Clinical Radiology 74 (2019) 166.e15–166.e21

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

Making the invisible visible: improving detectability of MRI-invisible residual cervical cancer after conisation by DCE-MRI

J.-W. Huang †, J.-C. Song †, T. Chen, M. Yang, Z.-L. Ma*

Department of Radiology, First Affiliated Hospital of Nanjing Medical University, Nanjing, China

ARTICLE INFORMATION

Article history:
Received 9 March 2018
Accepted 25 October 2018

Keywords:
Cervical cancer
Conization
Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI)
Residual tumor

AIM: To determine whether dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) quantitative parameters increase the detectability of MRI-invisible residual cervical cancer after conisation.

MATERIALS AND METHODS: This retrospective study included 59 patients with MRI-invisible cervical cancer, but positive conisation pathology. Thirty-five patients were confirmed to have residual cervical cancer, and 24 patients showed non-residual cervical cancer. DCE-MRI quantitative parameters were calculated in the anterior or posterior cervix according to the conisation position. Receiver operating characteristic (ROC) analysis was used to find the threshold of DCE-MRI parameters in differentiate residual cervical cancer patients from non-residual cervical cancer patients after conisation.

RESULTS: For patients with residual cervical cancer, the K^{trans} and V_e values were significantly higher than in their counterparts with non-residual cervical cancer (0.610±0.395 versus 0.366±0.305/min, p=0.013; and 0.703±0.270 versus 0.540±0.280%, p=0.028; respectively). The K^{trans} showed the highest area under the ROC curve (AUC) of 0.705 (p=0.004) with a sensitivity of 67.6% and specificity of 68%.

CONCLUSION: DCE-MRI quantitative parameters increased the detectability of MRI-invisible residual cervical cancer after conisation.

Introduction

Cervical cancer is the most common gynaecological malignancy and the second most common cause of cancer death in Chinese women.[1] In recent years, conisation has become an important means of diagnosing early-stage cervical cancer; however, it has been reported[2] that about 65% of the patients have no residual tumour after conisation. It may be suggested that a less radical procedure, such as a less radical surgery, may be sufficient in this selected population mostly for fertility-sparing reasons.[3,4]

Conventional magnetic resonance imaging (MRI) based on morphological changes has some limitations for lesion detection and characterisation.[5–7] It is not sensitive enough to assess the residual tumour after conisation during early-stage cervical cancers. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a non-invasive imaging technique that can characterise tissue vasculature and

* Guarantor and correspondent: Z.-L. Ma, Department of Radiology, First Affiliated Hospital of Nanjing Medical University, Nanjing, China. Tel.: +86 13675123420.

E-mail address: mazhanlong@126.com (Z.-L. Ma).

† Joint first authors.

https://doi.org/10.1016/j.crad.2018.10.013

is sensitive to tumour angiogenesis.[8,9] Tumour tissues have more neovascularisation in contrast to the normal uterus; hence, the regional blood volume and vascular permeability differences might be detected by DCE-MRI. A previous study suggested that DCE-MRI was significant in the discovery and diagnosis of early breast cancer and even in-situ cancer.[10] In addition, another study also suggested that DCE-MRI can predict early recurrence of breast cancer;[11] however, the use of DCE-MRI quantitative parameters to help detect MRI-invisible residual cervical cancer after conisation has not been explored.

Consequently, the purpose of this study was to investigate the value of DCE-MRI quantitative parameters in detecting MRI-invisible residual cervical cancer after conisation.

Patients and methods

Study population

This retrospective study was approved by the institutional review board and the requirement for informed consent was waived. Fifty-nine patients with MRI-invisible cervical cancer, but positive conisation pathology, were enrolled retrospectively into this study from January 2013 to September 2017. The inclusion criteria were as follows: (1) patients underwent cervical conisation <2 weeks before MRI, and then radical hysterectomy was performed 1 week after MRI; (2) patients underwent complete MRI, including DCE-MRI; (3) no obvious cervical lesions were observed via MRI after conisation. The exclusion criteria consisted of failure of DCE-MRI technique or no surgery after the MRI examination. Patients with cervical lesions that were visible on MRI were also excluded from this study. Clinical data, including age and the International Federation Gynecology and Obstetrics (FIGO) stage of cervical cancer were recorded.

MRI technique

All imaging examinations were performed with 3 T MRI scanners (MAGNETOM TrioTim; Siemens, Erlangen, Germany) using a 16-element pelvic phased-array coil. As per the standard pelvic MRI protocol, the images obtained included transverse T1-weighted turbo spin-echo (TSE) images (993 ms repetition time [TR]/26 ms echo time [TE], 3.5 mm section thickness, 250 field of view [FOV]) and transverse (4,430 ms TR/129 ms TE, 3.5 mm section thickness, 250 FOV), coronal (4,000 ms TR/77 ms TE, 4 mm section thickness, 300 FOV), and sagittal (4,000 ms TR/129 ms TE, 3 mm section thickness, 250 FOV) T2-weighted TSE images of the uterus. Then single-shot echo-planar imaging (TR/TE, 6600/91 msec; section thickness, 2.6 mm; FOV, 250) was performed with a diffusion module. Diffusion was measured using b-values of 1,000 s/mm^2. After a routine MRI examination, a three-dimensional (3D) T1-weighted gradient recalled echo sequence was undertaken to acquire DCE-MRI data. This protocol was performed with parameters (5.32 ms TR/1.85 ms TE, 3.5 mm section thickness, 250 FOV, 15° flip angle). After two acquisitions, a bolus of Gd-diethylenetriaminepenta-acetic acid (Gd-DTPA 0.1 mmol/kg; Magnevist, Bayer, Berlin, Germany) was injected at a rate of 3 ml/s through a 20 G antecubital intravenous line. A bolus injection was undertaken with a MRI-compatible power injector (Spectris; Medrad, Pittsburgh, PA, USA) followed by a 15 ml saline flush. The DCE-MRI was continued for 4 min after the Gd-DTPA injection.

Image analysis

Two experienced genitourinary radiologists with 6 and 9 years of experience in pelvic MRI, respectively, evaluated the data independently, blinded to all clinical information and the pathological results. A consensus was adopted if the two radiologists offered different opinions.

MRI-invisible cancer is here defined as a cervical cancer that was not seen on the T2-weighted images, DWI/ADC images, or contrast-enhanced T1-weighted images after conisation (Fig 1a,b,d,e). The size of the tumour, histological type, lymph node metastasis, and lymphovascular invasion were analysed in the hysterectomy specimen.

For DCE-MRI quantitative parameter measurements, pharmacokinetic analysis was carried out using non-commercial software, Omnikinetics (GE Healthcare, Shanghai, China) with the two-compartment extended tofts model. A fully automated image-based individualised AIF (iAIF) estimation method was used as the AIF estimation method. The parameters including the volume transfer constant between blood plasma and extracellular–extravascular space (EES; K^{trans}), rate constant between EES and blood plasma (K_{ep}), volume of EES space per unit volume of tissue (V_e), and fractional blood plasma volume per unit volume of tissue (V_p) were derived from the entire ROI of each patient. The radiologists manually drew ROIs along contours of the anterior or posterior cervix according to the conisation position, extending 5 mm to the myometrium. After each ROI placement, colour-coded, pixel-wise, parametric perfusion maps of K^{trans}, and K_{ep} were generated with sample patients as shown in Fig 1g–f.

Statistical analysis

Statistical analysis was performed using the PASW statistical software (version 18.0; SPSS, Chicago, IL, US). Values are presented as mean ± SD. DCE-MRI quantitative parameters were compared using the independent-samples *t*-test. For the receiver operating characteristic (ROC) analyses, the area under the ROC curve (AUC) was calculated and AUCs were compared using non-parametric methods[12] and optimal thresholds were obtained by maximising the Youden index.[13] A *p*-value of <0.05 was regarded as significant.

Results

Patients and clinicopathological features

A total of 59 patients were included in the present study. All patients underwent cervical conisation <2 weeks before

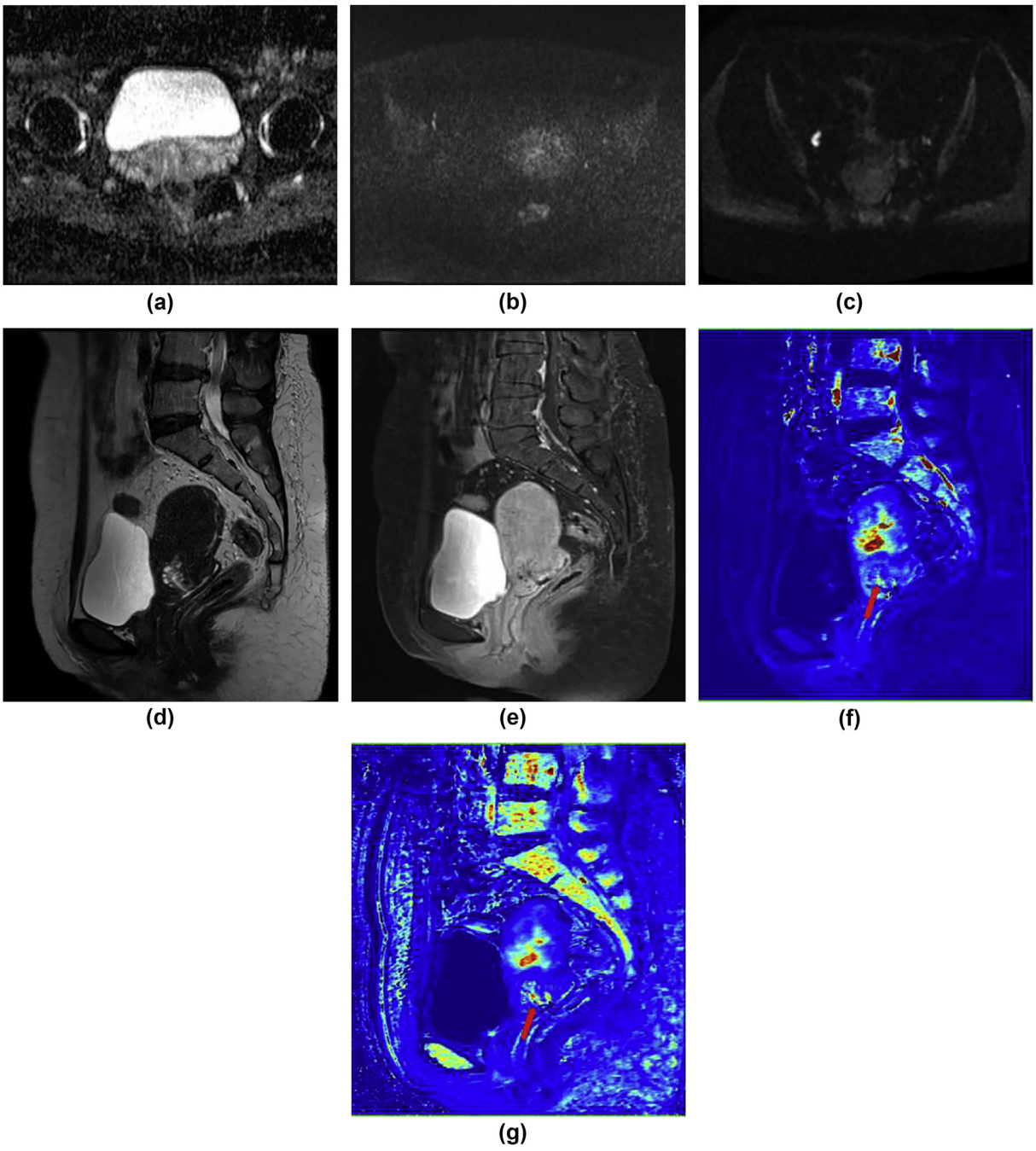

Figure 1 A 35-year-old woman with MRI-invisible residual cervical cancer but positive conisation pathology. (a) Axial DWI and (b) ADC map, (d) sagittal T2-weighted, and (e) contrast-enhanced images show no visible cancer. (c) Axial DWI shows a metastatic lymph node. (f) The colour-coded K^{trans} map and (g) K_{ep} map show that a heterogeneous abnormal intensity was identified.

the MRI examination and then underwent a radical hysterectomy and pelvic lymphadenectomy. Of these, 34 patients (median age, 42.1 years; range, 28–64 years) were confirmed as having residual cervical cancer at surgery, and 25 patients (median age, 44.1 years; range, 29–63 years) showed non-residual cervical cancer. Of those with residual cervical cancer, 30 (88.2%) patients were FIGO stage Ib and four (11.8%) were stage IIa. There were 29 (85.3%) patients with squamous cell carcinoma and five (14.7%) with adenocarcinoma. Lymph node metastasis was detected in nine (25.7%) patients, and lymphovascular invasion was found in four (11.4%) patients. The clinical and pathological characteristics of all 34 patients with residual cervical cancer were shown in Table 1.

Radiological results

Table 2 summarises the results of DCE-MRI quantitative parameters. K^{trans} and V_e value showed a significant difference between patients with residual cervical cancer and

Table 1
Patient and pathological characteristics with residual cervical cancer after conisation

	After conisation
	Cervical cancer (+)
No. patients	34
Median age (years)	42.6±9.0
Size (cm)	2.24±1.34
FIGO stage	
I b	30
II a	4
Histological type	
Squamous cell carcinoma	29
Adenocarcinoma	5
Lymph node metastasis	9
Lymphovascular invasion	4

Data are the mean ± standard deviation.
FIGO, International Federation Gynecology and Obstetrics.

their counterparts with non-residual cervical cancer: The K^{trans} value was significantly higher in patients with residual cervical cancer patients (0.610±0.395 versus 0.366±0.305/min, p=0.013), and V_e value were also significantly higher in residual cervical cancer patients (0.703±0.270 versus 0.540±0.280%, p=0.028); however, K_{ep} and V_p values showed no significant difference between patients with residual cervical cancer and those with non-residual cervical cancer ($p \geq 0.05$). Fig 2 illustrates the comparison of K^{trans} and V_e values in patients with residual cervical cancer and those with non-residual cervical cancer.

The ROC analysis was used to find the reasonable threshold of K^{trans} and V_e to differentiate patients with residual cervical cancer patients from those with non-residual cervical cancer (Table 3). The K^{trans} showed the highest AUCs with 0.705 (p=0.013), with sensitivity of 67.6% and specificity of 68%. The V_e showed the highest AUCs with 0.659 (p=0.038), with sensitivity of 52.9% and specificity of 80%, respectively. K^{trans} showed a significantly higher AUC than V_e (Fig 3).

Discussion

The present study evaluated the usefulness of perfusion parameters derived from DCE-MRI in the detection of MRI-invisible residual tumours after conisation in cervical cancers. The present results showed that residual cervical cancer patients had higher K^{trans} and V_e values than those with non-residual cervical cancer.

Conisation is the primary treatment for IA1 cancers and has low recurrence rates if resection margins are clear.[14] When treated with radical hysterectomy after a diagnostic conisation, no residual tumour is found in 65% of these patients. Therefore, less radical surgeries may be used in patients with early-stage cervical cancer mostly for fertility-sparing reasons, under strict eligibility criteria; in this subgroup identification of residual tumour after conisation may be of value.

Several prognostic factors for early-stage cervical cancer include tumour size, lymphovascular invasion, lymph node metastasis, and depth of stromal invasion. Tumour size is of great importance because it is the only factor that can be determined preoperatively and is used in planning surgical procedures.[15–17] Reportedly, if the long-axis diameter of cervical cancer exceeds 20 mm, the tumour is associated with worse long-term survival rates.[18,19] In the present study, the median sizes of MRI-invisible residual cervical cancers were 2.24±1.34 cm (range: 0.7–6 cm), and the maximum size can reach 6 cm. MRI-invisible residual cervical cancers had a relatively high risk of lymph node metastasis (9/34) and lymphovascular invasion (4/34). Fig 1c shows a metastatic lymph node. Therefore, it is vital to rapidly and accurately identify MRI-invisible residual cervical cancers. These are very difficult to identify solely on the basis of conventional MRI. DCE-MRI is a dynamic image acquisition performed after the administration of an intravenous bolus of gadolinium-based contrast agent. DCE-MRI can accurately reflect tumour angiogenesis.[20] Recent research has reported that DCE-MRI parameters can be used in the diagnosis of early oesophageal cancer and increase the cure rate of the disease.[21] Moreover, DCE-MRI parameters are used widely in assessing early therapeutic responses, including cervical cancer.[22] To the authors' knowledge, the value of DCE-MRI quantitative parameters in the detection of MRI-invisible residual cervical cancers has not yet been explored.

In the present study, residual cervical cancer patients had higher K^{trans} and V_e values than non-residual cervical cancer patients. Angiogenesis is the basis of tumour growth, invasion, metastasis, and recidivism.[23] Lesions with higher vascular permeability adhere more strongly to tumour tissue. K^{trans} was found to be correlated with vascular permeability, and hence angiogenesis within residual cervical cancer. Similarly, with respect to the contrast agent exchange constant V_e, it has been shown that the loss of function of cell–cell adhesion molecules, such as e-cadherin, is a crucial step in tumour progression.[24] This loss of function leads to a larger interstitial space, which is reflected by a higher V_e value. The K_{ep} and V_p value showed no significant difference between patients with residual cervical cancer and those with non-residual cervical cancer. In addition, K_{ep} was found to be affected solely by the contrast medium concentration and fractional volumes in the tumour EES and might thus more accurately reflect the tumour capillary permeability.[25] The present results showed that K_{ep} is close to the established threshold

Table 2
Results of quantitative parameters of DCE-MRI

	After conisation		p-Value
	Cervical cancer (+)	Cervical cancer (−)	
K^{trans} (/min)	0.610±0.395	0.366±0.305	0.013[a]
K_{ep} (/min)	0.664±0.281	0.523±0.246	0.050
V_e (%)	0.703±0.270	0.540±0.280	0.028[a]
V_p (%)	0.325±0.065	0.423±0.100	0.656

Data are the mean ± standard deviation.
[a] Comparisons of K^{trans} and V_e between residual cervical cancer patients and non-residual cervical cancer patients after conisation: p<0.05.

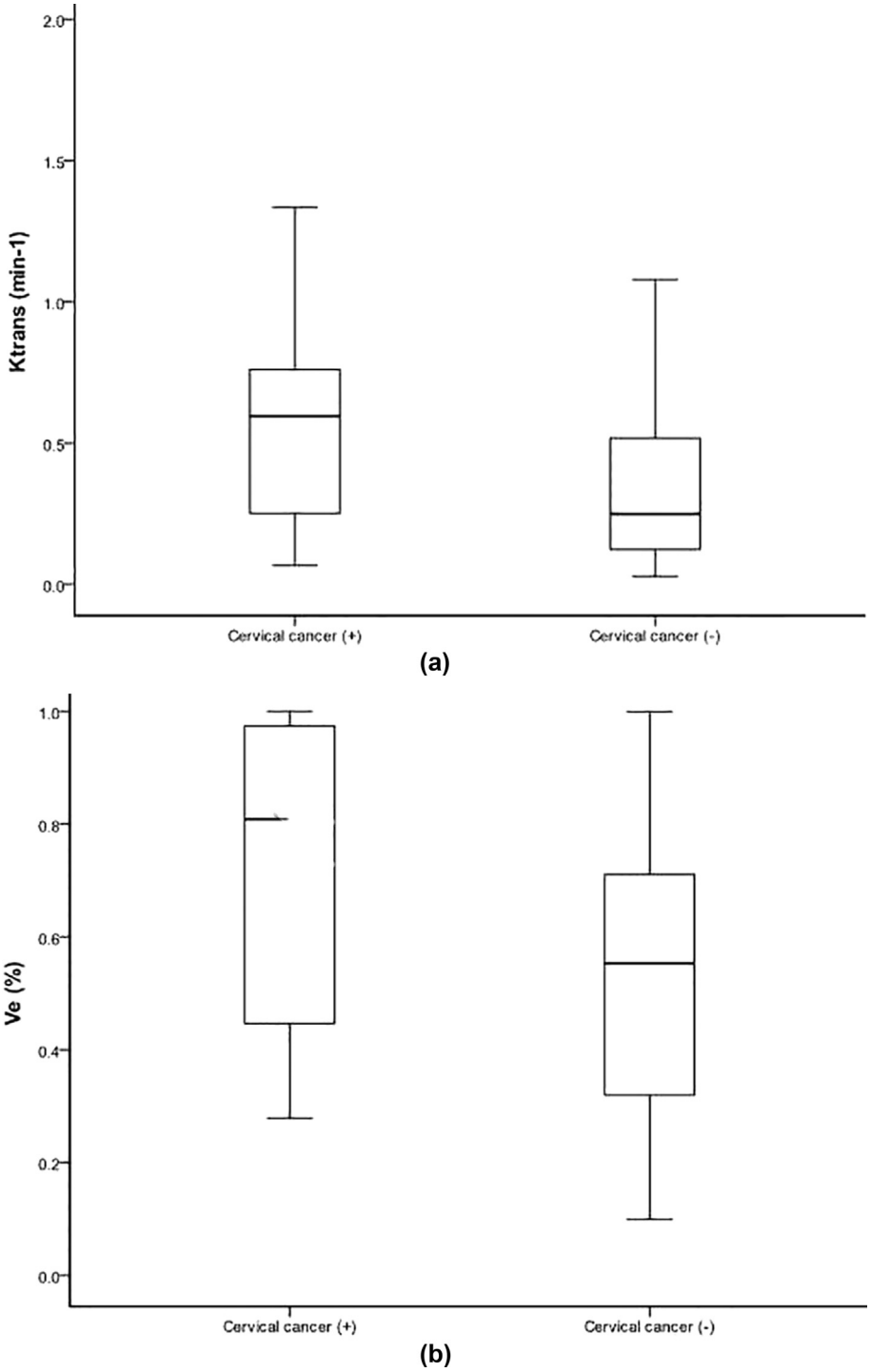

Figure 2 Boxplots showing Ktrans and V_e in residual cervical cancer patients and non-residual cervical cancer patients. (a) Ktrans and (b) V_e were significantly higher in patients with residual cervical cancer than in those with non-residual cervical cancer (0.610±0.395 versus 0.366±0.305/min, p=0.013; and 0.703±0.270 versus 0.540±0.280%, p=0.028, respectively).

Table 3
Effectiveness of DCE-MRI quantitative parameters for discriminating residual cervical cancer patients from non-residual cervical cancer patients

Variable	Cut-off value	AUC	Sensitivity (%)	Specificity (%)	p-Value
K^{trans} (/min)	>1.356	0.705	67.6	68	0.008
V_e (%)	>1.329	0.659	52.9	80	0.038

(p=0.050). This finding must be validated in a larger cohort of patients and must be interpreted with care. Therefore, K_{ep} may also have a certain differential diagnostic value in large samples. These results concur with the findings of other authors.[21]

There are several limitations to the present study. First, the patients undergo cervical conisation before the MRI

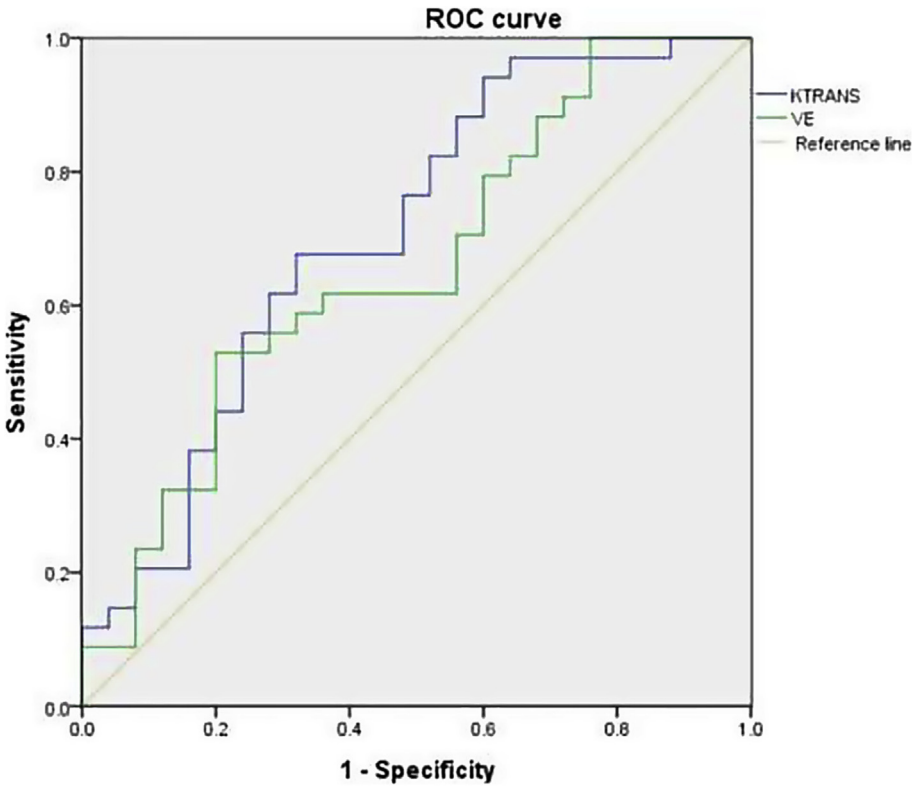

Figure 3 ROC curves displaying the diagnostic performance for Ktrans and V_e in discriminating residual cervical cancer patients from non-residual cervical cancer patients. For Ktrans, ROC analysis shows a highest AUC of 0.705 (p=0.008), with the optimal cut-off point of 1.356/min, sensitivity of 67.6% and specificity of 68%. V_e resulted in an AUC of 0.659 (p=0.038), with the optimal cut-off point of 1.329%, sensitivity of 52.9% and specificity of 80%.

examination, distortion of the cervix, local haemorrhage, oedema, and inflammatory changes caused by conisation.[26] This might have some adverse influence on the estimation of the diagnostic ability of DCE-MRI; however, an attempt was made to control the time of conisation and all of the patients had the same conisation condition before MRI to reduce the data error. Second, the scope of the whole anterior or posterior cervix is too large to affect the accuracy of the data. This research is preliminary, and future studies will require larger sample sizes and further study.

In conclusion, the present preliminary results suggest that DCE-MRI quantitative parameters may be used to increase the detectability of MRI-invisible residual cervical cancer after conisation.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The authors thank LetPub (www.letpub.com) for providing linguistic assistance during the preparation of this manuscript. This work was supported by the National Natural Science Foundation of China (grant no. 81471723).

References

1. Torre LA, Bray F, Siegel RL, *et al*. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;**65**:87–108.
2. Kamimori T, Sakamoto K, Fujiwara K, *et al*. Parametrial involvement in FIGO stage IB1 cervical carcinoma diagnostic impact of tumour diameter in preoperative magnetic resonance imaging. *Int J Gynecol Cancer* 2011;**21**:349–54.
3. Mitchell DG, Snyder B, Coakley F, *et al*. Early invasive cervical cancer: tumour delineation by magnetic resonance imaging, computed tomography, and clinical examination, verified by pathologic results, in the ACRIN 6651/GOG 183 intergroup study. *J Clin Oncol* 2006;**24**:5687–94.
4. Jung DC, Ju W, Choi HJ, *et al*. The validity of tumour diameter assessed by magnetic resonance imaging and gross specimen with regard to tumour volume in cervical cancer patients. *Eur J Cancer* 2008;**44**:1524–8.
5. Dhanda S, Thakur M, Kerkar R, *et al*. Diffusion-weighted imaging of gynecologic tumours: diagnostic pearls and potential pitfalls. *Radio-Graphics* 2014;**34**:1393–416.
6. Woo S, Kim HS, Chung HH, *et al*. Early stage cervical cancer: role of magnetic resonance imaging after conisation in determining residual tumour. *Acta Radiol* 2016;**57**:1268–76.
7. Park JY, Lee JW, Park BK, *et al*. Postoperative outcomes of MRI-invisible stage IB1 cervical cancer. *Am J Obstet Gynecol* 2014;**211**:161–8.
8. Ovrebo KM, Ellingsen C, Hompland T, *et al*. Dynamic contrast-enhanced magnetic resonance imaging of the metastatic potential of tumours: a preclinical study of cervical carcinoma and melanoma xenografts. *Acta Oncol* 2013;**52**:604–11.
9. Sahdev A, Sohaib SA, Wenaden AE, *et al*. The performance of magnetic resonance imaging in early cervical carcinoma: a long-term experience. *Int J Gynecol Cancer* 2007;**17**:629–36.
10. Nadrljanski M, Maksimovic R, Plesinac-Karapandzic V, *et al*. Positive enhancement integral values in dynamic contrast enhanced magnetic

resonance imaging of breast carcinoma: ductal carcinoma in situ versus invasive ductal carcinoma. *Eur J Radiol* 2014;**83**:1363–7.
11. Choi EJ, Choi H, Choi SA, *et al*. Dynamic contrast-enhanced breast magnetic resonance imaging for the prediction of early and late recurrences in breast cancer. *Medicine (Baltimore)* 2016;**95**:e5330.
12. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1998;**44**:837–45.
13. Schisterman EF, Perkins NJ, Liu A, *et al*. Optimal cut-point and its corresponding Youden Index to discriminate individual using pooled blood samples. *Epidemiology* 2005;**16**:73–81.
14. Noel P, Dube M, Plante M, *et al*. Early cervical carcinoma and fertility-sparing treatment options: MRI imaging as a tool in patient selection and a follow-up modality. *RadioGraphics* 2014;**34**:1099–119.
15. Kristensen GB, Abeler VM, Risberg B, *et al*. Tumour size, depth of invasion, and grading of the invasive tumour front are the main prognostic factors in early squamous cell cervical carcinoma. *Gynecol Oncol* 1999;**74**:245–51.
16. Steed H, Capstick V, Schepansky A, *et al*. Early cervical cancer and parametrial involvement: is it significant? *Gynecol Oncol* 2006;**103**:53–7.
17. Van de Putte G, Lie AK, Vach W, *et al*. Risk grouping in stage IB squamous cell cervical carcinoma. *Gynecol Oncol* 2005;**99**:106–12.
18. Levy A, Caramella C, Chargari C, *et al*. Accuracy of diffusion-weighted echo-planar MRI imaging and ADC mapping in the evaluation of residual cervical carcinoma after radiation therapy. *Gynecol Oncol* 2011;**123**:110–5.
19. Lucas R, Lopes DJ, Cunha TM. Added value of diffusion-weighted MRI in detection of cervical cancer recurrence: comparison with morphologic and dynamic contrast-enhanced MRI sequences. *Diagn Interv Radiol* 2015;**21**:368–75.
20. Ng CS, Wei W, Bankson JA, *et al*. Dependence of DCE-MRI biomarker values on analysis algorithm. *PLoS One* 2015;**10**:e130168.
21. Lei J, Tian Y, Zhu SC, *et al*. Preliminary study of IVIM-DWI and DCE-MRI in early diagnosis of esophageal cancer. *Eur Rev Med Pharmacol Sci* 2015;**19**:3345–50.
22. Kim JH, Kim CK, Park BK, *et al*. Dynamic contrast-enhanced 3-T MRI imaging in cervical cancer before and after concurrent chemoradiotherapy. *Eur Radiol* 2012;**22**:2533–9.
23. Fidler IJ, Ellis LM. The implications of angiogenesis for the biology and therapy of cancer metastasis. *Cell* 1994;**79**:185–8.
24. Herzig M, Savarese F, Novatchkova M, *et al*. Tumour progression induced by the loss of E-cadherin independent of beta-catenin/Tcf-mediated Wnt signaling. *Oncogene* 2007;**26**:2290–8.
25. Yu J, Xu Q, Huang DY, *et al*. Prognostic aspects of dynamic contrast-enhanced magnetic resonance imaging in synchronous distant metastatic rectal cancer. *Eur Radiol* 2017;**27**:1840–7.
26. Charles-Edwards EM, Messiou C, Morgan VA, *et al*. Diffusion-weighted imaging in cervical cancer with an endovaginal technique: potential value for improving tumour detection in stage Ia and Ib1 disease. *Radiology* 2008;**249**:541–50.