

Diagnostic Accuracy of MRI in Primary Cervical Cancer

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ABSTRACT

Introduction: Magnetic resonance imaging (MRI) studies obtained during the initial staging of patients affected by uterine cervical cancer were compared to the final histological report after surgery. **Methods:** Data were retrieved from published papers. **Results:** MRI detection of lymph node metastases shows a sensitivity of 49.3% (1209 patients) and a specificity of 87.7% (1182 patients). Parametrial involvement detection has 66.2% sensitivity (1288 patients) and 83.6% specificity (1282 patients). MRI tumor size evaluation shows significant error. Even detection of over 1 cm diameter primary tumor can fail. MRI appears promising in the detection of myometrial and endometrial involvement. **Conclusions:** Primary uterine cervical cancer evaluation with routine MRI has a limited accuracy especially in the detection of lymph node involvement and parametrial invasion. It is not sensitive enough to replace histology of dissected nodes and parametria. Tumor size estimation is imprecise. Detection of myometrial and endometrial invasion using MRI might be possible. Awareness of MRI limitations is crucial in primary cervical cancer staging.

Keywords: Cervical Cancer; MRI; Parametrial; Lymph Node Involvement

1. Introduction

Uterine cervical cancer is the third most common gynaecologic malignancy reported in the United States [1]. In 2007 11,150 new cases were diagnosed and 3670 deaths were expected in the United States [1]. Currently, the International Federation of Gynecology and Obstetrics (FIGO) staging for cervical carcinoma is primarily based on physical examination. Staging errors are strongly associated with poor prognosis [1]. Exclusive FIGO clinical staging has been reported as accurate in only 29% of cases [2].

FIGO staging does not include lymph node status and tends to underestimate in 20% - 30% of low stage cervical cancer patients when compared to surgical staging. FIGO understaging has been reported in up to 23% of stage IIb disease, and 40% to 64% in stage IIIb. About 40% of the patients receive an inaccurate preoperative staging [3].

Together with parametrial extension and positive surgical margins, one of the most important prognostic factors in cervical cancer is the presence of lymph node metastasis.

Imaging technologies, as Computed Assisted Tomo-

graphy (CAT), Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) might have an impact in determining the proper treatment for patients with cervical cancer.

International papers screened using PubMed were reviewed. Sensitivity and specificity of routine MRI for 1) primary tumour detection; 2) internal of involvement; 3) myometrial invasion; 4) lymph node involvement; 5) parametrial invasion; 6) bladder invasion; 7) rectal invasion and 8) vaginal invasion were noted. MRI tumor size evaluation was compared to histologic tumor size. Radiological findings were compared to the postoperative histological report.

2. Methods

2.1. Literature Search and Study Selection

This study was approved by San Camillo-Forlanini Institutional Review Board.

A literature search of international studies was carried out to identify articles on MRI preoperative diagnostic performance in patients with cervical carcinoma. MEDLINE database (2000 to 2011) was searched for the following terms: "cervical cancer, cervical neoplasm, MRI, parametrial and lymph nodes" as medical subject head-

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ings (MeSH) and “specificity and sensitivity” as text words. Only original articles with raw data including comparison between immediately preoperative MRI results and post-operative histopathology were included. Eighty two papers were found to be eligible and 40 fulfilled inclusion criteria at least partially. Only 24 papers had complete data on lymphnode extension and/or parametrial invasion.

2.2. Data Evaluation

Two observers independently performed data evaluation, and discrepancies in judgement were solved by the independent appraisal of a third reviewer. The following items were extracted: 1) year of publication; 2) MRI technique (most authors used T1 weighted images [T1w] and T2 weighted images [T2w]; some of them compared different signals [4,5], or did not specify MRI techniques [6,7]; best results were used for analysis); 3) total sample size; 4) presence or absence of tumor in sites like lymph nodes, parametria, etc.; 5) and tumor size data indicated in centimeters.

Sensitivity and specificity values for lymph node and parametrial invasion (**Tables 1-2**), expressed as percentage, rounded up/down to the first significant digit, were calculated from published data.

3. Results

Table 1 reports the sensitivity and specificity of routine MRI in detecting lymph node metastases in case of cervical cancer (1444 patients). Overall sensitivity is 51.4% and specificity is 86.6%. **Table 2** reports MRI sensitivity and specificity in detecting parametrial invasion in cervical cancer (1341 patients). Overall sensitivity is 66.2% and specificity is 83.8%.

As to other endpoints, like detection of invasion of proximal structures, data were less homogeneous because of limited numbers or differences in study design.

Invasion of the serosal and muscle layer of the bladder. Rockall *et al.*, highlighted 13 false positives out of 112 patients with an overall sensitivity of 100.0% and a specificity of 88.0% for bladder invasion detection with MRI [6]. Hertel *et al.*, calculated a sensitivity of 64.0%

Table 1. MRI detection of lymph node metastases: computation of sensitivity and specificity values.

Patient (N°)	Sensitivity (%)	Patient (N°)	Specificity (%)	Reference
101	36.0	101	84.0	[22]
150	37.0	150	92.0	[15]
55	33.3	55	97.4	[27]
119	89.0	119	67.0	[20]
172	37.0	172	94.0	[11]
36	57.0	36	73.0	[21]
44	27.0	44	94.0	[23]
113	36.0	113	97.0	[12]
92	73.0	92	93.8	[40]
109	25.0	109	87.0	[7]
41	82.0	41	87.0	[13]
27	50.0	-	-	[28]
22	38.5	22	44.4	[41]
62	72.9	62	93.1	[31]
31	71.0	31	92.0	[14]
35	73.0	35	83.0	[29]
99	77.7	99	85.6	[17]
53	33.0	53	92.0	[24]
83	64.3	83	69.1	[6]
1444 ^a	51.4 ^b	1417 ^c	86.6 ^d	This work

^aThe number indicates the total number of patients; ^bThe number is obtained as $\Sigma (\text{patient}_n \times \text{sensitivity}_n) / 1444$ and represents the overall sensitivity; ^cThe number indicates the total number of patients; ^dThe number is obtained as $\Sigma (\text{patient}_n \times \text{specificity}_n) / 1417$ and represents the overall specificity.

Table 2. MRI detection of parametrial invasion: computation of sensitivity and specificity values.

Patient (N°)	Sensitivity (%)	Patient (N°)	Specificity (%)	Reference
101	52.0	101	63.0	[22]
-	-	150	97.0	[15]
119	80.0	119	91.3	[20]
112	100.0	-	-	[6]
172	53.0	172	75.0	[11]
44	21.0	-	-	[23]
113	38.0	113	99.0	[12]
85	77.8	85	88.2	[40]
41	97.0	41	91.0	[13]
75	100.0	75	93.0	[4]
103	60.0	103	73.0	[8]
159	59.3	159	61.5	[33]
31	100.0	31	96.0	[14]
38	90.0	38	92.0	[5]
95	50.0	95	97.8	[18]
53	67.0	53	92.0	[24]
1341 ^a	66.2 ^b	1335 ^a	83.8 ^b	This work

^aThe number indicates the total number of patients; ^bThe number is obtained as $\Sigma (\text{patient}_n \times \text{sensitivity}_n) / 1341$ and represents the overall sensitivity; ^cThe number indicates the total number of patients; ^dThe number is obtained as $\Sigma (\text{patient}_n \times \text{sensitivity}_n) / 1335$ and represents the overall specificity.

with a specificity of 88.0% for MRI detectable bladder involvement [7]. Postema *et al.*, found a sensitivity and a specificity of 77.0% and 97.0%, respectively, for bladder invasion detection by MRI [8]. 5 of eighteen patients, suspected on MRI to have mucosal bladder invasion were not confirmed at histology. Overall MRI specificity and sensibility for the MRI detection of mucosal bladder invasion was 93.5 and 100% in the 92 patient series [9].

MRI detection of rectal involvement. Rockall *et al.*, found 10 false positives out of 112 patients with 100.0% sensitivity and 91.0% specificity [6]. According to Rajaram *et al.*, MRI correctly assessed both spaces with accuracy of 88.9 % in vesicocervical space, and 66.7% for rectovaginal space [10]. Hricak *et al.*, showed that neither CAT nor MRI were able to detect four cases presenting with tumor in the rectum [11]. Hertel *et al.*, calculated a MRI sensitivity of 50.0% and a specificity of 86.0% for rectal invasion [7].

MRI detection of vaginal invasion. Choi *et al.*, [12] in 23 patients reported a sensitivity of 87.0% and a specificity of 79.0% with 3 false negatives. Sheu *et al.*, [13] identified vaginal involvement in 9 patients, with 2 false negatives and 6 false positives at histological comparison. The sensitivity was 82.0% and specificity 84.0%. Errors in the assessment of vaginal invasion occurred in 8 cases out of 11. In the Sheu's study [14], overall sensitivity and specificity for vaginal invasion detection were 75.0% and 88.0%, respectively.

Uterine body involvement cannot be established by the examining gynaecologist. Sahdev *et al.*, [15] found, for internal os involvement detection, a MRI sensitivity of 90.0% and a specificity of 98.0%.

MRI detection of myometrial invasion. This was observed through MRI by Sahdev *et al.*, [15] with a sensitivity of 100.0% and a specificity of 99.0%. MRI correctly detected all of the 7 tumors extending to the endometrium on 150 patients enrolled in his study. According to Wang *et al.*, [16], tumors extending to the uterine body were identified by MRI in 3 out of 4 patients. In one case microscopic extension to the endometrium was not detected by MRI. Yoo *et al.*, [17] studied 99 patients and reported sensitivity and specificity for deep myometrial invasion MRI detection of 46.6%, and 84.5%, respectively.

Primary tumor detection by MRI. Sahdev *et al.*, [15] pointed out a 20/60 incidence of suspect lesions at MRI when no tumor was histologically detectable and suggested scar lesions as the culprit. The false negative rate, for the detection of small tumors (<1 cm diameter), was 50.0% (14/28). Fischerova *et al.*, [18] observed a tumor detection sensitivity of 44% at MRI, with a specificity of 94.3% for tumor bulks $\leq 1 \text{ cm}^3$. Itoh *et al.*, [19] set tumor detection sensitivity at 75.0% in a stage I patient. Lesions over 2 cm were detected in 83.0% of cases and in 60% under 2 cm. de Souza *et al.*, [20] observed a tumor detection sensitivity of 87.0% and specificity of 65.0% in 43

patients with tumor volumes of $\leq 1 \text{ cm}^3$. Sensitivity and specificity in patients with conization were 95.1% and 57.9%, respectively, while the same values in patients without conization were 98.2%, and 66.7%, respectively.

According to Sahdev *et al.*, [15], whose study included microscopic stage Ia tumors, detection sensitivity and specificity of the primary tumor was 65.0% and 77.0%, respectively. The total false-positive MRI rate was 30.6% (19/62) possibly due to tissue post-biopsy oedema or chronic inflammation. Fischerova *et al.*, [18], had a more favourable experience and found MRI sensitivity for tumor detection of 82.9%, with a specificity of 84.2%. de Souza *et al.*, [20] found false positives in 9 over 119 cases with an overall sensitivity of 96.9% and a specificity of 59.1%. Total results are influenced by low MRI performance in case of small primary tumors.

Tumor size estimation. According to Sahdev *et al.*, [15], there is an average tumor size estimation error of 9 mm, with 95% limits of agreement from 12.6 mm to 13.0 mm when compared with histology. Error drops to 3 mm if the tumor exceeds 10 mm. Park *et al.*, [21] showed a volume estimation error of 71.9% if the lesion was confined to the cervix and up to 18.8% if extending to the vagina. Sheu *et al.*, [13], for tumors over 1 cm, observed the overestimation of tumor size in 3 patients: this was due to inability to differentiate tumor from tissue oedema resulting from previous biopsy or previous cone biopsy. In two cases tumor size was underestimated and errors in measurement were due to indistinct lesion margin. According to Sheu *et al.*, [14], tumor size detected by MRI was $3.23 \pm 1.75 \text{ cm}$ (mean \pm standard deviation) compared with $2.79 \pm 1.76 \text{ cm}$ at pathology evaluation. Over-estimation of tumor size was consistent in tumors larger than 10 mm.

4. Discussions

Routine MRI equipment has been updated periodically, but no trend towards a better diagnostic accuracy has been found [22], and, in all the papers we reviewed, the authors used standard 1.5 Tesla equipment. Advanced MRI techniques, like ultra-small particles of iron oxide (USPIO) [23], endorectal/phased-array coils [16], contrast media enhancement [14] and others (endovaginal opacification [15], dynamic MRI imaging, short tau inversion recovery [STIR] sequence [5]) have been used in a limited number of studies but are not addressed by our review. All these techniques might improve diagnostic accuracy of MRI studies. MRI results vary according to the radiologist's experience [8,22].

Only the results with routine MRI in a clinical setting have been considered in this paper.

The overall patient sample set is biased [23] as patients with inoperable tumors were excluded. However, it should be noted that bulky tumors were well represented

in all reviewed papers. Tissue preparation for histology could possibly lead to dehydration and shrinkage of the tumor mass. MRI overestimation and underestimation of tumor volume were equally represented in the available data.

Tumor detection and size estimation. MRI evaluation does not precisely correlate with histologic tumor size unless the tumor is bulky (at least 1 cm diameter) [24]. Tumor size estimation by MRI [25] seems accurate in Ib to IIb stages, with a correlation of 0.93%. The problems observed with MRI evaluation of primary tumor size are: 1) no detection; 2) impossibility of margin definition; 3) confusion with peritumoral reaction or scars. The issue is possibly relevant only if the tumor is confined to the cervix (**Figures 1(A)-(B)**). The incidence of false positive diagnoses with MRI in Ia1 tumors was 33.0% (20/60), while false negatives reached 50.0% [12]. Correct diagnoses were mostly obtained in cases with a previous cone biopsy suggesting scar and not tumor detection. Some recent data reported by Fischerova *et al.*, are encouraging [18] showing an overall sensitivity of 82.9% and a specificity of 84.2% in primary tumor detection. For volumes under 1 cm^3 , the values became 44.0% and 94.3%, respectively.

Internal os involvement and myometrial invasion. Preliminary data suggest good results with MRI in the definition of cervical internal os involvement. Myometrial and endometrial invasion detection is possible by MRI (**Figure 1(D)**) [9]. This issue is not unrelated to tumor bulk. Some lesions misdiagnosed as bulky first stages (**Figure 1(C)**), with unfavourable outcome might include relatively more advanced cases with uterine body invasion demonstrable identified by MRI. Bipat *et al.*, [26] in 21 patients shows that MRI has a good chance of visualizing the internal os. No false-negatives for involvement of the uterine corpus and 3 false positives with suspect uterine body invasion were observed by the authors.

Lymph node involvement. Lymph node invasion is difficult to determine with certainty by MRI and no definite cut-off has been established as regards volume or maximum diameter of nodes.

Criteria for nodal involvement are not standardized. Sahdev *et al.*, [15] suggests that the prediction of nodal status was most accurate when a 9 mm cut-off was applied to the short-axis diameter of the lymph node [27]. de Souza *et al.*, [20], using a cut-off volume of 5.2 cm^3 , observed that lymph node metastasis could be predicted with a 78.6% sensitivity and a 72.5% specificity. A cut-off of 2.8 cm^3 improves sensitivity to 89.0% but this gives a poor specificity of only 67.0%. Park *et al.*, [21] reports that using 1 cm diameter cut-off sensitivity and specificity were 57.0% and 73.0%, respectively, while Narayan *et al.*, [28] with the same cut-off observes a MRI sensitivity of 50.0%. MRI apparently might fail

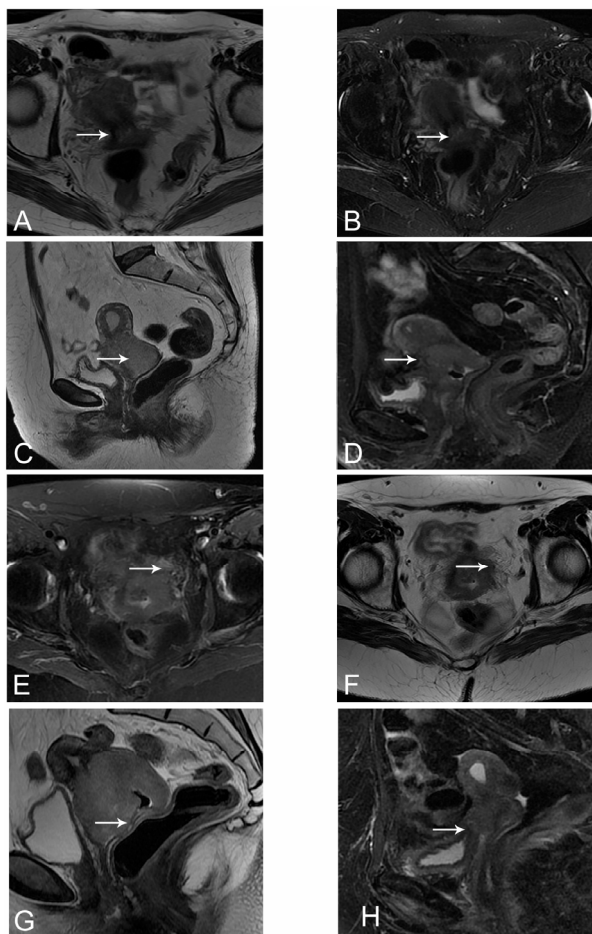


Figure 1. (A and B, respectively) T2 weighted (T2w) pulse sequence MRI showing uterine cervical cancer detection and invasion. A small lesion confined to the cervix, evaluated through axial T2w and T2w fat-saturated images. (C) A bulky cervical lesion, invading posterior fornix without rectal or bladder invasion, assessed by sagittal T2w MRI. (D) Cervical cancer with myometrial, (E-F) parametrial, (G) rectal (H) and vaginal invasion detected by: 1) (D) T2w fat-saturated MRI; 2) (E and F, respectively) axial T2w and T2w fat-saturated MRI; 3) (G and H) sagittal T2w fat-saturated MRI.

because lymph node size can be unaffected in early invasion and large nodes are observed in association with incidental clinical conditions. Sheu *et al.*, [14] found 2 false negatives and 2 false positives, with 71.0% sensitivity and 92.0% specificity. Enlargement of lymph nodes due to reactive hyperplasia rather than tumor metastases was noted in 2 patients. In 3 out of 35 women micrometastatic disease was missed by MRI, and 4 patients with abnormally enlarged lymph nodes at MR imaging had negative findings at histological examination. The sensitivity and specificity were 73.0% and 83.0%, respectively [29]. Hong *et al.*, indicate that MRI lymph node detection could be related to tumor bulk. The sensitivity and specificity were 7% and 99.3% in the nonbulky tu-

mor group, 43.8% and 97.1% in the bulky tumor group [30].

Comparison of proximal and distal node detection. Some preliminary findings suggest better MRI results for lower pelvis metastatic node detection. Choi *et al.*, [12] confirmed the presence of lymph node metastasis in 22 pelvic regions in 17 patients with a sensitivity of 36.0% and a specificity of 97.0%. Of 3 patients with suspect para-aortic lymph nodes metastases at MRI, surgical resection proved metastases in 2 with a sensitivity of 100.0% and with 1 false positive due to previous tuberculous lymphadenitis. According to Bellomi *et al.*, [31], MRI sensitivity and specificity in detecting metastatic lymph nodes in the lower pelvis were 80.0% and 88.0%, respectively, while were 37.5% and 97.5% for upper iliac nodes. Overall MRI sensitivity was 72.9% and specificity 93.1%. Hertel *et al.*, [7] analyzed para-aortic and pelvic lymph nodes separately, with a MRI sensitivity of 25.0% for the pelvic region and of 0% for the para-aortic region. The specificity was 87.0% and 98.0%. Yoo *et al.*, [17] reported 99 patients and showed sensitivity and specificity for MRI in determining pelvic lymph node metastases of 77.7% and 85.6%, respectively. MRI failed to detect the presence of paraaortic lymph node metastases in all of the three patients with positive nodes. Discrepancies between MRI and surgical findings could be explained by new lesions appearing in previously apparently unaffected lymph nodes.

Parametrial invasion. MRI sensitivity and specificity in the detection of parametrial invasion indicates problems in the differentiation between abnormal and simply reactive tissue (**Figures 1(E)-(F)**).

Recent studies suggest an even better specificity value for parametrial involvement detection. Fujiwara *et al.*, [4] demonstrated a sensitivity of 67.8% and a specificity of 95.7% for parametrial involvement detection. Fischerova *et al.*, [18], showed a sensitivity of 50.0%, and a specificity of 97.8%, respectively, for parametrial invasion. If the cervical stromal ring appears intact at MRI, parametrial extension has been reported in 0 to 6% of cases [25].

Parametrial involvement and tumor bulk. Hricak *et al.*, [11] focused on MRI capability to detect advanced cancer stage (\geq Ib) showing a sensitivity of 53.0% and a specificity of 75.0%. Jena *et al.*, [32] observed that tumor volume at MRI in parametrial invasion cases ranges from 17.3 cm³ to 99.2 cm³. The best sensitivity of 59.3% and specificity of 61.5% was found for a tumor volume of 36.4 cm³. Park *et al.*, [21] reported an accuracy of 84.4% compared with surgical specimen findings, with only 2 patients up-staged (6.3%) but 3 down-staged (9.4%) including one with no visible tumor at MRI. Choi *et al.*, [12] showed a sensitivity of 38.0% for 226 parametria analyzed, with an accuracy of 94.0%. It may be that

specificity is negatively affected by increasing tumor bulk. According to Testa *et al.*, MRI provided low sensitivity (2/5, 40.0%) for the presence of parametrial infiltration [33].

MRI interpretation might vary according to different radiologists. Reviewing parametrial invasion, Postema *et al.* [8], showed that reader nr. 1 reported a sensitivity of 20.0% and a specificity of 97.0%, while reader nr. 2 observed a sensitivity and a specificity of 60.0% and 73.0%, respectively.

Bladder, rectal and vaginal invasion. Data on rectal invasion detected by MRI in cervical cancer patients are scant and conflicting. Sensitivity varies from 50 to 100% in limited reports. MRI overdiagnoses bladder and rectal invasion. MRI might lead to detection of clinically unsuspected lesions and has determined restaging in one instance [14]. Absolute sensitivity and specificity for MRI detection of rectal invasion (**Figure 1(G)**) seems to be aligned to those observed in parametrial tumor detection. Vaginal invasion might possibly be underdiagnosed by MRI (**Figure 1(H)**).

5. Conclusions

MRI use is encouraged for cervical cancer staging. There seems to be good correlation between histological and MRI tumor bulk. There is a high probability of non extension to parametria if cervical integrity is observed at MRI and good indication of extension to proximal structures. Primary preoperative evaluation of uterine cancer by MRI does not accurately predict the nodal status and the degree of myometrial and parametrial invasion [17], but MRI shows encouraging progress in the detection of uterine myometrial and endometrial invasion, where CAT scans mostly fail.

MRI has been proposed as a substitute for invasive cystoscopy and proctoscopy in the initial screening of cervical cancer and preliminary data seem encouraging.

In general, the role of modern imaging techniques still remains undefined in the current management of uterine cervical cancer. MRI and CAT have been approved for use of initial staging in patients with cervical cancer by Medicare and Medicaid Services [33]. Due to its good tissue contrast, MRI is the preferred imaging technique for tumor detection and invasion evaluation in advanced stage disease [22]. In patients with negative results by MRI and CAT, the use of PET has been approved by health care providers such as Medicare [34]. A preliminary report by Testa *et al.*, [33] shows that Ultrasound (US) and MRI has similar sensitivity and specificity in preoperative staging. US has the advantages over MRI of low cost and widespread availability.

Despite all limitations, introduction of MRI has improved staging in cervical cancer patients according to Chung *et al.*, [3] and the American College of Radiology

Imaging Network (ACRIN) study [11], from 30% - 40% to about 70% accuracy [17].

Selman *et al.*, [35] reports a pooled negative likelihood ratio of 50% for lymph-node metastasis detection by MRI in a meta-analysis of the literature. Adding a sentinel lymph node biopsy can raise the accuracy to 94%. Intraoperative histology could lead to a better primary staging of uterine cervical cancer. According to Rajaram, the incidence of positive nodes in stage IB patients, is approximately 15% [10]. Thus sentinel lymph node (SLN) evaluation, is a practical approach to reduce extensive lymph node dissection.

SLN evaluation is an established technique for melanoma and breast carcinoma staging and its use in vulva, lung and cervical carcinoma treatment is being actively discussed [36-39]. A combined imaging and histology approach might be warranted in the management of uterine cervical carcinoma.

Awareness of MRI limitations is crucial in primary cervical cancer staging.

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