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Assessment of uterine enhancement rate after abdominal radical trachelectomy using dynamic contrast-enhanced magnetic resonance imaging

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Abstract

Purpose The purpose of this study was to assess uterine enhancement rate after abdominal radical trachelectomy (ART) using dynamic contrast-enhanced (DCE) magnetic resonance (MR) imaging.

Methods Ten patients with early uterine cervical cancer, who were treated by ART, were included in this study. Each patient underwent DCE MR imaging using a 3 T unit to assess uterine enhancement rate at three times (before surgery and 1 and 3 months after surgery). The radiologist calculated mean signal intensities of the anterior and posterior myometrium and also measured the signal intensities of the urine in the bladder on the same image, which was expressed as the myometrium-to-urine signal intensity ratio. In the time–intensity ratio curve, enhancement parameters (peak signal intensity ratio and peak time) of the uterine body were compared across the three MR examinations.

Results The peak signal intensity ratio was 6.96 ± 0.98 on MR examinations before surgery, 6.14 ± 0.81 1 month after surgery, and 6.26 ± 0.63 3 months after surgery ($p = 0.069$). The peak time was 57.6 ± 3.4 s on MR examinations before surgery, 56.4 ± 4.4 s 1 month after surgery, and 53.2 ± 8.0 s 3 months after surgery ($p = 0.304$). No significant differences were found in either the peak signal intensity ratio or peak time across the three MR examinations.

Conclusions That no significant decrease of uterine enhancement rate was found after surgery suggests the uterine function and fertility may be preserved after ART.

Keywords Trachelectomy · Cervical cancer · Magnetic resonance imaging

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Introduction

Uterine cervical cancer, which is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in females worldwide, accounted for 9 % of total new cancer cases and 8 % of the total cancer deaths among females in 2008 [1]. Because cervical cancer is caused by the human papillomavirus virus which is spread during intercourse, the prevalence rates of cervical cancer have increased among young women, especially in her 20s and 30s of reproductive ages [2–4].

For the preservation of fertility in patients with early-stage cervical cancers, the vaginal radical trachelectomy (VRT) procedure was developed by Dargent et al. at the end of the 1980s, who reported the results of a series of patients with early cervical cancer who were treated by VRT [5]. Subsequently, Smith et al. reported the abdominal radical trachelectomy (ART) procedure [6]. Since 2008, radical trachelectomy has become a standard procedure recommended by the National Comprehensive Cancer Network to treat early-stage cervical cancer (stages IA2–IB1) patients who wish to preserve their fertility [7].

Most frequent complication after ART is cervical stenosis, and this was most likely associated with cerclage placement or failure to use tools or techniques that would prevent stenosis such as an intrauterine cannula [8]. The other complications include infection or abscess formation, leg lymphedema, lymphocyst, and amenorrhea [8, 9]. Another problem after radical trachelectomy is preterm delivery, which may be caused by: (1) an increased risk of infection because of a decreased infection barrier caused by the shortening of the cervix, and the absence of a cervical mucus plug; (2) cervical incompetence; or (3) decreased uterine blood flow [10]. Decreased uterine blood flow can also lower placental perfusion and lead to immaturity of the fetus [10].

While uterine artery-preserving techniques of radical trachelectomy for preserving the function of the remaining uterus have been the subject of an increasing number of reports, the evaluation of uterine blood flow remains insufficient. Although uterine blood flow after radical trachelectomy has been assessed using Doppler sonography [11] and computed tomography (CT) [12, 13], we were unable to find any reports assessing uterine enhancement rate after radical trachelectomy using magnetic resonance (MR) imaging. Therefore, the aim of the present study was to assess uterine enhancement rate after ART using dynamic contrast-enhanced (DCE) MR imaging.

Materials and methods

Patients

The present study was approved by the human research committee of the institutional review board of our hospital, and complied with the guidelines of the Health Insurance Portability and Accountability Act of 1996. Furthermore, written informed consent was provided by all study subjects at enrollment. Between May 2010 and October 2013, 13 consecutive patients were diagnosed with early uterine cervical cancer and received ART treatment at our University Hospital. Of these, 10 patients for whom DCE MR imaging was performed using a 3 T unit to assess uterine enhancement rate at three times [before surgery and 1 month (median 33 days; range 28–56 days) after surgery, and 3 months (median 95 days; range 91–141 days) after surgery] were included in this study. The remaining three patients were excluded from this study, because we could not get informed consent form one patient and all three MR examinations could not be performed in two patients.

Surgery criteria

The inclusion criteria for ART treatment were as follows: International Federation of Gynecology and Obstetrics (FIGO) stage IA1 with LVSI to IB1, no evidence of extra uterine metastases in the preoperative examination, cervical cancer histology of squamous cell carcinoma or adenocarcinoma, tumor size of <2 cm, and a desire to preserve fertility.

Surgery procedure

All 10 patients underwent ART. First, bilateral pelvic lymph node dissection and lymphadectomy were performed. The resected nodes were sent for frozen-section examination. If lymph node metastasis was revealed, we altered the surgical procedure to radical hysterectomy. The main trunk of uterine artery was identified from iliac artery and skeletonized to preserve. Moreover, the descending branches of the uterine artery were identified and ligated. The cervix and the paracervical connective tissue were usually removed through the vagina. The uterus was transected slightly below the internal os. Surgical margins were carefully evaluated by frozen-section examination and cytological diagnosis of the preserved internal os. When a negative margin state was confirmed, two permanent cerclages were performed with a nylon suture and the vaginal cuff was anastomosed to the cervical stump. The catheter was removed about 1 month after surgery.

MR imaging

MR imaging was performed using a 3-T MR imaging system (Achieva Quasar Dual 3T; Philips Medical Systems, Amsterdam, the Netherlands) at the menstrual or early proliferative phase. MR imaging was performed for each patient before surgery and one and 3 months after surgery. A phased-array body coil was used to allow whole pelvic coverage. All MR images were obtained using the parallel imaging technique at 2-mm section thickness with no intersection gap. Sagittal fat-suppressed keyhole-based DCE MR imaging (4D THRIVE) sequence (TR/TE, 3.1/1.5 ms; flip angle, 10; imaging matrices, 384×384; field of view, 26×26 cm) were obtained for all patients. The slice number and data acquisition time of the 4D THRIVE sequence were 50 slices and 4 s, respectively. The 4D THRIVE sequence was repeated fifteen times without interval. At the start of the 4D THRIVE sequence, gadopentetate dimeglumine (Magnevist; Bayer Healthcare, Berlin, Germany) was injected intravenously through a 22-gauge cannula typically placed in the antecubital vein using a commercially available power injector. The injection volume and injection rate were 0.2 ml/kg and 3 ml/s, respectively. The injection sites were recorded for each patient. Injections were made at the same site for each of the three MR imaging sessions.

MR image review

An experienced radiologist with 15 years of post-training experience at interpreting genitourinary images reviewed all MR images and defined regions of interest (ROIs). The ROIs were separately placed, as large as possible, within both the anterior and posterior myometrium of the uterine body, while taking care to avoid the endometrium and transitional zone. The mean signal intensities of the anterior and posterior myometrium were calculated. The radiologist also measured the signal intensities of the urine in the bladder on the same image, which was expressed as the myometrium-to-urine signal intensity ratio. In the time–intensity ratio curve of each MR examination, the peak signal intensity ratio and the peak time were recorded. The peak signal intensity ratio was defined as the maximum signal intensity ratio during repeated fifteen 4D THRIVE scanning. The peak time was defined as the time to reach peak signal intensity ratio from the time of injection of contrast material. For each patient, we considered postoperative uterine enhancement rate to be significantly decreased when the peak signal intensity ratio of postoperative MR examinations were less than 80 % of those of preoperative MR examinations.

Statistical analyses

Statistical analyses were performed using SPSS version 18.0 (SPSS, Inc, an IBM Company, IL, USA). Post hoc analyses were performed to compare the peak signal intensity ratio and peak time across the three MR examinations of each patient. The variables were either tested by the Tukey HSD or the Games–Howell test if the Levene's test was $p > 0.05$ or $p < 0.05$, respectively. A p value of <0.05 was considered to be statistically significant.

Results

Patient characteristics are summarized in Table 1. The median age was 32 years (age range 26–40 years). Histological subtypes were squamous cell carcinoma ($n = 6$) and adenocarcinoma ($n = 4$). The clinical FIGO stages were stage I A1 with LVSI ($n = 1$), stage IA2 ($n = 2$), and stage IB1 ($n = 7$).

In all patients, we attempted to preserve the uterine artery; however, the unilateral uterine artery was ligated in one patient. In addition, there was a post-surgical complication (an abscessed lymphocyst) in another patient. No patients developed amenorrhea. All patients had a regular menstrual cycle. Of the 5 of 10 patients who attempted to become pregnant after ART, two patients (40 %) became pregnant. One patient suffered from preterm premature rupture of membranes at 36 weeks of gestation; however, she delivered a 2252 g baby by cesarean section. One patient continues the pregnancy. Neither local recurrence nor distant metastasis was observed in the postoperative follow-up period.

Table 1 Patient characteristics

Characteristics	Value
Number of patients	10
Age (years)	
Mean	32
Range	26–40
Histological subtype	
Squamous cell carcinoma	6
Adenocarcinoma	4
Clinical FIGO stage	
IA1 with LVSI	1
IA2	2
IB1	7
Parity	
None	9
One	1

The peak signal intensity ratio and the peak time of each MR examination are summarized in Table 2 and those of the 10 enrolled patients are summarized in Tables 3 and 4. The peak signal intensity ratios were 6.96 ± 0.98 on MR examinations before surgery, 6.14 ± 0.81 at 1 month after surgery, and 6.26 ± 0.63 at 3 months after surgery ($p = 0.069$) (Fig. 1). The peak time was 57.6 ± 3.4 s on MR examinations before surgery, 56.4 ± 4.4 s at 1 month after surgery, and 53.2 ± 8.0 s at 3 months after surgery. Peak signal intensity ratio and peak time did not differ significantly across the three MR examinations ($p = 0.304$) (Table 2).

No significant decrease of postoperative uterine enhancement rate was found in six patients (60 %) (Fig. 2). However, postoperative uterine enhancement rate significantly decreases both 1 and 3 months after surgery in one patient (10 %), at only 1 month after surgery in two patients (20 %), and at only 3 months after surgery in one patient (10 %) (Fig. 3). In five postoperative MR examinations of four patients with significantly decreased uterine enhancement rate, the decrease rate of uterine enhancement rate ranged from 24 to 39 % (mean 31 %). A patient with decreased uterine enhancement rate both one and 3 months after surgery suffered from thin endometrium and amenorrhea after ART, but there were no clinical symptoms after ART in the remaining three patients with decreased uterine enhancement rate. Meanwhile, although decrease of postoperative uterine enhancement rate was not observed in the patient who underwent unilateral uterine artery ligation, a significant decrease was observed 3 months after surgery in the patient with the abscessed lymphocyst. In summary, uterine enhancement rate at 3 months after

Table 2 Peak signal intensity ratio and peak time of each MR examination

	Before surgery	One month after surgery	Three months after surgery
Peak signal intensity ratio	6.96 ± 0.98	6.14 ± 0.81	6.26 ± 0.63
Peak time (s)	57.6 ± 3.4	56.4 ± 4.4	53.2 ± 8.0

Table 3 Peak signal intensity ratio of the 10 enrolled patients

Patient number	Before surgery	One month after surgery	Three months after surgery
1	9.4	5.7	6.2
2	7.1	7.5	7.6
3	7.0	6.7	6.3
4	7.8	6.9	5.2
5	6.4	4.8	6.1
6	6.3	5.9	5.6
7	6.4	6.2	6.2
8	6.7	5.0	6.5
9	6.0	6.3	6.4
10	6.6	6.4	6.5

Table 4 Peak time of the 10 enrolled patients

Patient number	Before surgery	One month after surgery	Three months after surgery
1	52	60	48
2	60	56	56
3	60	52	36
4	52	60	60
5	56	60	56
6	60	56	44
7	60	48	56
8	60	52	60
9	60	60	56
10	56	60	60

A unit of peak time is second

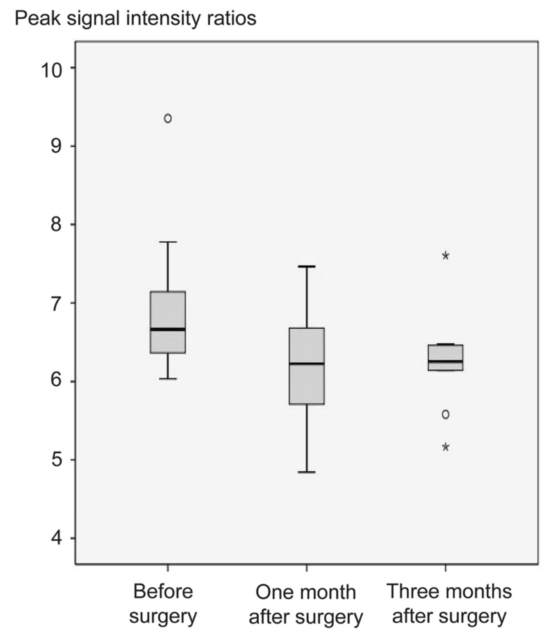

Fig. 1 *Box* and *whisker plots* showing quantitative measurements of peak signal intensity ratio of three MR examinations. *Boundary of boxes closest to zero* 25th percentile, *line within boxes* median, and *boundary of boxes farthest from zero* 75th percentile. *Error bars* smallest and largest values within 1.5 box lengths of 25th and 75th percentiles. *Outliers* are represented as individual points. The peak signal intensity ratios were 6.96 ± 0.98 on MR examinations before surgery, 6.14 ± 0.81 at 1 month after surgery, and 6.26 ± 0.63 at 3 months after surgery. There was no significant difference in peak signal intensity ratio across three MR examinations

surgery did not decrease in comparison to preoperative enhancement rate in 80 % of the patients.

Discussion

MR imaging is an effective method used for the detection of primary tumors, the extension of local spread, and the evaluation of lymph node metastases in patients with uterine cervical cancer [14]. T2-weighted images and dynamic contrast-enhanced images provide an adequate estimation of the tumor size and the extent of locoregional disease [14–16]. MR imaging is also a helpful and non-invasive tool for the assessment before and after ART [17–19]. Although Doppler sonography can be used to assess organ blood flow, it has some problems with respect to intraobserver reproducibility, technical failure, and unreliable measurement. In contrast, MR imaging allows for objective examination; its advantage over CT is that it avoid radiation exposure. Dynamic susceptibility contrast (DSC) MR imaging, also known as perfusion MR imaging, is commonly used to measure the blood flow of brain parenchyma or brain tumors [20]. However, because DSC MR imaging is affected by motion-induced artifacts and is susceptible to artifacts arising from bone and air, it is difficult to use in the abdominopelvic regions. Although arterial spin labeling (ASL) MR imaging, which is performed without a contrast agent, has recently come into use for the quantitative evaluation of cerebral blood flow in various central nervous disorders [21], usage in the abdominopelvic regions has not been sufficiently evaluated. We, therefore, assessed uterine enhancement rate using conventional DCE MR imaging.

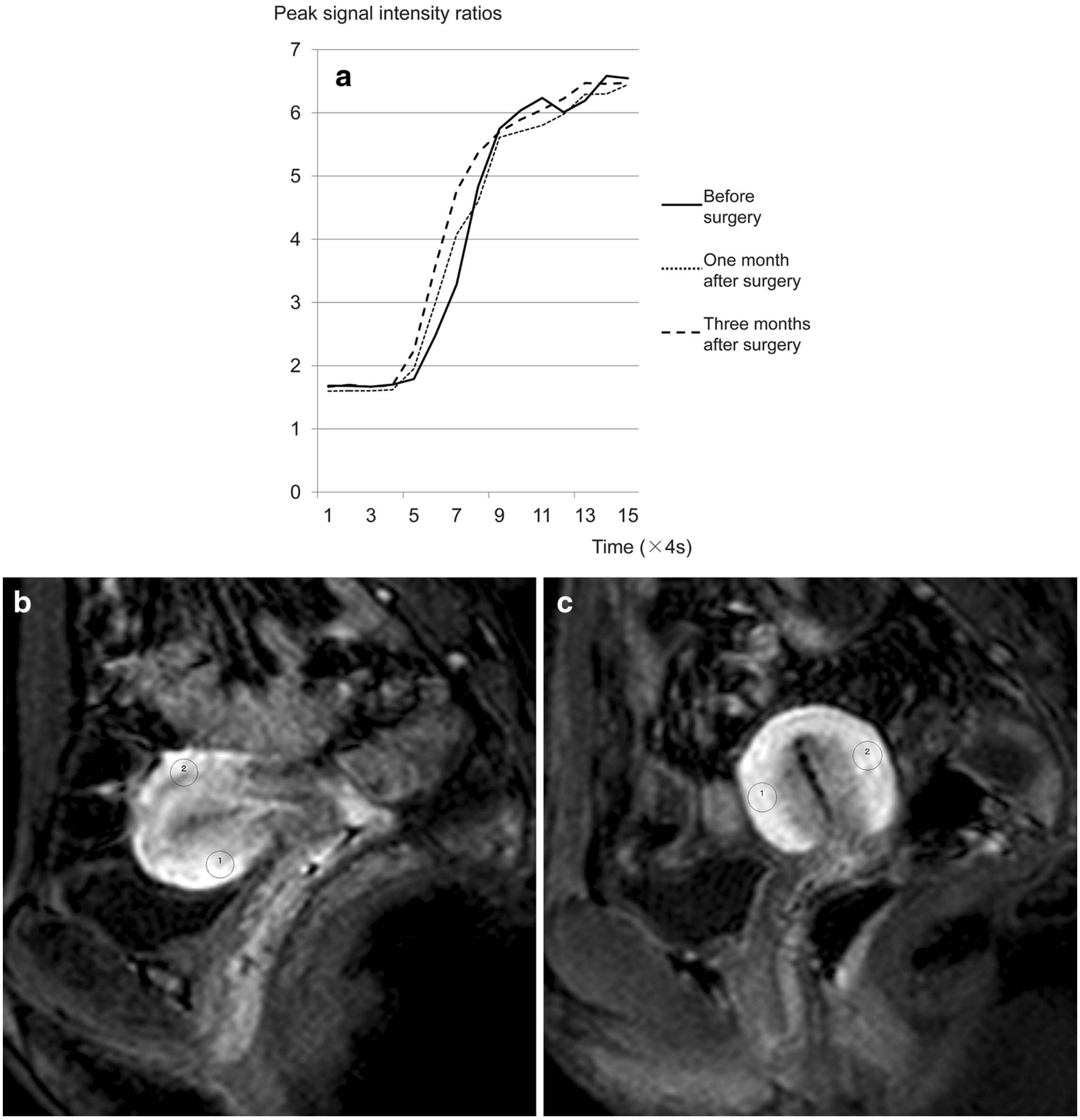

Fig. 2 A 28-year-old woman with squamous cell carcinoma of the uterine cervix. **a** Time–signal intensity ratio curves of three MR examinations show maintained uterine enhancement rate after surgery. **b** Sagittal dynamic contrast-enhanced fat-suppressed 4D THRIVE (TR/TE 3.1/1.5 ms) image at the peak time before surgery shows moderate enhancement of the uterine body. **c** Sagittal dynamic contrast-enhanced fat-suppressed 4D THRIVE (TR/TE 3.1/1.5 ms) image at the peak time 3 months after surgery shows moderate enhancement of the uterine body (as was observed before surgery). In **b**, **c** the *solid lines* show the contours of ROI on MR images

Klemm et al. used Doppler sonography to determine whether uterine blood supply was decreased after radical trachelectomy [11]. They concluded that uterine perfusion after radical trachelectomy with pelvic and parametric lymphadenectomy remains unchanged [11]. That we found no significant differences in peak signal intensity ratio or peak time between the preoperative and postoperative MR examinations among the patients of our series suggests uterine enhancement rate is preserved after radical trachelectomy.

Tang et al. evaluated uterine blood supply in patients who underwent ART with the uterine artery preserved or sacrificed using CT angiography [13]. They concluded that the ovarian artery became the dominant supplying vessel after ART and that the benefit of preserving the uterine arteries during ART is probably very limited [13]. That we did not observe a decrease in postoperative uterine enhancement rate in the patient who underwent unilateral uterine artery ligation suggests that the presence or absence of the uterine artery may only have a limited effect on

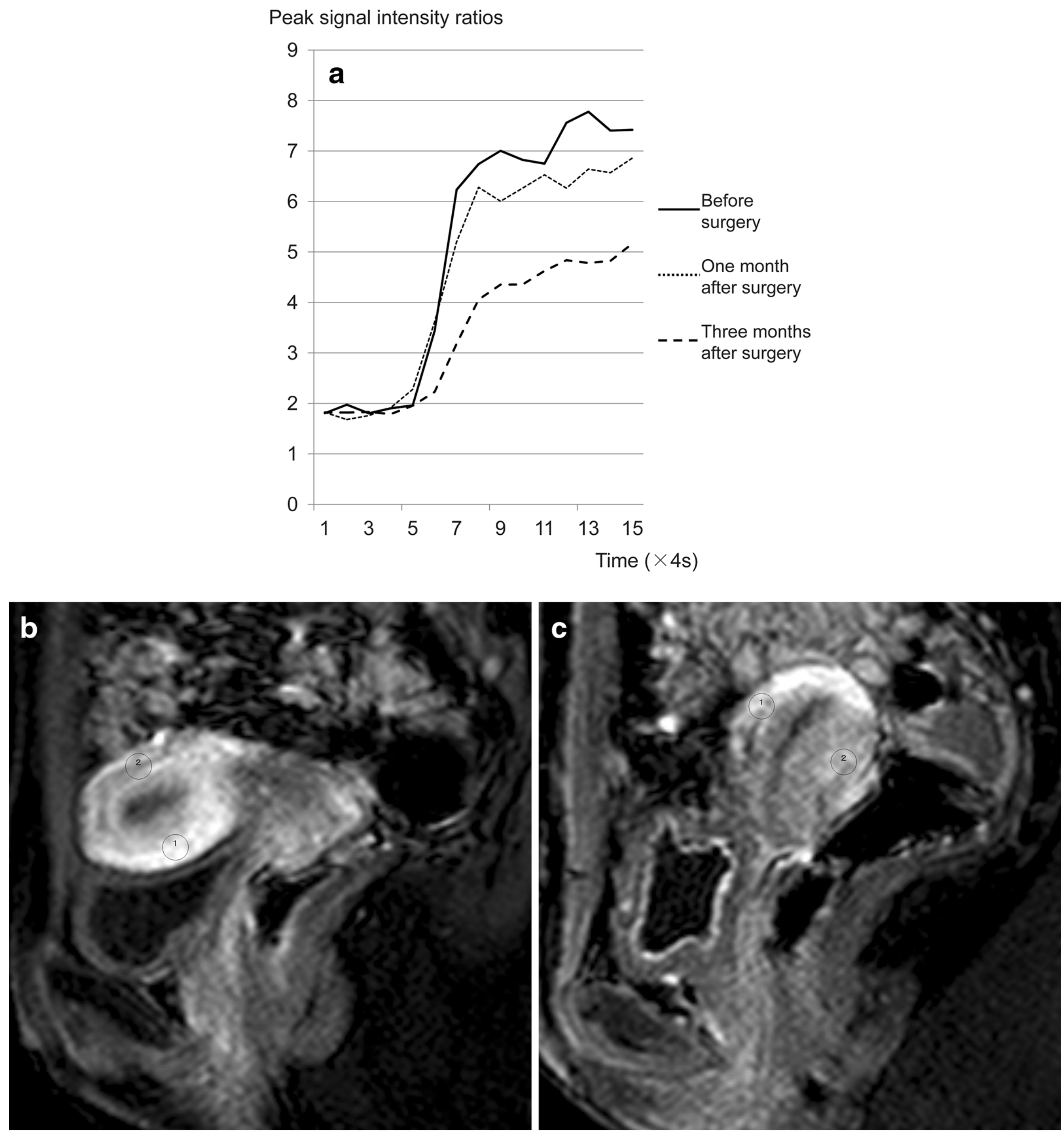

Fig. 3 A 36-year-old woman with adenocarcinoma of the uterine cervix. **a** Time–signal intensity ratio curves of three MR examinations show decreased uterine enhancement rate after surgery. **b** Sagittal dynamic contrast-enhanced fat-suppressed 4D THRIVE (TR/TE 3.1/1.5 ms) image at the peak time before surgery shows moderate enhancement of the uterine body. **c** Sagittal dynamic contrast-enhanced fat-suppressed 4D THRIVE (TR/TE 3.1/1.5 ms) image at the peak time 3 months after surgery shows poor enhancement of the uterine body (compared with before surgery). In **b**, **c** the *solid lines* show the contours of ROI on MR images

uterine enhancement rate. However, further studies are required to confirm the impact of preserving the uterine artery in trachelectomy.

Umemura et al. reported two patients who experienced pregnancy and delivery after VRT [12]. They evaluated the effects of changes of blood supply to the uterus on the pregnancy courses using 3D CT, and concluded that ligation and cutting of several supplying arteries by VRT induced new arterial vascularization and new collateral circulation and that it did not seem to affect fetal growth or placental function [12]. Kim et al. reported that 23 of 35 (66 %) women who attempted to conceive after radical trachelectomy were successful, and that 13 of 20 (65 %) live births resulted in full-term births [22]. Speiser et al. reported that while there was no impairment of fertility after VRT, premature labor was the main problem in pregnancy after VRT [23]. In a systematic review, Pareja et al. reported that of 113 patients attempted to become pregnant after ART, and 67 (59.3 %) were able to conceive [8]. Park et al. reported that 10 out of 18 patients (55.6 %)

who underwent laparoscopic radical trachelectomy were able to become pregnant [24]. In our series, two of the five patients who attempted to conceive after ART became pregnant.

Although the main purpose of trachelectomy is to preserve female fertility, it was estimated that infertility rate after trachelectomy is between 25 and 30 % [25]. Isthmic stenosis occurs frequently in patients who received radical trachelectomy and it is one of the causes of infertility following radical trachelectomy [26]. However, in our series, a patient with decreased uterine enhancement rate both one and 3 months after surgery suffered from thin endometrium and amenorrhea after ART. Therefore, we assumed that the disorder of implantation might be caused by endometrial hypoplasia due to decreased uterine blood flow after ART. The assessment of uterine enhancement rate may be able to predict the fertility rate after ART. However, further accumulation of cases and follow-up study are necessary to determine the clinical impact of DCE MR imaging.

The present study has several limitations. First, because the study was conducted at a single institution, the cohort was very small. Second, we could not evaluate long-term uterine enhancement rate (more than 3 months) after ART. Long-term evaluation is needed, especially in the patient who showed a decrease of uterine enhancement rate 3 months after ART. Third, because no patients in our series underwent ligation of the bilateral uterine artery in our series, we wish to evaluate the influence of uterine enhancement rate in patients with bilateral uterine artery ligation.

In conclusion, MR imaging was useful and non-invasive method for evaluating uterine enhancement rate after ART. No significant differences were found in either the peak signal intensity ratio or the peak time between before and after ART. No significant postoperative decrease of uterine enhancement rate suggests that the uterine function and fertility may be preserved after ART.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest associated with this article.

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