

# Preoperative Triage of Early Stage Operable Ca Cervix

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## ABSTRACT

**Aim:** Carcinoma (Ca) cervix is staged clinically and early stages undergo radical hysterectomy but many cases need adjuvant radiotherapy (RT)-based on the high and intermediate risk factors on histopathology, thus increasing morbidity and cost. This study evaluated the role of preoperative MRI in triaging patients of early stage operable Ca cervix to identify patients likely to require adjuvant RT after surgery.

**Materials and methods:** In total, 28 cases of operable Ca cervix clinically staged as I B1 underwent a preoperative MRI and based on the criteria of tumor size, depth of stromal invasion (DOSI), and parametrial involvement were triaged into low and high risk for receiving adjuvant treatment. They underwent radical hysterectomy and the specimen was subjected to pathologic examination. The pathologic characteristics and need for adjuvant treatment were studied.

**Results:** MRI evaluation could accurately evaluate the tumor size and DOSI and parametrial metastasis in all cases of Stage B1 Ca cervix. Based on these risk criteria, the cases were triaged into low risk (13) and high risk (15) to predict the requirement of adjuvant treatment. There was a statistically significant difference in the requirement of adjuvant RT in the two risk groups (15.38 vs 66.66%).

**Conclusion:** MRI can effectively estimate the tumor size and DOSI and parametrial metastasis in early stage (Stage I B1) Ca cervix and can further triage them to high- and low-risk groups to effectively predict the requirement of postoperative adjuvant RT.

**Clinical significance:** Surgery could be avoided in patients likely to require adjuvant RT by this triage, thus reducing morbidity.

**Keywords:** Adjuvant radiotherapy, Carcinoma cervix, Depth of stromal invasion, Parametrial metastasis, Preoperative triage, Tumor diameter.

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## INTRODUCTION

Class III radical hysterectomy with bilateral pelvic lymphadenectomy is the standard surgery performed for clinical Stage B1 cervical cancer. The wide parametrial resection involving extensive ureteric dissection and the pelvic lymphadenectomy as part of the surgery results in substantial morbidity. Adjuvant treatment in the form of radiotherapy (RT) may be required in a proportion of these patients based on high-risk features on histopathological examination (HPE). These patients treated by dual modalities of surgery and RT encounter substantial morbidity both short and long term. Hence, one of the primary concerns while planning treatment for Ca cervix is to avoid exposing the patient two modalities of treatment as far as possible, thus keeping the morbidity to a minimum. A method of selecting patients unlikely to require adjuvant RT for radical hysterectomy and considering primary concurrent chemoradiotherapy (CCRT) in others would considerably reduce this iatrogenic morbidity.

Carcinoma cervix still remains a clinically staged disease for various reasons and is based on the concept of "anatomic compartmental spread" of disease. One of the prime purposes of clinical staging in Ca cervix is to assess the surgical curability of the disease and select patients for surgery. Tumor size assessment is not only difficult clinically especially in large and endophytic tumors but is also inaccurate and is rarely considered in choosing primary treatment.<sup>1-3</sup> Tumor size however forms an intermediate risk factor while considering adjuvant treatment after surgery and is a risk factor that can be preoperatively assessed with reasonable accuracy by MRI.<sup>4</sup> Tumor size is also considered as an independent risk factor for lymph nodal metastasis (LNM) and parametrial metastasis (PM) in many studies. Accurate determination of tumor size may not only help in triaging patients to low and high-risk groups and thereby assist in selecting the ideal primary treatment modality but can also help in tailoring the extent of

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surgery in the low-risk group.<sup>5</sup> Tumor architecture also decides the behavior of this malignancy and hence the prognosis. An exophytic tumor on the cervix behaves less aggressively than an infiltrative one and hence the depth of stromal invasion (DOSI) carries a significant importance as a prognostic risk factor and postoperatively does influence decision on adjuvant treatment (Sedill's criteria).<sup>6</sup> Although the actual DOSI is available only after the final histopathology report (HPR), a preoperative MRI can, with reasonable accuracy, evaluate the DOSI in Ca cervix.<sup>7</sup>

Large tumor size [tumor diameter (TD) >2 cm] and deep stromal invasion (DSI) [stromal invasion >50%] have thus been suggested as the most important risk factors for occult PM and LNM in Ca cervix.<sup>8,9</sup> A good preoperative MRI not only evaluates the TD accurately regardless of the site and size of the tumor, it can also with reasonable accuracy assess the DOSI in the cervix and thereby has the potential to predict both PM and LNM, which are both high-risk factors for adjuvant treatment after surgery in apparently operable

stages of Ca cervix.<sup>10</sup> Thus, MRI has the potential to identify patients for surgical management and even consider less radical surgery in some patients based on tumor size and DOSI. Identification of TD and DOSI is also important because even with the best of imaging, LNM and occult PM may be missed preoperatively.<sup>11</sup> This was also the basis of the proposed a new surgico-pathologico-radiological system of staging for Ca cervix where imaging (USG/CT Scan/MRI/PET-CT scan) is proposed to be part of staging when available.<sup>1</sup>

## MATERIALS AND METHODS

This was a prospective observational study conducted in oncology center of a tertiary teaching hospital from January 20, 2016, to December 31, 2019. The aim of this study was to evaluate the role of MRI as a preoperative imaging modality in assessing the TD, DOSI and occult parametrial metastasis (OPM) in clinically operable stages of Ca cervix and to triage patients based on MRI findings into high- and low-risk groups to predict requirement of postoperative adjuvant RT. Necessary ethical clearance was obtained from the institutional ethical committee for this observational study.

All patients with biopsy proven Ca cervix found to be clinically operable after clinical staging and preliminary evaluation and planned for surgical treatment after the institutional tumor board were eligible. Patients who consented to be part of the study were enrolled after obtaining a written informed consent and underwent a preoperative MRI of the pelvis and abdomen prior to the planned type III radical hysterectomy. Patients who had undergone conizations were excluded from the study.

The patient variables studied included age, clinical stage of disease and adjuvant treatment where required. The pathologic variables included histology, TD, DOSI, LVSI, LNM, OPM and margins. Preoperative staging was done using the FIGO clinical staging system using permitted investigations where required. MRI evaluation was done using a 1.5 T axial T1 weighted FSE sequence with 5 mm slice thickness and an interslice gap of 2 mm and an axial t2 weighted FSE sequence with slice thickness 2 mm and interslice gap of 1 mm and a sagittal T2-weighted FSE with 3 mm slice thickness, interslice gap of 3 cm. Largest TD was determined by measuring all these measurements in the three sections. The DOSI was measured on T2W images in the low-signal intensity stroma of the cervix. PM was looked for and documented where obvious. LN enlargement was noted separately but was not included in the triage because enlargement did not always confirm metastasis and vice versa.

Type III radical hysterectomy-included ligating uterine artery at its origin, dissection of the entire course of the ureter up to its entry into the bladder, and resection of the cardinal and uterosacral ligaments as laterally as possible along with paracolpos and 2 cm of disease-free cuff of vagina. Pelvic lymphadenectomy included systematic clearance of all node bearing fatty tissue laterally till the genitofemoral nerve, medially till the internal iliac artery, superiorly till the mid common iliac arteries, inferiorly till the circumflex iliac vessels, and posteriorly till the obturator nerve (internal iliac, external iliac, obturator groups of lymph nodes).

The resected specimen was subjected to standard grossing and sampling techniques. Primary tumor diameter (PTD) and DOSI were measured during grossing and during histology. DOSI during HPE was expressed as fraction of the cervical wall thickness into <50% or >50% invasion. Tumor grade, lymph vascular space invasion (LVSI) and OPM were also recorded during microscopic examination.

Patients were administered adjuvant CCRT as indicated by the high risk (nodal metastasis, PM, and positive vaginal margins) and intermediate risk factors [Sedill's Criteria—any two or more of PTD >2 cm, deep stromal invasion (DSI) and LVSI].<sup>9</sup> Data were analyzed to study the accuracy of MRI in preoperative assessment of PTD and DOSI and PM and where present.

## RESULTS

During the study period, 202 patients were diagnosed to have Ca cervix on biopsy, and 64 were clinically staged as operable (Stage I A-8, Stage I B1-28, Stage I B2-15, Stage II A1-11) and were planned for RH. Totally, 62 patients completed the procedure (RH not done in two cases—one due to positive pelvic LN metastasis on frozen section (FS) and one due to bladder infiltration). All 28 cases of Stage I B1 were included in this study, and the patient characteristics are presented in Table 1. The median age was 49.5. Squamous cell Ca was the most common (78.5%) followed by adeno Ca and adenosquamous Ca. The PTD measured on MRI ranged from 1.0 to 4.5 cm with a mean of 1.60 cm and 12 (42.5%); patients had >50% DOSI; four patients showed evidence of parametrial invasion and five had enlarged pelvic lymph nodes. Based on the criteria discussed (PTD >2 cm, DOSI >50% and OPM), the cases were triaged, 13 into low risk and 15 into high risk (Table 2).

Table 2 compares the MRI parameters and pathological characteristics of the two groups. There were statistically significant differences in the PTD, DOSI both on MRI and on HPR in the two groups. The tumor size estimated on MRI correlated well to the final HPR reported tumor size and so was the estimation of cases with deep stromal invasion (DOSI >50%). MRI also could pick up all cases of OPM detected on final HPR. There were 13 cases triaged into the low-risk group and 15 in the high-risk group based on these factors. There were statistically significant differences in the tumor size (1.5 vs 2.61 cm), cases with deep stromal invasion (02 vs 10), and LN

**Table 1:** Patient characteristics (n = 28)

	No (%)
Age median (range), years	49.5 (39–73)
Parity median (range)	2 (0–6)
<b>Histology</b>	
Squamous cell carcinoma	22 (78.5)
Adenosquamous carcinoma	01 (3.5)
Adeno Ca	05 (17.8)
Others	00
<b>MRI parameters</b>	
PTD, median (range)	1.60 (1–4.5)
DOSI >50%	12 (42.85)
Parametrial invasion	04
Involvement of corpus	05
LN enlargement	05
<b>Pathological characteristics</b>	
Tumor size, median (range)	1.65 (0.9–3.8)
Deep stromal invasion >50%, no (%)	12 (42.85)
OPM, no (%)	04 (14.28)
LN metastasis, no (%)	08 (28.57)
Vaginal margin +ve, no (%)	00 (0.0)
LVSI, no (%)	07 (25%)
<b>Adjuvant treatment</b>	
RT/CCRT	12 (42.85)
No	16 (57.14)

**Table 2:** Clinicopathological characteristics after risk stratification

Characteristic	Low risk (n = 13) (PTD <20 mm. PM Free and DOSI <50%)	High risk (n = 15) (PTD >20 mm/ or DOSI >50%/ or OPM)	p value
Age median (range), years	50 (39–73)	49 (40–72)	0.465
<b>Histology</b>			
Squamous cell carcinoma	10 (76.92)	12 (80)	
Adenocarcinoma	03 (23.18)	02 (13.33)	
Adeno-squamous	0	01 (06.66)	
Others	0	0	
<b>MRI parameters</b>			
PTD, median (range)	1.41 (0.9–1.6)	2.61 (1.8–3.8)	<0.0001
DOSI >50%	02 (15.38)	10 (66.66)	0.006
Parametrial invasion	Nil	04 (26.66)	0.1016
LN enlargement	01	04 (26.66)	0.191
<b>Pathological characteristics</b>			
Tumor size-median (range)	1.5 (0.9–1.9)	2.54 (1.5–4.5)	<0.0001
Deep stromal invasion >50% no (%)	01 (07.69)	11 (73.33)	<0.0001
OPM, no (%)	0	04 (26.66)	0.1016
LN metastasis, no (%)	01	07 (46.66)	0.0377
LVSI, no (%)	02	05 (33.33)	0.2740
<b>Adjuvant treatment</b>			
CCRT/RT	02 (15.38)	10 (66.66)	0.0093
No CCRT/RT	11 (84.61)	5 (33.33)	

metastasis (01 vs 07) in the two groups. OPM and LVSI though higher in the high-risk group were not found to be statistically significant (0 vs 4 and 02 vs 05). However, there was statistically significant difference in the requirement of adjuvant RT in the two groups (15.38 vs 66.66%), thus implying that MRI triage preoperatively can definitely predict the requirement of adjuvant RT in early stage Ca cervix. The indications of adjuvant CCRT are shown in Table 3. LN metastasis on HPR in the two groups also showed statistically significant difference suggesting that the high-risk factors studied possibly could also predict chance of LN involvement especially in cases with LVSI. The preoperative triage using MRI for assessment of cervix and parametrium achieved a positive predictive value of 66.67 negative predictive value of 84.62 and this improved to 80 and 100%, respectively, when MRI findings were combined with finding of LVSI on histology (Tables 3 and 4).

## DISCUSSION

Deciding the mode of treatment of early stage ca cervix has always depended among other factors on avoiding two modalities of treatment (surgery and RT) in the same patient. Clinical staging in Ca cervix is often inaccurate and gives grossly inadequate information especially in early and operable stages of Ca cervix, and hence, many patients end up requiring adjuvant RT/CCRT after surgery, thus increasing the morbidity and cost. This forms the basis of including imaging (when available) in the proposed new FIGO

**Table 3:** Indications for adjuvant RT (n = 12)

Indication	Low risk (n = 2)		High risk (n = 10)		
	Nos	Remarks	Indication	Nos	Remarks
LN Mets	01	Also had DSI and LVSI	LN Mets + OPM	03	PTD >2: 04 DSI: 03
DSI + LVSI	01	By Sedill's criteria	LN Mets only	04	PTD >2: 04 DSI: 04
			OPM only	01	PTD >2 DSI
			Sedill's criteria	02	PTD >2: 02 DSI: 02 LVSI: 02

DSI, deep stromal invasion; OPM, occult parametrial mets; LVSI, lymph vascular space invasion; Sedill's criteria for optional adjuvant; RT: PTD >2 cm, LVSI+, DSI (any 2 out of 3)

**Table 4:** MRI in predicting adjuvant treatment in stage I B1

MRI (less LN assessment) alone in predicting adjuvant treatment in Stage I B1				
Preoperative triage MRI-Cx and parametria	Required adjuvant RT	No adjuvant RT	Total	
High risk	10	5	15	Sensitivity: 83.33
Low risk	2	11	13	Specificity: 68.75
	12	16	28	PPV: 66.67
				NPV: 84.62
				Accuracy: 75%
MRI including LN assessment alone in predicting adjuvant treatment in Stage I B1				
Preoperative triage MRI including LN	Required adjuvant RT	No adjuvant RT	Total	
High risk	11	4	15	Sensitivity: 91.67
Low risk	1	12	13	Specificity: 75%
	12	16	28	PPV: 72.33
				NPV: 92.31
				Accuracy: 82.1
MRI and LVSI on biopsy in predicting adjuvant treatment in Stage I B1				
Preoperative triage MRI and LVSI	Required adjuvant RT	No adjuvant RT	Total	
High risk	12	5	17	Sensitivity: 100
Low risk	0	11	11	Specificity: 81.25
	12	16	28	PPV: 80
				NPV: 100
				Accuracy: 89.29

staging system.<sup>12</sup> In this study, we demonstrate the possible role of MRI in evaluating two local factors i.e. TD, DOSI, and their utility in preoperative triage of clinical Stage 1 B1 tumors into high and low risk for the requirement of adjuvant CCRT postsurgery.

TD is known to be an independent prognostic factor for parametrial and LN metastasis both of which warrant adjuvant RT after surgery. TD can be assessed preoperatively both during examination and by imaging.<sup>4,13</sup> Kodama et al. have demonstrated a significant correlation between MRI-based and histopathological tumor size in Stage IB1 cervical cancer.<sup>10</sup> Kammimori et al. have also

demonstrated that OPI was not evident with TDs <20 mm making them ideal candidates for surgical treatment.<sup>14</sup> TD has also been studied by many to evaluate the role of less radical surgery by omitting parametrectomy in selected cases of early Ca cervix.<sup>15,16</sup> In our study, there was excellent correlation between the MRI median PTD (1.60 cm) and the median PTD reported on HPE (1.62). The low-risk group did show lower chances of OPM and LN metastasis.

DOSI is another important risk factor for parametrial and LN metastasis, both being definite indications for adjuvant treatment after surgery.<sup>5,17</sup> OPM in final HPR is one of the commonest indications for adjuvant RT in early stage Ca cervix. Both tumor size and deep stromal invasion have been shown to be risk factors for parametrial invasion in many studies especially in presence of LVSI. T2-weighted images in MRI have been used to study tumor size, extent (oblique and sagittal sections), parametrial invasion (oblique axial sections), and DOSI. Recent studies have shown that three-dimensional MRI assessment of cervical tumor is highly accurate and far superior to clinical examination, USG, and CT scan in the evaluation of disease extent.<sup>13,18</sup> Our study has shown that MRI assessment of deep stromal invasion correlated well with the DOSI reported in HPR. Bhatla et al. in the FIGO Cancer report on Ca cervix has endorsed the role of MRI and has proposed an MRI and path-based new staging system for Ca cervix.<sup>12</sup>

Currently, there are ongoing studies (Con cerv study, GOG 278 and SHAPE Trial) evaluating the role of less radical surgery based on the premise that early Ca cervix with low risk of parametrial metastasis may not need extensive parametrial resection, thereby limiting the morbidity.<sup>19–21</sup> Thus, triaging operable early stage Ca cervix to low risk and high risk not only gives an idea regarding the possible requirement of adjuvant RT, thus making it possible to avoid surgery when the risk of OPM and LN metastasis is high (administer primary CCRT) but also opens up the possibility of limiting the radicality of surgery when the perceived risk of parametrial metastasis is low and thereby limiting cost and morbidity without compromising oncological safety. Jung et al. in their study identified a low-risk group of early stage Ca cervix based on a cutoff TD <10 mm with no obvious PMI on MRI where a less radical surgery without parametrial resection was tried as an effective option.<sup>22</sup>

This study has demonstrated that local cervical factors in the form of tumor size and DOSI as assessed by MRI was reasonably accurate and could triage patients into low and high-risk groups based on predicted requirement of adjuvant RT after surgical treatment. MRI can not only prognosticate the requirement of adjuvant treatment after surgery but also has the potential to limit the extent of surgery in low-risk group once favorable evidence is available from the ongoing trials. Combining these findings with the pathological information of LVSI on the tissue biopsy and functional imaging of lymph nodes with PET CT scan would greatly improve the accuracy of the triage. This study was limited by the low numbers, and the possibility of inter observer variation as the MRI and pathological specimens were reported by different clinicians though in the same center. The progression-free survival too has not been monitored.

## CONCLUSION

We have demonstrated that MRI can effectively estimate the tumor size, DOSI, and detect OPM in early stage (Stage I B1) Ca cervix and can further triage them to high- and low-risk groups based on these

findings, which can effectively prognosticate the requirement of adjuvant RT. Combining the MRI findings with LVSI on preoperative biopsy improves the accuracy of triage further. This triage also has the potential for selecting patients for less radical surgery once suitable evidence for the same emerges.

## CLINICAL SIGNIFICANCE

Surgery could be avoided in patients likely to require adjuvant RT by this triage, thus reducing the increased morbidity and cost due to dual modality treatment.

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