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FULL PAPER

Application of FLASH-3D dynamic contrast-enhanced imaging for diagnosis of endometrial carcinoma

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Objective: To investigate the application and value of fast low-angle shot three-dimensional (FLASH-3D) dynamic contrast-enhanced MRI for the pre-operative staging of endometrial carcinoma.

Methods: This prospective study enrolled 48 patients with complete clinical data and pathologically confirmed endometrial carcinoma from July 2012 to March 2014. After routine MRI examination, subjects underwent FLASH-3D dynamic contrast-enhanced examination. The dynamically enhanced features of the uterine wall and tumours were analyzed. FLASH-3D pre-operative staging and findings in relation to myometrial invasion were compared with post-operative pathological results in a double-blind manner.

Results: There were 48 cases of pathologically proven endometrial carcinoma, including 34 patients with Stage I (Stage Ia 22 cases and Stage Ib 12 cases), 9 with Stage II, 3 with Stage III and 2 with Stage IV. The staging accuracy for endometrial carcinoma was 81% (39/48) using

FLASH-3D dynamic contrast-enhanced sequences. The sensitivity, specificity and accuracy for the determination of deep myometrial invasion were 84%, 90% and 88%, respectively. There was no significant difference compared with the results of post-operative pathology ($p > 0.05$).

Conclusion: FLASH-3D dynamic contrast-enhanced imaging may be valuable for the early diagnosis and pre-operative staging of endometrial carcinoma. Its high accuracy for assessing deep myometrial invasion makes FLASH-3D imaging an important tool for selecting the optimal therapeutic protocol and for prognosis estimation.

Advances in knowledge: FLASH-3D can significantly improve the accurate assessment of the depth of tumour invasion into the myometrium and may thus help to guide clinical surgical choices and post-operative evaluation. FLASH-3D is thus a promising technique for the routine examination of female pelvic tumours.

INTRODUCTION

Endometrial cancer comprises several types of epithelial malignancies that originate from the endometrial glands of the uterus and has the potential to invade the myometrium and form distant metastases. Endometrial carcinoma is the most frequent gynaecological malignancy that predominantly occurs in post-menopausal females. They are the most common type of gynaecological cancers, with incidences in North America and Europe only slightly less than those of mammary, lung and colorectal carcinomas. The incidence of endometrial cancer in China has been increasing annually, secondary to cervical cancer.^{1–3} The main symptoms of endometrial carcinoma are abnormal vaginal bleeding, irregular vaginal discharge and lower abdominal pain. The 5-year survival rate for most females

(>75%) with International Federation of Gynecology and Obstetrics (FIGO) Stage I, following appropriate treatment, is 90%.^{3,4} The accurate assessment of pre-operative stage is thus important for guiding treatment options and determining prognosis. Pre-operative imaging methods include CT, MRI and ultrasound, among which MRI is the most effective.^{4,5} Its arbitrary azimuth imaging and good resolution for soft-tissue contrast mean that MRI has been widely used for FIGO staging of endometrial carcinoma.⁶ Fast low-angle shot three-dimensional (FLASH-3D) dynamic contrast-enhanced imaging involves a fast, low-angle shot technique with three-dimensional (3D), fat-suppressed angiographic sequences. In this prospective study, we investigated the application and value of FLASH-3D dynamic contrast-enhanced imaging for the diagnosis and

pre-operative staging of endometrial carcinoma in 48 patients with complete clinical data and pathologically confirmed endometrial carcinoma.

METHODS AND MATERIALS

Patients

This study was approved by the institutional review board at the Shenzhen Longhua New District Central Hospital and The First Affiliated Hospital of Shenzhen University. All study participants provided written, witnessed informed consent; consent from the next of kin, caretakers or guardians on behalf of the minors/children provided signed informed consent. This research was in accordance with the Helsinki Declaration. The exclusion criteria for patients were (1) any MRI examination contraindication, (2) an incomplete MRI examination, (3) any contraindication to surgery and (4) no post-operative histological findings available for review.

Finally, a total of 48 consecutive patients with complete clinical data and pathologically confirmed endometrial carcinoma underwent FLASH-3D imaging following routine MRI examination from July 2012 to March 2014. The mean age of the patients was 44.2 ± 9.6 years. There were 21 pre-menopausal and 27 post-menopausal females, and their symptoms at presentation included vaginal bleeding, vaginal spotting and increased vaginal discharge. All patients underwent resections 1–14 days (mean 8 days) after routine MRI scans. Surgeries included total hysterectomy, hysterectomy and bilateral tubal oophorectomy, and pelvic lymph node dissection. The histopathological results of the tumours were analyzed according to the FIGO staging standards published in May 2009.⁷

MRI examination

Routine MRI

Routine MRI was performed using a Siemens Magnetom® Avanto 1.5-T (Siemens, Erlangen, Germany) superconducting MRI scanner. Patients were advised to drink enough water to fill the bladder while avoiding excessive filling of the bladder which would result in discomfort and motion artefacts. Venous access in the elbow was established in all cases in preparation for FLASH-3D. Routine plain scan: joint Body Matrix MR coil and Spine Matrix MR coil (Siemens, Erlangen, Germany), field of view 320×320 mm, matrix 256×256 mm, 3–5 mm thick and 20% layers apart. Scan sequence: (1) horizontal axis: T_1 weighted imaging [spin echo (SE) sequences, repetition time (TR) 400 ms and echo time (TE) 11 ms]; T_2 weighted imaging (T2WI) [turbo SE (TSE) sequences, TR 6500 ms and TE 83 ms]; (2) sagittal position (parallel to the long axis of the uterus oblique sagittal plane): T2WI (TSE sequences, TR 6500 ms and TE 83 ms); (3) sagittal position: T2WI (parallel to the long axis of the uterus oblique sagittal plane), respiratory gating, blade sequences and fat-suppression technique, TR 3610 ms, TE 86 ms, one excitation; (4) sagittal position: diffusion-weighted imaging sequences, b -value = 1000, three excitations.

Fast low-angle shot three dimensional

FLASH-3D was performed with FLASH-3D volume interpolated gradient echo fat-suppressed angiographic sequences, TR/TE 4.74/2.38 ms, deflection angle of 10° , field of view 320×320 mm,

matrix 256×256 mm, one excitation, sagittal position (parallel to the long axis of the uterus oblique sagittal) scanning, 3 mm thick, 20% layers apart. After the plain scan, high-pressure syringes were used for the rapid intravenous bolus injection of contrast agent (gadolinium diethylenetriamine penta-acetic acid) *via* the elbow vein (0.1 mmol kg^{-1} , total 20 ml, flow rate 3 ml s^{-1}), followed by the injection of an equivalent volume of saline solution at the same speed. Using auto trigger enhancement scanning, images were collected after 30, 60, 90, 120 and 180 s, respectively, with 18 s per acquisition time, for a total of five times, to generate FLASH-3D dynamic contrast-enhanced images.

MRI image analysis and evaluation

The images were evaluated by two radiologists using a double-blind method, with an emphasis on dynamic contrast-enhanced sequences of the uterine wall and tumour stages, the thickness of the endometrium, tumour morphology, disruptions of the junctional zone and uterine muscle invasion. All cases were staged according to the latest FIGO staging system, and the results were compared with post-operative histopathology results.

Statistical analyses

The results of FLASH-3D dynamic contrast-enhanced sequences for staging endometrial carcinomas and for evaluating the depth of myometrial invasion were compared with the results of histopathological FIGO staging. The sensitivity, specificity and accuracy of the two methods were calculated using SPSS® v. 19.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). Confidence intervals (95%) were calculated, and a value of $p < 0.05$ was considered statistically significant.

RESULTS

After routine MRI scanning, 48 patients underwent resections within 2 weeks: 17 underwent total hysterectomy, 27 hysterectomy and bilateral tubal oophorectomy, and the other 4 underwent pelvic lymph node dissection or biopsy. Two cases of Stage III C with pelvic lymph nodes and/or abdominal aortic lymph node enlargement, lymph node dissection, post-operative found metastases, and two cases of Stage IV invasion of rectal and inguinal lymph node metastasis, puncture biopsy were confirmed. The post-operative histopathology results revealed 36 endometrial adenocarcinomas, 5 serous carcinomas, 2 mucinous adenocarcinomas, 4 clear cell carcinomas and 1 adenosquamous carcinoma. According to the latest FIGO staging standards, the surgical–pathological staging results demonstrated 34 Stage I (Stage Ia 22 and Stage Ib 12), 9 Stage II, 3 Stage III and 2 Stage IV. By contrast, FLASH-3D dynamic contrast-enhanced sequences identified 29 cases of Stage I, 6 Stage II, 2 Stage III and 2 Stage IV. There was no significant difference in staging accuracy between FLASH-3D and surgical–pathological techniques. The overall staging accuracy of FLASH-3D was 81% (39/48) (Table 1).

Among these 48 cases, histopathology revealed 12 cases with no muscle invasion, 17 with shallow invasion and 19 with deep-muscle invasion. FLASH-3D dynamic MR-enhanced sequences revealed early manifestation of endometrial enhancement in 18 patients, early enhancement of junctional zone and late enhancement of the outer myometrium in 13, and obvious early

Table 1. Comparison of fast low-angle shot three-dimensional (FLASH-3D) dynamic contrast-enhanced MRI and histopathology findings for determining the International Federation of Gynecology and Obstetrics stage in patients with endometrial cancer

FLASH-3D	Histopathology				Total
	I	II	III	IV	
I	29	2	0	0	31
II	4	6	1	0	11
III	1	1	2	0	4
IV	0	0	0	2	2
Total	34	9	3	2	48

enhancement of the whole myometrium and late endometrial enhancement in 17. In terms of evaluating tumour infiltration of the myometrium, FLASH-3D dynamic MR-enhanced sequences indicated no muscle invasion in 9, shallow invasion in 13 and deep-muscle invasion in 16. The accuracy of correctly judging the depth of myometrial invasion was 79% (38/48). The sensitivity, specificity, accuracy, positive-predictive value and negative-predictive value for evaluating tumour invasion of the uterus muscle were 84%, 90%, 88%, 84% and 90%, respectively. There was no significant difference between FLASH-3D dynamic MR-enhanced sequence and histopathological results (Table 2).

In addition, conventional sagittal T2WI scanned images underestimated the depth of invasion in eight cases; four because the junctional zone was thinner and portions had disappeared. However, FLASH-3D dynamic contrast-enhanced sequences clearly showed that the enhancement zone was partially broken and demonstrated superficial invasion of the myometrium (Figure 1a–d). In addition, conventional imaging underestimated invasion in two cases of leiomyomas of the uterus, one of uterine adenomyosis and one of hydrometra. By contrast, invasion was overestimated in five older and postmenopausal females as a result of a thinner junctional zone and muscle layer, which blurred the distinction between the shallow and deep muscle layers and muscle layer decomposition. However, FLASH-3D dynamic contrast-enhanced sequences clearly showed tumour infiltration of the deep muscle, and cervical stroma and serous layer integrity (Figure 2a,b). Four patients were misdiagnosed by FLASH-3D and sagittal T2WI images as a result of the muscle layer being thinner, with parts of the junctional zone missing; tumour boundaries and muscle signals lacking contrast; and tumours that extended to the uterine horn and merged multiple fibroids (Figure 3a,b).

DISCUSSION

Endometrial cancer is one of the three types of malignant tumours of the female reproductive system. The surgical treatment of endometrial cancers differs according to their grading and stage, and includes total hysterectomy, hysterectomy and bilateral tubal oophorectomy, and pelvic lymph node dissection. Pre-operative imaging staging and evaluation are therefore important for establishing the appropriate surgical treatment, post-

Table 2. Comparison of fast low-angle shot three-dimensional (FLASH-3D) dynamic contrast-enhanced MRI and histopathology findings for determining depth of myometrial invasion

FLASH-3D	Histopathology			Total
	0	1	2	
0	9	1	0	10
1	3	13	3	19
2	0	3	16	19
Total	12	17	19	48

0, no invasion; 1, less than half myometrium invaded; 2, invasion of at least half the myometrium.

operative evaluation and prognosis. MRI is currently recognized as the most accurate imaging technique.^{1,4,8,9} Recent improvements in MRI pelvic coils and software technology mean that the clinical application of functional MRI has become well established, including the application of FLASH-3D dynamic contrast-enhanced imaging techniques that allow continuous, thin-layer scanning. The temporal and spatial resolutions of FLASH-3D are also enhanced.^{4,10,11} In addition to the speed of imaging, the high signal-to-noise ratio aids the detection of small lesions and early endometrial cancer.

FLASH-3D dynamic contrast-enhanced imaging has several advantages: (1) ultrashort TR, TE and small angles of radio-frequency pulses (TR 3–8 ms, TE 1–3 ms and radiofrequency pulse-excited angle 10–15°) increase the time resolution; (2) FLASH-3D can be combined with k-space technology; (3) spatial resolution is improved; (4) volume interpolation reconstruction techniques mean that layers can overlap, thus allowing 3D reconstructions; (5) the scanning speed is fast, and the entire 3D volume can be scanned in around 12 s, using different imaging parameters, whereas multiple scan phases allow dynamic arterial and venous phase imaging. FLASH-3D imaging combined with a Siemens Magnetom Avanto 1.5-T superconducting MR scanner in our hospital (Shenzhen Longhua New District Central Hospital and The First Affiliated Hospital of Shenzhen University) can clearly display 11 contrast among the endometrium, muscle layer and tumour. FLASH-3D is also able to detect signal foci or small lesions on T2WI, thus providing clearer information for the early diagnosis of muscular invasion, and cervical and lymph node metastases in patients with endometrial carcinoma.^{11–13} Based on the detection of endometrial damage, junctional zone disruption and the extent of myometrial invasion, FLASH-3D can assess the degree of tumour infiltration and FIGO staging, which have great clinical significance.

Prognosis is closely related to stage in patients with endometrial cancer. The later the stage, the poorer the therapeutic effect and prognosis. According to FIGO staging criteria, the post-operative recurrence rate of early endometrial cancer is about 10–15%, with 5-year survival rates for Stage I and Stage II of 81–91% and about 67–77%, respectively. Although the proportion of patients diagnosed with advanced endometrial cancer is relatively low, their prognosis is significantly poorer than for patients with early-stage tumours, and the 5-year survival rates

Figure 1. Stage Ia endometrial carcinoma. Sagittal T_2 weighted images with fat saturation (a) showing an isointense endometrial nodule located at the base of the uterus. The junctional zone (JZ) of the posterior wall of the uterus is thin and partially interrupted, with a fuzzy margin between the JZ and the endometrium (white arrow). Sagittal fat-suppressed T_1 weighted fast low-angle shot three-dimensional (FLASH-3D) pre-dynamic contrast-enhanced (DCE) image (b) revealing the hypointense tumour invading the endometrium, the JZ and the shallow myometrium (white arrow). There is no obvious difference in signals between the lesion and the uterine wall. Sagittal fat-suppressed T_1 weighted FLASH-3D DCE 30s image (c) revealing the obviously enhanced subendometrial structure (dark arrowheads) and slightly enhanced endometrial tumour during the early stage. There are significant differences in signals between the subendometrial structure and the lesion. The lesion interrupts the subendometrial structure (white arrow). The degree of enhancement is is: endometrium > myometrium > JZ. Sagittal fat-suppressed T_1 weighted FLASH-3D DCE 180-s image (d) revealing moderately enhanced endometrial tumour with a clear margin compared with the homogeneously enhanced myometrium. Endometrial and JZ invasion are clear, and myometrial invasion shows <50% of its thickness (white arrow).

for Stages III and IV endometrial cancer are approximately 32–60% and 5–20%, respectively.^{3,4,14} Accurate pre-operative diagnosis and staging thus not only help to guide the clinical treatment plan but may also impact on post-operative evaluation and prognosis. Dynamic contrast-enhanced MRI has been shown to be superior to conventional T2WI and vaginal ultrasound.^{2,4,9,15} FLASH-3D dynamic contrast-enhanced MRI technology provides more accurate pre-operative staging, is able to determine the depth of myometrial and pelvic invasion, and can provide a direct basis for early diagnosis. Shin et al¹⁵ studied 199 patients with endometrial cancer and reported an accuracy of MR of 81% for endometrial carcinoma staging, compared with an accuracy of dynamic contrast-enhanced MR of 84.2%. In the current study, the staging accuracy of FLASH-3D dynamic contrast-enhanced imaging for endometrial carcinoma was 81% (39/48), which was similar to that of surgical–pathological

staging ($p > 0.05$), in accord with previous reports.^{4,10,13,16} The value of pre-operative staging focuses on early-stage (Stages I and II) disease. However, the accurate staging of early tumours is difficult because of the need to detect small lesions in the endometrium, given that tumours are only mildly enhanced by dynamic contrast during the early stage. By contrast, tumours are increasingly enhanced in later stages. The ability of FLASH-3D to display the contrast between the endometrium, muscle layer and tumour thus increases the chances of detecting signal foci or small lesions on T2WI.

Tumour infiltration of the myometrium and the depth of infiltration are closely related to lymph node metastasis, relapse rate and prognosis. The depth of myometrial invasion determines the need for lymph node dissection; when the tumour infiltrates less than half of the muscle layer, the rate of lymph

Figure 2. Stage Ia endometrial carcinoma. Sagittal turbo spin echo T_2 weighted image (a) showing a bulky, irregular, homogeneous signal of the endometrial tumour invading out from the uterine wall interrupting the junctional zone in the superficial myometrium, suggesting no invasion of the deep myometrium (dark arrow) and uterine serosal layer (white arrowheads). Sagittal fat-suppressed T_1 weighted fast low-angle shot three-dimensional dynamic contrast-enhanced 120-s image (b) showing moderately enhanced endometrial tumour with a clear margin compared with the more-enhanced muscular layer of the uterus. The lesion breaks through the endometrium and obliterates the superficial myometrium, with no deep myometrial invasion (dark arrowheads). This lesion corresponds to the International Federation of Gynecology and Obstetrics Stage Ia.

node metastases is low, whereas infiltration into at least half of the muscle layer suggests that the tumour may have spread through the lymphatic vessels in the deep-muscle layers, indicating the need for lymph node dissection during surgery.^{2,13,16} Enhanced MRI represents one of the most accurate methods for the pre-operative assessment of the depth of myometrial invasion. In patients with deep invasion of the myometrium, dynamic contrast-enhanced MRI significantly improves the signal-to-noise ratio for tumour and uterine wall muscle, allowing more accurate determination of the depth of myometrial invasion.^{4,16,17} T2WI- and T_1 weighted imaging-enhanced scanning have demonstrated accuracies of 73–86% and 78–88%, respectively, for assessing depth of muscle

invasion, and this accuracy can be further increased to 82–92% for enhanced dynamic scanning.^{9,16–18} The results of the current study showed that dynamic enhanced FLASH-3D imaging technology increased the accuracy of pre-operative evaluation of depth of myometrial invasion. The study by Emlik⁴ has demonstrated that in differentiation of deep myometrial invasion from superficial myometrial invasion, the sensitivity, specificity, accuracy, PPV and NPV were 100%, 85%, 89%, 68.4%, and 100% on dynamic 3D FLASH volume interpolated gradient echo MR images. The current study demonstrated an accuracy of 79% for discriminating among tumours without muscular invasion, those with shallow invasion and those with deep muscle invasion. The sensitivity, specificity and accuracy for

Figure 3. Stage II endometrial carcinoma, coexisting with multiple leiomyomas of the posterior wall of the uterine body and Nabothian cysts. Sagittal turbo spin echo T_2 weighted image (a) showing increased uterine volume. An irregular, mixed-signal endometrial tumour invades into the superficial muscle layer (white arrowheads) resulting in interruption of the junctional zone (JZ) and infiltration of the cervical stroma (white arrow). Sagittal fat-suppressed T_1 weighted fast low-angle shot three-dimensional dynamic contrast-enhanced 90-s image (b) showing a moderately enhanced endometrial tumour with a clear margin, compared with the more enhanced muscular layer of the uterus. The lesion breaks through the endometrium and obliterates the underlying JZ, indicating superficial myometrial invasion (dark arrowheads), and cervical infiltration is clearly depicted (white arrow).

evaluating tumour invasion of the uterus muscles were 84%, 90% and 88%, respectively, which were similar to those in previous studies.^{4,10,17,18} However, assessment of the depth of myometrial invasion was impaired by the absence of the junctional zone, endometriosis, adenomyosis, uterine fibroids, thinning, tumours at the muscle layer boundary lacking contrast with the muscular layer and distractions such as tumours that extended to the uterine horn.^{8,19,20} Four such cases were misdiagnosed on T2WI sequences and dynamic contrast-enhanced FLASH-3D images.

The results of this study confirm the importance of MRI in the diagnosis of endometrial cancer. FLASH-3D dynamic contrast-enhanced imaging may play a valuable role in the

early diagnosis and pre-operative staging of endometrial carcinoma. FLASH-3D can significantly improve the accurate assessment of the depth of tumour invasion into the myometrium and may thus help to guide clinical surgical choices and post-operative evaluation. FLASH-3D is thus a promising technique for the routine examination of female pelvic tumours.

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