3345
C	0.651 (0.456-0.815)*	0.675 (0.480-0.833)*	.8593

Abbreviations: AUC, area under the curve; CE MRI, contrast-enhanced magnetic resonance imaging.
*Data are AUC values, with 95% CIs in parentheses.

Table 6. Interobserver agreement of dynamic CE MRI and single-phase CE MRI in the evaluation of deep myometrial invasion.

	DYNAMIC CE MRI	SINGLE-PHASE CE MRI
A vs B	0.64 (0.33-0.95)*	0.63 (0.34-0.92)*
A vs C	0.66 (0.36-0.96)*	0.60 (0.31-0.89)*
B vs C	0.79 (0.52-1.00)*	0.50 (0.17-0.83)*

Abbreviation: CE MRI, contrast-enhanced magnetic resonance imaging.
*Data are κ values, with 95% CIs in parentheses.

planes was expected to improve the diagnostic performance of CE MRI in the assessment of deep myometrial invasion; however, although the performance of single-phase CE MRI was better than that of dynamic CE MRI for all readers in this study, statistically significant differences were not demonstrated between dynamic CE MRI and single-phase CE MRI (Table 5). We assume that the use of T2WI and DWI for reference and the small number of patients in the study might have been responsible for this unexpected result, but future studies are needed to clarify our assumptions.

The improved temporal resolution of dynamic CE MRI was expected to increase tumor-myometrium contrast, but as shown in this study, dynamic CE MRI did not show better tumor-myometrium contrast than single-phase CE MRI in women with endometrial cancer. Instead, decreasing signal acquisition for spatial information led to deterioration of the image quality,[24] as was also demonstrated in this study (Figure 4). Another reason for performing dynamic CE MRI in women with endometrial cancer is the expectation of demonstrating SEE, which is a thin layer of enhancement between the endometrium and the myometrium.[21] In women with endometrial cancer, myometrial invasion can be ruled out by demonstrating an intact SEE on dynamic CE MRI, which is useful information when fertility-sparing management is under consideration.[15,21,25] However, the role of dynamic CE MRI in the selection of fertility-sparing management may be limited, given that SEE cannot be demonstrated on dynamic CE MRI in many women, especially premenopausal women.[15,21] Our study also showed that SEE was not frequently demonstrated on dynamic CE MRI. Furthermore, Nakao et al[26] reported that 8 (40%) of 20 women with intact SEE on dynamic CE MRI were eventually found to have myometrial invasion. Given these findings, we need to reconsider whether dynamic CE MRI should be used to select women for fertility-sparing management.

In the last few decades, the workload in radiology has dramatically increased with the advent of the PACS, increased utilization of advanced cross-sectional imaging with much larger sets of data, and an overall increase in the number of imaging studies.[27] The increasing workload has resulted in high rates of radiologist burnout, and this trend has only continued to worsen.[28,29] In this study, dynamic CE MRI produced 2.4 times more images than single-phase CE MRI, meaning that radiologists would need to invest more time and effort in interpreting CE MRI. Since CE MRI does not require high temporal resolution for endometrial cancer, single-phase CE MRI may be a better choice than dynamic CE MRI in the era of radiologist burnout.

Our study has several limitations. First, the small number of the study population and retrospective nature of this study may

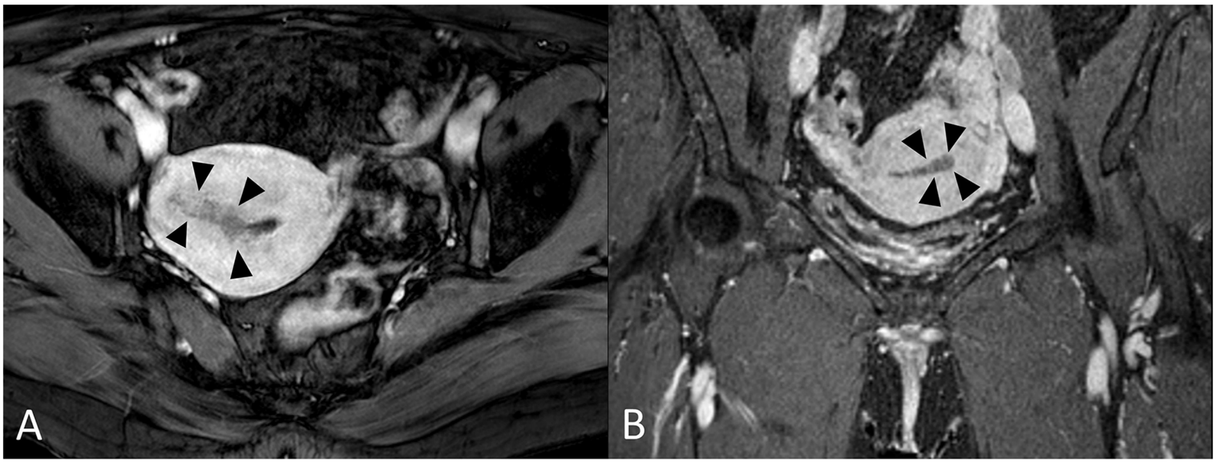

Figure 4. Stage IA endometrial cancers. On dynamic CE MRI (A) obtained in a 45-year-old woman, an endometrial mass invading less than half of the myometrium is seen in the right upper endometrial cavity (arrowheads). The SI difference ratio between the tumor and the myometrium was 0.24, and the grading of the diagnostic image quality was questionable in 1 reviewer and adequate in 2 reviewers. On single-phase CE MRI (B) obtained in a 66-year-old woman, an endometrial mass invading less than half of the myometrium is seen in the left upper endometrial cavity (arrowheads). The SI difference ratio was 0.25, and the grading was adequate in all reviewers. CE MRI, contrast-enhanced magnetic resonance imaging; SI, signal intensity.

have introduced bias. Second, although we tried to control for confounding variables by matching age and pathologic staging, this study could not be completely free from selection bias because we were not able to perform both dynamic CE MRI and single-phase CE MRI in the same women. The third limitation is that DWI, which has been increasingly highlighted,[5,6] was not compared with CE MRI. We know that readers are curious about the comparison of CE MRI and DWI, but we believe that the question should be addressed after clarifying the preferable acquisition method for CE MRI. Finally, all women enrolled in this study were scanned only with a 1.5T MRI unit. Since the magnetic field strength could affect spatial and temporal resolution, additional studies will be needed to elucidate the effects of magnetic field strength on CE MRI.

Conclusions

When performing CE MRI in women with endometrial cancer, single-phase CE MRI can provide comparable tumor-myometrium contrast to dynamic CE MRI, while also offering improved image quality and reducing the number of images. In addition, high-spatial-resolution, single-phase CE MRI can be reformatted into multiple preferred imaging planes obtained at the same time. Therefore, single-phase CE MRI might be a better option for women with endometrial cancer than dynamic CE MRI. We hope that our experience will also be helpful in assessing whether high temporal resolution is required for CE MRI in the case of other tumors.

Author Contributions

Conceptualization: Moon MH, Cho JY. Data acquisition: Jang S. Data analysis or interpretation: Lee MS, Kim TM, Moon MH, Oh S. Drafting or critical revision of the article: all authors. Approval of the final version of the article: all authors.

Ethics Approval and Consent to Participate

This retrospective, single-institutional comparative study was approved by the institutional review board of Seoul Metropolitan Government Seoul National University (SMG-SNU) Boramae Medical Center (institutional review board [IRB] No. 16-2017-27), and the requirement for informed consent was waived due to the retrospective nature of the study.

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