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Magnetic Resonance Imaging (MRI) and Three-Dimensional Transvaginal Ultrasonography Scanning for Preoperative Assessment of High Risk in Women with Endometrial Cancer

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Background: To evaluate the diagnostic performance of MRI and 3D-TVS for assessment of deep myometrial invasion (MI), cervical involvement (CI), and Lymph node metastases (LNM) in endometrial cancer staging before surgery.





Material/Methods: From January 2016 to December 2017, we reviewed data from 314 women with endometrial cancer who underwent preoperative MRI and 3D-TVS before surgery. The diagnostic sensitivity, specificity, PPV, NPV, and accuracy in detecting MI, CI, and LNM were estimated based on ultimate pathology results.

Results: The sensitivity, specificity, PPV, NPV, and accuracy of MRI in the diagnosis of MI were 89.19%, 88.97%, 67.35%, 97.99%, and 89.01%, respectively, and the indexes of 3D-TVS for MI were 86.36%, 91.07%, 79.17%, 94.44%, and 89.74%, respectively. The sensitivity, specificity, PPV, NPV, and accuracy of MRI for CI were 75% and 92.35%, 40.9%, 98.13%, and 91.2%, respectively. The indicators of 3D-TVS were 77.78%, 94.29%, 63.63%, 97.06%, and 92.4%, respectively. There were no significant differences in sensitivity, specificity, NPV, and accuracy between MRI and 3D-TVS in the diagnosis of MI and CI. For MI and CI, the sensitivity of combined MRI and 3D-TVS was higher than any other single method ($P < 0.05$). For LNM, the sensitivity, specificity, PPV, NPV, and accuracy of MRI were 58.33%, 96.26%, 63.63%, 95.37%, and 92.43%, respectively.

Conclusions: 3D-TVS is equivalent to MRI in predicting MI and CI. Combined MRI and 3D-TVS can improve the assessment sensitivity, and they are useful in optimizing individualized surgical procedures. The sensitivity of MRI for LNM prediction needs to be improved.

MeSH Keywords: **Endometrial Neoplasms • Magnetic Resonance Imaging • Ultrasonography**

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Background

Endometrial cancer (EC) is the sixth most common malignant disease, with an annual incidence of approximately 290 000 cases. The cumulative risk of endometrial cancer in women under age 75 is estimated to be 1.6% in high-income countries and 0.7% in low-income countries [1]. The mainstay treatment of EC is surgical staging procedure involving total hysterectomy with bilateral salpingo-oophorectomy (BSO). Lymphadenectomy is performed in cases with high-risk factors, including: (1) Tumor grade 3 (poorly differentiated), (2) More than 50% myometrial invasion, (3) Lymphovascular space invasion, (4) Non-endometrioid histology (serous, clear cell, undifferentiated, small cell, anaplastic, and (5) Cervical stromal involvement. The differentiated grade of the tumor can be confirmed by endometrial sampling before the operation, but the status of myometrial invasion, cervical stromal involvement, and lymph node infiltration can only be estimated by imaging techniques preoperatively, gross visual inspection, and frozen section during surgery.

Magnetic resonance imaging (MRI) is considered to be the most accurate imaging technique for preoperative evaluation of EC with its excellent soft tissue contrast resolution [2,3].

Three-dimensional transvaginal ultrasonography (3D-TVS) has many advantages in evaluating myometrial invasion. The coronal view provides valuable information for the myometrial invasion of the uterine corners. The three-dimensional display technology can strengthen the distinction between tissue boundaries. We therefore evaluated and compared the diagnostic value of 3D-TVS and MRI in the assessment of deep myometrial invasion (MI), cervical involvement (CI) and Lymph node metastases (LNM) in endometrial cancer staging preoperatively, aiming to help oncologist individualize the surgery plan.

Material and Methods

314 women with histologically proven endometrial cancer were referred to Department of Obstetrics and Gynecology, The First Affiliated Hospital of Xian Jiaotong University from January 2016 to December 2017. They were examined with MRI (n=182) and 3D-TVS (n=78), who were all participated in the study.

All women were treated according to the FIGO 2015 guidelines: standard surgery included hysterectomy and bilateral salpingo-oophorectomy (BSO). In addition, high-risk patients require pelvic lymphadenectomy. (Tumor grade 3, More than 50% of myometrial invasion. Lymphovascular space invasion. Non-endometrioid histology, Cervical stromal involvement.). Radical hysterectomy, BSO and pelvic lymphadenectomy should undergo in Stage II patients (CI) while stage III/IV patients

should have debulking surgery. In addition, omental resection was recommended for patients with type 2 pathology (serosal or clear cell adenocarcinoma). Surgical specimens were comprehensively evaluated by two senior pathologists. according to 2014 WHO Classification of tumors of female reproductive organs pathology [4]

Pelvic MRI scanning was used to evaluate the invasive depth of myometrium and cervical stroma. All patients received pelvic scanning using 3.0 T MR (Signa HDx 3.0T, GE Medical Systems) with an 8US torso-phased array (TORSOPA) coil. The patient was examined in supine position and kept the bladder partially filled. The criteria for MRI myometrial invasion diagnosis was whether the junctional zone (JZ) was disrupted or interrupted. If the JZ was visible, a smooth continuous endometrial-muscle surface was seen and no muscle layer infiltration was determined. If the low signal intensity circular JZ between the endometrium and the muscular layer was irregular or incomplete, the muscle layer was regarded as infiltrated (Figure 1A). If the signal intensity of the tumor on T2W was greater than half, it was regarded as a deep muscle layer infiltration (Figure 1B). Cervical infiltration is exhibited in Figure 1C. The diameter of the lymph nodes on the short axis >10 mm was considered pathological (Figure 1D). All diagnoses were made by 3 senior imaging doctors in our hospital.

2D-TVS was employed using a GE Voluson E8 Expert equipped with a multifrequency endovaginal probe (5–9 MHz) by the same observer (TXY) to assess the vascularization of the myometrium and endometrium. After the 2D-TVS was performed in sagittal and transverse planes, tumor dimensions and cervical and myometrial invasion were evaluated primarily and registered on a coded sheet as previously described. We obtained 1–3 3D volumes in the sagittal plane and stored them. The 3D sampling frame covers the uterus and sets the scanning angle to cover the entire uterus and cervix. Automated analysis of VOCAL in a thickness of about 1 cm was performed using 4D browsing by a second observer (WW) (version 10.2 GE Healthcare). The criteria for judging the depth of myometrial invasion were: (1) the junction between the endometrium and the muscular layer is completely determined, as the tumor was confined to the endometrium; (2) half of the layer thickness is determined to be no more than 50% of the depth of the muscle layer, and the thinnest part of the normal muscular layer was smaller than the muscle in the sagittal, axial, and coronal planes; (3) the thinnest part of the normal muscle layer is more than 50% in the sagittal, axial, and coronal planes beyond the thickness of the muscle layer; and (4) the expansion of the malignant tumor tissue to the serosa layer was determined to be infiltrated beyond the uterine serosa layer. The criteria for judging the involvement of the cervix were: (1) The cervical cervix to the external cervix was completely determined to be unaffected by the cervix; and (2) the cervix is



Figure 1. Myometrial invasion, cervical invasion, and lymph node metastasis in patients with MR findings. Stage IA endometrial cancer in a 53-year-old premenopausal woman. Arrow refers to the infiltration of superficial muscle (A). Stage IB endometrial cancer in a 55-year-old postmenopausal woman. Arrow refers to deep myometrial infiltration (B). Stage II endometrial cancer in a 60-year-old postmenopausal woman. Arrow refers to the infiltration of cervical interstitial (C). Stage IIIc endometrial cancer in a 48-year-old premenopausal woman with lymph node metastasis, the arrow refers to the lesion lymph nodes (D).

destroyed by the tumor or the cervical canal was enlarged due to the growth of the tumor tissue, and it was also pressurized by the vaginal probe. Those that do not move were judged to be involved (Figure 2).

Statistics

Statistical analysis was performed using SPSS for Windows (version 18.0). A z test was performed to compare the sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), and accuracy of the MRI, with 3D-TVS with surgical-pathologic findings as the reference standard. A p value of less than 0.05 was considered statistically significant.

Results

Table 1 shows the characteristics of the 314 patients. Among these patients, 277 were in stage I, 12 were in stage II, 23 were in stage III, and 2 were in stage IV, based on the 2015 FIGO staging classification. In regard to histological typing, 256 patients had endometrioid adenocarcinoma, 6 patients had mucinous adenocarcinoma, 12 had serous carcinoma, 3 had clear cell carcinoma, and 13 had mixed carcinoma. Histological results demonstrated that 240 patients had less than 50% myometrial invasion and 74 had greater than 50% myometrium invasion. Cervical stromal involvement was observed in 10 patients.

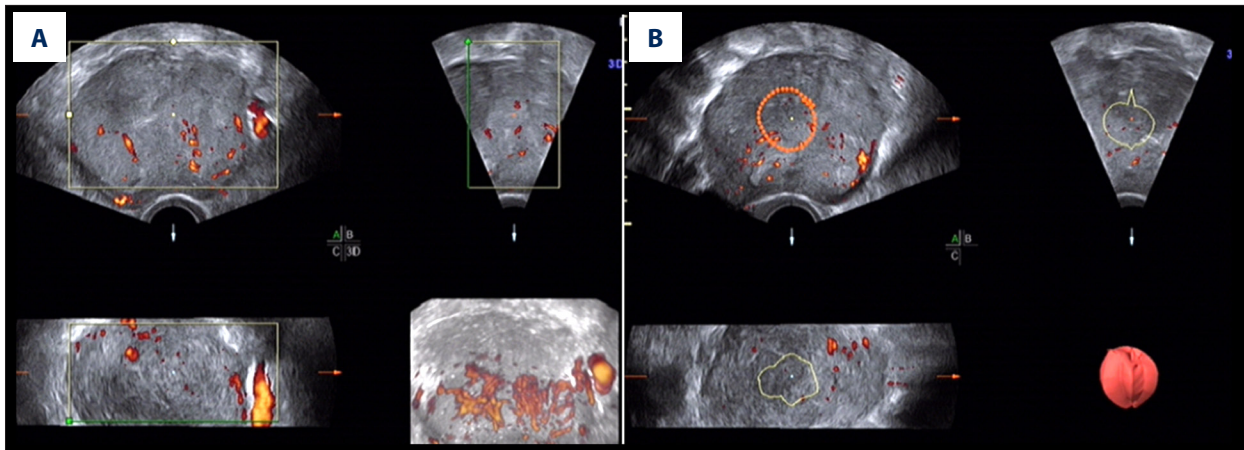


Figure 2. Three-dimensional ultrasound images of Stage IB endometrial cancer in a 56-year-old post-menopausal woman (A). We selected 3 images from the different sections and stored them (B). We analyzed the neovascularization vascularization index of lesion infiltrating to muscle and then automatically analyzed the myometrial invasion depth using VOCAL software. The results showed superficial muscle infiltration.

Table 1. Characteristics of the patients with endometrial cancer.

Characteristics (n=314)	Number
Age	54.1 (Range: 32–78)
FIGO stage	314
IA	240
IB	37
II	12
IIIA	10
IIIB	0
IIIC	13
IVA	2
IVB	0
Histological grade	
GX	24
G1	118
G2	121
G3	43

Characteristics (n=314)	Number
Dominant histological type	
Endometrioid carcinoma	280
Mucinous adenocarcinoma	6
Serous adenocarcinoma	12
Clear cell adenocarcinoma	3
Undifferentiated carcinoma	0
Mixed carcinoma	13
Myometrial invasion	
<50%	240
≥50%	74
Cervical stromal involvement	
Yes	17
No	297
Lymph node metastases	
Yes	13
No	164
Not removed	137

Thirty-one percent of all patients (119) underwent pelvic lymph node dissection, of which 13 had pelvic node metastasis.

By comparing the imaging assessment results with the postoperative pathological results, the results showed that MRI and 3D-TVS had no significant difference in sensitivity, specificity, NPV, or accuracy in the diagnosis of deep myometrium invasion and cervical infiltration ($P>0.05$). 3D-TVS predicted that PPV in deep myometrium invasion was higher than did MRI (79.17% vs. 67.35%). 3D-TVS predicted PPV of cervical infiltration was

higher than did MRI (63.63% vs. 40.9%), and the difference was statistically significant ($P<0.05$) (Table 2, 3). However, the sensitivity of MRI and 3D-TVS for diagnosing cervical infiltration was not high (75% vs. 77.78%).

The sensitivity of combined MRI and 3D-TVS was higher than that of any other single method for preoperative evaluation of deep myometrial invasion and cervical infiltration ($P<0.05$), but the specificity was reduced (Table 4).

Table 2. Comparison of MRI and 3D-TVS results with histologic findings of deep myometrial invasion.

	Histology: deep myometrial invasion			Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%)	NPV (%)	Accuracy (%)
	≥50%	<50%	Total					
MRI								
≥50%	33	16	49	89.19	88.97	67.35	97.99	89.01
<50%	4	129	133					
Total	37	145	182					
3D-TVS								
≥50%	19	5	24	86.36	91.07	79.17	94.44	89.74
<50%	3	51	54					
Total	22	56	78					

Table 3. MRI and 3D-TVS in preoperative evaluation for cancer in detecting cervical invasion.

	Histology: cervical invasion			Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%)	NPV (%)	Accuracy (%)
	Yes	No	Total					
MRI								
Yes	9	13	22	75.00	92.35	40.90	98.13	91.20
No	3	157	160					
Total	12	170	182					
3D-TVS								
Yes	7	4	11	77.78	94.29	63.63	97.06	92.40
No	2	66	68					
Total	9	70	79					

Table 4. Optimizing the predictive value of deep myometrial invasion and cervical invasion in endometrial cancer patients.

Imaging	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%)	NPV (%)
Deep myometrial invasion				
MRI+3D-TVS	96.5	39.1	34.6	96.7
Cervical invasion				
MRI+3D-TVS	82.1	67.4	48.1	91.4

Table 5. MRI in preoperative evaluation for cancer in lymph node metastases.

	Histology: lymph node metastases			Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	PPV (%)	NPV (%)	Accuracy (%)
	Yes	No	Total					
MRI								
Yes	7	4	11	58.33	96.26	63.63	95.37	92.43
No	5	103	108					
Total	12	107	119					

Table 5 shows the value of combined examination in predicting deep myometrial invasion and cervical infiltration.

Discussion

A non-invasive examination is needed that can accurately determine the staging of endometrial cancer before surgery, which can provide patients with the best surgical methods and reduce the surgical complications caused by excessive surgical range. Recently, MRI has been widely recognized as a reliable method for diagnosis, staging, and guiding treatment and follow-up of endometrial cancer due to its high resolution of soft tissue and multi-azimuth and multi-sequence imaging [5–7]. Manfredi et al. [8] reported that the sensitivity, specificity, PPV, and NPV of conventional MRI combined with contrast-enhanced dynamic for the identification of deep myometrium invasion was 87%, 91%, 87%, and 91%, respectively. Hwang et al. [9] reviewed all studies focusing on MRI for preoperative evaluation of deep myometrium invasion in EC, and concluded that the sensitivity of MRI for deep myometrium invasion was low (50–84%) but the specificity was high (50–100%). Several studies have demonstrated that in combined MRI and 2D-US, the sensitivities are 50–89% and specificities are 81–100% [10–15]. In the present study, the sensitivity and specificity of MRI for predicting deep myometrium invasion were 89.19% and 88.97%, respectively, and the PPV, NPV, and accuracy were 67.35%, 97.99%, and 89.01%, respectively, which is basically consistent with previous research results.

In middle-income countries, 2D-TVS is a routine method using magnetic resonance equipment for preoperative evaluation staging; its sensitivity and accuracy are lower than that of MRI. 3D-TVS, which can visually and intuitively observe the relationship between the state of blood perfusion in the tumor and the spatial structure of the three-dimensional structure, as well as analyzing the color brightness and the grayscale value quantitatively in the interesting region. It has the advantage of predicting the deep myometrial invasion, in contrast to 2D-TVS, due to its ideal resolution for soft tissue, multi-orientation, and multi-sequence imaging. In our study, the sensitivity and specificity of 3D-TVS for deep myometrial invasion

were 86.36% and 91.07%, respectively, while the PPV, NPV, and accuracy were 79.17%, 94.44%, and 89.74%, respectively. By comparison, the sensitivity, specificity, negative predictive value, and diagnostic accuracy of 3D-TVS and MRI diagnosis were not significantly different. The positive predictive value of 3D-TVS was higher than that of magnetic resonance, indicating that 3D-TVS and MRI have same diagnostic value for deep myometrial invasion. Furthermore, our study showed that MRI combined with 3D-TVS can achieve higher sensitivity (up to 96.5%) for predicting deep myometrial invasion.

Cicinelli [15] and Rockall [16] assessed the value of MRI in CI, reporting that the sensitivities ranged from 19% to 100% and specificities from 87% to 100%. Our study suggests that the sensitivity, specificity, PPV, NPV, and accuracy of MR in predicting cervical infiltration were 75%, 92.35%, 40.9%, 98.13%, and 91.2%, respectively. The indicators of 3D-TVS were 77.78%, 94.29%, 63.63%, 97.06%, and 92.4%, respectively. There was no significant difference in sensitivity, specificity, NPV, or accuracy between MRI and 3D-TVS in the diagnosis of cervical infiltration ($P > 0.05$). The PPV of 3D-TVS for predicting cervical infiltration was significantly higher than that of MRI (63.63% vs. 40.9%) ($P < 0.05$). We found that the individual sensitivity of MRI and 3D-TVS in the estimation of CI was inferior to that of MI, and the combination of these 2 examinations can increase the sensitivity to 83.5%. On account of higher specificity (more than 90%), they are superior for excluding non-invasive cervical cancer. At present, cervical infiltration refers specifically to cervical interstitial infiltration, whereas in the FIGO guidelines prior to 2009, cervical mucosal infiltration was included. Because it clearer and more easily evaluates cervical interstitial infiltration than infiltration of the cervical mucosa for MRI, the sensitivity and specificity of MRI for cervical interstitial infiltration in our study were high compared to the retrieved literature. The 2015 FIGO guidelines for the corpus uteri recommend radical hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy, and selective aortic node dissection as primary treatment for clinically overt cervical involvement. Since diagnostic curettage is a poor predictor of cervical interstitial infiltration, the combination of preoperative MR and 3D-TVS may be a good way to assess cervical infiltration. Of course, it also requires multi-center data support

and improvement of the MRI and ultrasound imaging skills of physicians.

3D-TVS cannot predict lymph node metastases. Previous studies have reported the sensitivity of MRI to be 46–56% and the specificity to be 88–95% [17,18]. Our study shows that in predicting LNM, the sensitivity, specificity, PPV, NPV, and accuracy of MR were 58%, 96%, 63%, 95%, and 92.43% respectively. The sensitivity for evaluating lymph node metastasis using MR was not high, as MR was capable of finding lymph node metastasis only when nodes were swollen (>10 mm). To compensate for the low sensitivity of MRI in lymph node staging, glucose metabolism in the lymph node could be determined preoperatively by FDG PET/CT [19]. However, few studies have been performed on LN staging by PET/CT in endometrial cancer. Signorelli [20], Horowitz [21], and Kitajima [22] reported that the sensitivity was 53.3–63% and the specificity was 94.7–99.6%, which does not show a distinct advantage compared to our data.

It is essential to predict the depth of myometrium invasion, cervical stromal involvement, and lymph node metastasis of endometrial carcinoma before surgery. We found that the combination of MRI and 3D-TVS significantly improves the sensitivity and can help surgeons choose the most appropriate surgical approach. There was no significant difference in the accuracy, sensitivity, and NPV of MRI and 3D-TVS for predicting deep myometrial invasion and cervical infiltration ($P<0.05$). Because ultrasound examination is easier to perform, and as long as the training ultrasound doctor stores the corresponding image according to the standard, the software will automatically analyze it. 3D-TVS is easier to perform in low- and middle-income countries, as the inspection time is short, the cost is low, and it is easy to apply and promote. If the results of 3D-TVS and MRI disagree, a cross-sectional pathological specimen or sentinel lymph node biopsy can be used to improve the accuracy of the diagnosis and further standardize the scope of surgery.

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The evaluation of lymph node metastasis is still mainly dependent on MRI. Intravenous contrast-enhanced CT, which is simple and less time consuming, is helpful in identifying vascular structures and soft tissue metastases, and distinguishing lymph nodes from small bowel loops. Nonetheless, the overall reported sensitivity in detecting nodal metastasis is only about 40% [23]. Lin et al. [24] found magnetic resonance dynamic contrast-enhanced (MRI-DCE) to be best in predicting deep myometrial invasion in premenopausal endometrial cancer, whereas magnetic resonance diffusion weighted imaging (MRI-DWI) is superior in postmenopausal patients. Tanaka [25] showed intraoperative frozen section is better than MRI for the prediction of deep myometrial invasion. Antonsen et al. [26] found that PET-CT was superior to MRI and 2D-TVS in evaluating deep myometrial invasion, cervical interstitial infiltration, and lymph node infiltration. Therefore, MRI-DWI, MRI-DCE, FDG PET/CT, and intraoperative frozen section are also acceptable preoperative auxiliary examinations to estimate endometrial cancer high risk factors. Meanwhile, Jantarsaengaram [27] and Christensen [28] used VCI in multiplanar display mode of 3D-TVS to find the best image-processing method to improve the sensitivity. Further research is needed to assess and compare contrast-enhanced CT, MRI-DWI, MRI-DCE, FDG PET/CT, intraoperative frozen section, and MRI in evaluating deep myometrial invasion, cervical involvement, and lymph node metastases of endometrial cancer.

Conclusions

Preoperative MRI and 3D-TVS are good methods to use in predicting deep myometrial invasion and cervical infiltration in patients with endometrial cancer, and are allow accurate preoperative staging and individual treatment, as well as avoiding unnecessary surgery expansion and risk.

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