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Is MRI helpful in assessing the distance of the tumour from the internal os in patients with cervical cancer below FIGO Stage IB2?

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Abstract

Aim—To determine the ability of magnetic resonance imaging (MRI) in detecting tumour-free margins from the internal os (IO).

Materials and Methods—A database search yielded 79 women with early-stage cervical cancer who underwent radical hysterectomy and preoperative MRI. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of MRI in assessment of 5 and >5 mm IO involvement were calculated with histopathological surgical specimen findings considered to be the reference standard. A main and subset analysis was performed. The subset analysis included only those patients who would have been considered for radical trachelectomy.

Results—For predicting a distance between the tumour and the IO of 5 mm, MRI had a sensitivity of 73%, a specificity of 98.3%, a PPV of 95%, a NPV of 88.1%, and an accuracy of 89.8% for the main analysis, and sensitivity of 81.8%, a specificity of 93.2% a PPV of 69.2% a NPV of 96.5% and an accuracy of 91.4% for the subset analysis.

Conclusion—MRI has high specificity, NPV, and accuracy in detecting tumour from the IO, making MRI suitable for treatment planning in patients desiring trachelectomy to preserve fertility.

Introduction

Cervical cancer is the third most common gynaecological malignancy in the United States, with an estimated 12,900 new diagnoses and 4100 deaths in 2015.¹ Standard treatment for

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early-stage cervical cancer has traditionally been radical hysterectomy with pelvic lymphadenectomy; however, this surgery results in loss of fertility. Radical trachelectomy is now an accepted fertility-preserving option for patients with early-stage cervical cancer who desire future fertility. This procedure was first described in 1994 by Dargent and Mathevet and was initially performed via a vaginal approach.² The procedure includes removal of the cervix at the isthmus, the paracervical tissue, and upper vaginal tissue with placement of a permanent cerclage followed by anastomosis of the uterine corpus to the vagina. Appropriate candidates typically include patients who wish to preserve fertility, have no evidence of infertility, and have small tumours (<2 cm) limited to the cervix; however, larger tumours may not completely exclude the patient from trachelectomy as tumours >2 cm with minimal stromal invasion may still be treated successfully with trachelectomy.³ Trachelectomy compared with radical hysterectomy has lower complications⁴ and can be safe in low-risk patients who may or may not desire fertility preservation.⁵ Patients who have neuroendocrine tumours, clear cell carcinoma, or small cell carcinoma, stromal invasion >10 mm, lymphovascular space invasion, and lymph node involvement are not generally considered good candidates for trachelectomy.

Magnetic resonance imaging (MRI) plays an important role in the preoperative assessment of cervical cancer and is recommended by the European Society of Urogenital Radiology for patients, who are candidates for radical trachelectomy.⁶ The inherent soft-tissue contrast resolution of MRI may help physicians ascertain the size of the tumour, the involvement of the lower uterine segment/internal os (IO), and the presence of suspicious lymph nodes.⁶ The reported staging accuracy of MRI compared with physical examination ranges from 75–99% for cervical cancer^{7–12}; however, a physical examination cannot measure the tumour-free distance from the IO.

For adequate radical trachelectomy, most surgeons try to obtain a disease-free margin of >1 cm from the tumour edge to the endocervical resection margin/IO. Some clinicians, however, consider a 5 mm margin from the IO to be adequate¹³ to select patients who may undergo radical trachelectomy. The objective of the present study was to determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of MRI in determining lower uterine segment (LUS) involvement and distance of tumour from the IO. To the authors' knowledge, no other study has correlated the actual distance 5 and >5 mm from the tumour to the IO at MRI with distance measured at histopathology.

Materials and methods

After obtaining Institutional Review Board approval, cases of all women with cervical cancer who underwent radical hysterectomy were reviewed. Radical hysterectomy consisted of excision of the uterus with *en-bloc* parametrial excision, which includes the round, broad, cardinal, and uterosacral ligaments as well as the upper one-third to one-half of the vagina. Bilateral pelvic lymph node dissection was also performed.

Patients in this study underwent radical hysterectomy either for large tumours, high-grade disease, or confounding findings present on physical examination and initial pathology. Only

patients who had contrast-enhanced MRI imaging performed within 15 ± 3 days prior to hysterectomy were included in the study. The sagittal T2-weighted and dynamic sagittal T1-weighted images were obtained using a 1.5 T GE (Milwaukee, WI, USA) MRI system at a single institution. Axial T2-weighted sequences were also included. The imaging protocol included dynamic contrast-enhanced three-dimensional (3D) fast spoiled gradient-echo sequences, which are routinely acquired. These images were obtained over nine passes through the uterus 30 seconds after contrast medium administration at 5 mm section thickness using an eight-channel cardiac coil. On the sagittal T2- and T1-weighted contrast-enhanced images, the IO was defined as the interior narrowing of the uterus where the uterine vessels entered. The level of the IO also marked where the myometrial intermediate signal intensity changed to the low signal intensity of the cervical stroma. The distance of the tumour from the IO was measured in the craniocaudal dimension on the sagittal T2 and contrast-enhanced sagittal T1-weighted images and were read in conjunction to assess LUS involvement. The longest distance was measured and documented as ≤ 5 and >5 mm involvement. Intravenous gadolinium was administered at a dose of 0.1 mmol/kg of body weight, at a rate of 2 ml/s using an automatic Medrad injector. The contrast medium injection was followed by a 20 ml saline injection to wash out the contrast medium from the tubing.

Two radiologists specialising in gynaecological oncology imaging with experience of 11 and 17 years reviewed the MRI images on picture archiving computer software monitors in consensus for the size of the tumour (largest dimension), the distance of tumour from the IO using electronic callipers, and evaluated for the presence or absence of adenopathy. Cervical cancer was diagnosed if an intermediate to high signal intensity mass was seen in cervix, compared to the normal cervical stroma on the T2-weighted images, and/or an enhancing mass present within the cervix on the T1-weighted dynamic contrast-enhanced images. The findings on MRI were categorized as positive if the tumour involved the IO and negative if it did not involve the IO. In addition, distance of the tumour from the IO was categorised as ≤ 5 or >5 mm. Metastatic adenopathy was described as a lymph node measuring >1 cm in the short-axis diameter or central necrosis was seen within a subcentimetre lymph node (<1 cm). The radiologists and pathologist were blinded as to others' findings. For the present study, a pathologist specialising in gynaecologic pathology retrospectively evaluated the size of the tumour, tumour involvement of the IO, and the distance of tumour from the IO on the explanted specimens.

Pathological size of the tumour from the cone biopsies was not recorded as MRI was obtained after the cone biopsies. The tumour size was only recorded from the surgical specimen. Twenty patients underwent cone biopsies and this was performed 15 ± 7 days prior to MRI. In seven patients, the cone biopsy removed the entire tumour and no tumour was visible on imaging.

Statistical analysis

Final surgical pathology findings after hysterectomy and MRI findings were summarised in terms of frequencies and percentages. Patient age and tumour size were summarised in terms of mean, standard deviation (SD), and range. Pathology results were considered the

reference standard for assessing the accuracy of MRI. MRI results regarding involvement of the IO, distance of tumour from the IO, and lymph node status were tabulated against corresponding pathology results. Sensitivity, specificity, PPV, NPV, and accuracy were estimated for each endpoint. The accuracy was based on correlation of MRI findings with pathology findings and was calculated as the number of patients with true-negative or true-positive MRI findings divided by the total number of patients. For evaluation of distance of tumour from the IO, MRI findings were considered true-positive if MRI indicated that tumour involved the IO or was ≤ 5 mm from the IO and the pathology evaluation showed the same.

Statistical analysis was carried out using SAS, version 9 (SAS Institute, Cary, NC, USA). Logistic regression model was created taking into account the age of the patient, size of the tumour, and positive versus negative involvement of the IO by MRI. Pearson's correlation coefficient was used to assess correlation of the tumour size on imaging and pathology.

Subset analysis was also performed that included only patients more closely reflecting the true candidates for radical trachelectomy, i.e., patients with Stage IA1–IB1 disease and squamous, adenocarcinoma, or adenosquamous lesions. For this subset analysis, patients with IB2 disease, neuroendocrine tumours, and papillary squamous carcinoma were excluded.

Results

Main analysis

In the main analysis, 79 patients met the inclusion criteria and were included. Seventy-six patients had Stage IA–IB1 disease, and three patients had Stage IB2 disease (Table 1). The most common histopathological subtype was squamous cell cancer ($n=33$).

Tumour size

The average tumour size at MRI, which was performed prior to surgery, was 1.8 cm (SD 1.5 cm, range 0–4.8 cm). The average size of the tumour at pathology was 1.6 cm (SD 1.7, range 0–5.6 cm). Both on pathology and MRI, 35 patients had tumours >2 cm. Twenty patients who had tumours >2 cm (average size 2.9 cm, range 2–4.5 cm) had no involvement of the IO at pathology; however, two of these patients were misdiagnosed as involving the lower uterine at MRI. The assessment of tumour size on MRI with pathology showed a high correlation with an $r=0.9$ ($p<0.0001$; Fig 1). The value of r indicates the following correlations: 0=no correlation; 0–0.20=slight correlation; 0.21–0.40=fair correlation; 0.41–0.60=moderate correlation; 0.61–0.80=substantial correlation and 0.81–1.00=almost perfect correlation.

LUS involvement

For predicting involvement of the LUS, MRI had a sensitivity of 78.6% a specificity of 93.8%, a PPV of 73.3%, a NPV of 95.3%, and an accuracy of 91.1% (Table 2). For predicting a distance between tumour and the IO of ≤ 5 mm, MRI had a sensitivity of 73%, a specificity of 98.3%, a PPV of 95%, a NPV of 88.1%, and an accuracy of 89.8% (Table 3).

Lymph node metastases

Seven patients (8.9%) had lymph node metastases. For predicting involvement of lymph nodes, MRI had a sensitivity of 28.6%, a specificity of 95.8%, a PPV of 40%, a NPV of 93.2%, and an accuracy of 89.9% (Table 4).

Subset analysis

When the analysis was limited to patients who were considered candidates for radical trachelectomy (excluding the nine patients with Stage IB2 disease, neuroendocrine tumour, or papillary squamous carcinoma), a total of 70 patients were included. The mean age of these patients was 40.6 years (SD 9.6 years, range 23–75 years). The mean tumour size was 1.57 cm (SD 1.42 cm, range 0–3.9 cm).

LUS involvement

For predicting involvement of the IO, MRI had a sensitivity of 81.8%, a specificity of 93.2% a PPV of 69.2% a NPV of 96.5%, and an accuracy of 91.4% (Table 2). For predicting the distance from the IO of ≤ 5 or >5 mm, MRI had a sensitivity of 81.8%, a specificity of 97.9% a PPV of 94.7% a NPV of 92.1%, and an accuracy of 92.8%, (Table 3).

Lymph node metastases

For predicting involvement of lymph nodes, MRI had a sensitivity of 40%, a specificity of 95.4% a PPV of 40% a NPV of 95.4%, and an accuracy of 91.4% (Table 4). A multivariate analysis of the size of the tumour, the grade, and the type of tumour suggesting lymph node metastatic disease could not be performed due to the small number of patients with lymph node metastases.

Logistic regression analysis suggests that patients with positive MRI findings of IO involvement had a significantly higher chance of being pathology positive for involvement of the IO compared to patients with negative MRI findings (odds ratio=90.04, 95% confidence interval [CI]: 5.6–1447.2, $p=0.002$; Table 5). The size of the cervical cancer had no association with involvement of the IO.

Discussion

In the present study, MRI had high specificity in the main and the subset analysis of 93.8% and 93.2% and NPV of 95.3% and 96.5%, respectively, for predicting involvement of the IO. For assessment of ≤ 5 or >5 mm distance from the IO, MRI had a specificity of 98.3% and 97.9%, and a PPV of 95% and 94.7% in the main and the subset analysis, respectively. In other words, if MRI did not raise concern about IO involvement (≤ 5 mm), it was unlikely that the pathologic specimen would show IO involvement (margin ≤ 5 mm), and surgeons could proceed with the procedure with a very high likelihood of obtaining negative margins (Figs 2–6).

Several MRI studies have attempted to assess the involvement of the IO. A meta-analysis of four studies carefully selected for IO involvement showed that the estimates of specificity and NPV were 91% and 99%, respectively¹⁴; however, the four studies^{15–18} that were

included in this analysis did not measure the actual distance of the tumour from the IO.¹⁴ A recent retrospective study,¹⁹ measured the distance from the IO on MRI and based the involvement of the IO on the patient's outcome (hysterectomy). Their false-negative finding for involvement of the IO was low, as only 3/48 patients who had >10 mm distance from the IO underwent hysterectomy. In the present study, the NPV was 88.1% in the overall analysis and 92.2% in the subset analysis, suggesting that MRI is able to correctly predict tumour-free margins of >5 mm from the LUS. When patients with any histological subtype and tumour ≥ 2 cm were evaluated, three patients had involvement of the IO on MRI, and these MRI findings correlated with pathology, suggesting that MRI would be an appropriate examination to use in patients undergoing trachelectomy even when the tumour is small.

The size of the tumour measured at MRI had a high correlation with the tumour size on gross pathology ($r=0.9$). Several studies have evaluated tumour volumes and have found a similar correlation with MRI tumour volumes.^{9,16,20} One recent imaging study suggested that when the tumour size is ≥ 2 cm, patients are more likely to undergo radical hysterectomy than trachelectomy¹⁹ and corresponds to earlier literature that suggested patients may not be able to undergo trachelectomy if the tumours are >2 cm³; however, some studies have shown that expanding the criteria to include 2–4 cm allows for a fertility-sparing procedure in 30% more patients who are initially considered suboptimal candidates for trachelectomy^{21–24} and these patients usually have a favourable outcome. The present study supports these findings, as 20/35 of patients with tumours >2 cm did not have involvement of the IO and retrospectively may have undergone fertility-sparing surgery safely. The logistic regression analysis in the present study also showed that there was no correlation between the tumour size and involvement of the IO, which concurs with findings of a study by Cibula and colleagues.²⁵ Therefore, it is reasonable to suggest that patients who have tumours >2 cm on clinical examination and desire fertility-sparing surgery should undergo preoperative MRI to assess for factors that may preclude surgical resection, such as involvement of the IO, and are not denied this procedure based only on the clinical International Federation of Gynecology and Obstetrics (FIGO) stage.

Although most patients can undergo successful trachelectomy based on the clinical FIGO stage, 27% of all patients may need radical hysterectomy as a result of a positive resection margin or post-trachelectomy chemoradiation for positive pelvic lymph nodes on final pathology.²⁶ On imaging a lymph node is considered to be metastatic if it has a short-axis diameter of >10 mm, has central necrosis, or irregular borders. Some authors have suggested short-axis length of >7 mm may be a reasonable criterion for consideration of metastasis; however, this change increases the false-positive rate for prediction of lymph node metastases.¹⁶ Another small study of 30 patients used the cutoff size of 5 mm for lymph node metastases and had an overall sensitivity for the detection of nodal involvement of 57% (4/7), and a specificity of 83% (19/23).¹⁷

Nine percent of the present patients had pathologically proven lymph node metastases. False-negative MRI findings were seen in five patients. None of these patients had a short-axis lymph node diameter >5 mm. Two patients had adenosquamous cancer, two had moderately differentiated adenocarcinoma, and one had poorly differentiated adenocarcinoma. All five patients had microscopic disease in their lymph nodes. Patients

with FIGO IB2 disease and lower grades have an incidence of lymph node metastases ranging from 4–27%.^{27–29} Using >1 cm short axis measurement for defining suspicious lymph nodes^{30,31} and given the low pretest probability of having lymph node metastases in the present cohort, MRI still had an accuracy 89.9% and 91.4% in detecting lymph node involvement, in the total and the subset analyses, respectively.

The present study is limited by its retrospective nature. The study was performed in patients who underwent MRI followed by radical hysterectomy for cervical cancer and not trachelectomy, as it would have not been feasible to measure the distance from the IO on pathology of trachelectomy specimens. In addition, radiologists with a special interest in imaging of gynaecological oncology patients evaluated the examinations and so it is uncertain how MRI will perform in a general practice setting and whether these results would be reproducible. Performing MRI prior to trachelectomy is not standard at the authors' institution as FIGO Stage IA patients have a low incidence of lymph node metastases or IO involvement.³² Many of these patients with FIGO Stage 1A disease who had a preoperative MRI may have had worrisome physical or pathological findings that prompted the additional imaging, leading to selection bias. Another limitation of the present study is that inflammatory changes related to cone biopsy seen at MRI may have confounded the results.³³ Depth of cervical invasion was not assessed as the intent was to assess the tumour-free distance from the IO, as this is the most important factor to determine eligibility for trachelectomy²⁵ even if the tumours are small. The performance of T2-weighted images was not compared with T1-weighted dynamic contrast-enhanced images, which were used as an adjunct to the T2-weighted images.

In conclusion, the high accuracy of MRI is helpful in determining the involvement of the IO and the tumour-free margin and this makes it suitable for treatment planning in patients with early clinical FIGO Stage <1B2 cervical cancer desiring radical trachelectomy.

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Highlights

- Patients with cervical cancer who underwent hysterectomy were analyzed on MRI and pathology for involvement of the internal os.
- The distance of the tumor from the internal os was measured on MRI and Pathology and findings were tabulated as > and < 5 mm from the internal os.
- MRI has the ability to identify tumor involvement of the internal os.
- MRI can help select patients who can undergo trachelectomy safely.

Figure 1.

Pearson's correlation coefficient shows high correlation between the cervical tumour size measured on the MRI with pathology.

Figure 2.
(a) Axial T2-weighted and (b) sagittal 3D T1-weighted dynamic contrast-enhanced images show the normal anatomy of the uterus. The arrows show the IO.

Figure 3.
(a) Sagittal T2 and (b) sagittal 3D T1-weighted dynamic contrast-enhanced images show cervical cancer (arrow) that involves the IO (arrowhead).

Figure 4. Sagittal T2- and T1-weighted contrast-enhanced images show the mass in the cervix (arrow) and the IO (arrowhead). In this case, the tumour did not involve the IO and was >5 mm from the IO.

Figure 5.
(a) Sagittal T2-weighted images shows a cyst at the level of the IO (arrow) and normal endocervical lining (arrowhead). The cervical cancer is not visible on the sagittal T2 and (b) 3D T1-weighted contrast-enhanced images; however, on pathology there was microscopic involvement of the IO, likely related to endocervical spread.

Figure 6.

(a) Sagittal T2-weighted images shows a mass in the cervix (arrow) measuring 3.2 cm and is away from the IO (arrowhead). (b) 3D T1-weighted contrast-enhanced images shows a mass (arrow) in the cervix, which is 2.7 cm away from the IO (arrowhead).

Table 1Demographic and tumour characteristics of the patients with cervical cancer ($N=79$).

Characteristic	Number	%
Mean age (range)	40.8 years (23–75 years)	
Stage		
IA	28	35
IB1	48	61
IB2	3	4
Histological subtype		
Squamous	33	42
Adenocarcinoma	35	44
Adenosquamous	5	6
Papillary squamous	2	3
Neuroendocrine	4	5
Grade		
Well differentiated	38	48
Moderately differentiated	21	27
Poorly differentiated	15	19
Unknown	5	6

Table 2

Magnetic resonance imaging (MRI) and pathology findings for internal os (IO) involvement.

MRI IO involvement	Pathology IO involvement		
	Positive	Negative	Total
All patients			
Positive	11	4	15
Negative	3	61	64
Total	14	65	79
Subset patients			
Positive	9	4	13
Negative	2	55	57
Total	11	59	70

Table 3

Magnetic resonance imaging (MRI) and pathology findings for distance of tumour from internal os (IO).

MRI tumour distance from IO	Pathological tumour distance from IO		
	5 mm	>5 mm	Total patients
All patients			
5 mm	19	1	20
>5 mm	7	52	59
Total patients	26	53	79
Subset patients			
5 mm	18	1	19
>5 mm	4	47	51
Total patients	22	48	70

Table 4

MRI and pathology findings for lymph node involvement in patients with cervical cancer.

MRI lymph nodes	Pathology lymph nodes		
	Positive	Negative	Total
All patients			
Positive	2	3	5
Negative	5	69	74
Total	7	72	79
Subset patients			
Positive	2	3	5
Negative	3	62	65
Total	5	65	70

Table 5

Summary of logistic regression model estimating the probability of having pathologically positive internal os (IO) involvement in patients with cervical cancer based on size of the cervical cancer.

Involvement of the IO				
Factor	Odds Ratio	95% LCL	95% UCL	p-Value
Cervix cancer size (1 mm increase)	1.25	0.58	2.70	0.56
MRI (positive versus negative involvement of IO)	90.04	5.60	1447.22	0.002

Odds ratio of 1 means no difference, >1 means higher risk of IO involvement, and <1 means lower risk of IO involvement. LCL, lower confidence interval; UCL, upper confidence interval.