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Early Invasive Cervical Cancer:

MRI and CT Predictors of Lymphatic Metastases in the ACRIN 6651 / GOG 183 Intergroup Study

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Abstract

Purpose—To compare MRI, CT, clinical exam and histopathological analysis for predicting lymph node involvement in women with cervical carcinoma, verified by lymphadenectomy.

Methods—A 25-center ACRIN/GOG study enrolled 208 patients with biopsy-proven invasive cervical cancer for MRI and CT prior to attempted curative radical hysterectomy. Each imaging study was interpreted prospectively by one onsite radiologist, and retrospectively by 4 independent offsite radiologists, all blinded to surgical, histopathological and other imaging findings. Likelihood of parametrial and uterine body involvement was rated on a 5-point scale. Tumor size measurements were attempted in 3 axes. Association with histologic lymph node involvement, scored as absent, pelvic only and common iliac or paraaortic, was evaluated using Cochran-Mantel Haenszel statistics, univariate and multivariate logistic regression, generalized estimating equations, accuracy statistics and ROC analysis.

Results—Lymphatic metastases were found in 34% of women; 13% had common iliac nodal metastases, and 9% had paraortic nodal metastases. Based on the retrospective multi-observer re-reads, average AUC for predicting histologic lymph node involvement between MRI and CT for tumor size were higher for MRI versus CT, although formal statistic comparisons could not be

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conducted. Multivariate analysis showed improved model fit incorporating predictors from MRI, but not CT, over and above the initial clinical and biopsy predictors, although the increase in discriminatory ability was not statistically significant.

Conclusion—MRI findings may help predict the presence of histologic lymph node involvement in women with early invasive cervical carcinoma, thus providing important prognostic information.

In women with cervical carcinoma that involves their lymph nodes, surgery alone is not sufficient treatment, and pelvic irradiation will not be curative if the tumor has metastasized to lymph nodes above the irradiated field. Unfortunately, even FDG PET/CT is not sensitive for detecting cervical carcinoma lymphatic metastases that have short axis diameter less than 5 mm.[1] Therefore, prognostic indicators are used to stratify patients based on their risk of having lymphatic metastases.[2-13]

Cross-sectional imaging tests such as CT and MRI are increasingly used to determine the extent of cervical carcinoma, often replacing components of traditional FIGO.[14-17] The recent American College of Radiology Imaging Network (ACRIN) / Gynecologic Oncology Group (GOG) multicenter clinical trial compared the performance of MRI, CT and FIGO clinical staging of invasive cervical cancer, verified by pathologic analysis of hysterectomy specimens.[18-20] Since analysis of hysterectomy specimens is not a perfect predictor of clinical outcome,[2,4,6] the principal aim of our current analysis is to evaluate MRI and CT, using the presence of lymph node metastases diagnosed at hysterectomy and lymphadenectomy (defined throughout this paper as histologic lymph node involvement) as a surrogate of poor clinical outcome among women referred for curative radical hysterectomy. Although final outcome is affected by postoperative adjuvant treatment, recurrence is more likely in women with lymphatic metastases.[4,9,21-32]

METHODS

Each imaging site was required to have a proven record of 20 surgical cases of cervical cancer per year, 1.5 T MRI and helical CT equipment, and an adequately qualified and committed radiologist, gynecologic oncologist, and pathologist. All institutions had study-specific institutional review board (IRB) approval. Between March 2000 and November 2002, 208 participants were accrued from 25 academic and community health centers. Methodology is described in further detail in earlier publications from this trial.[17,18]

Participants

Consecutive participants with untreated biopsy-confirmed cervical cancer who were scheduled for curative hysterectomy based on pre-enrollment FIGO assessment were asked to participate. Imaging findings suspicious for metastatic involvement of lymph nodes (lymph node size greater than 1 cm in the short axis) were permitted to influence the decision to perform surgical biopsy or lymphadenectomy and potentially to cancel plans for radical hysterectomy. The interval between the first protocol imaging study and surgery could not exceed 6 weeks.

Data Acquisition and Analysis

All MRI and CT examinations met or exceeded standards agreed upon by the investigators. Technical parameters are described in greater detail in Hricak et al.[18]

No data were collected on women rejected for surgery on the basis of preoperative imaging findings, or on women who had retroperitoneal dissection only. All women had comprehensive pelvic lymph node dissection, but paraaortic dissection was performed at the discretion of the surgeon. Each surgeon completed a data form specifying the extent of disease found at surgery. Pathologists completed a similar form specifying presence or absence of malignancy in uterus

(including lower uterine segment), parametrium, and lymph nodes in specific left and right anatomic regions, and measured the diameter of the primary tumor on the fixed tumor specimen.

Image Interpretation

One set of MRI and CT data forms were completed prospectively at each site by separate radiologist co-investigators, blinded to results of any other imaging test or clinical/pathology data. Images were then distributed digitally for retrospective multi-reader analysis by a group of eight experts in gynecologic oncology, four each for CT and MR imaging. Individual imaging findings relevant for staging were recorded using a 5-point scale (ranging from 1 = cancer definitely not present to 5 = cancer definitely present), including involvement of cervical stroma, vagina, uterus (lower uterine segment or higher), parametrium, and lymph nodes. If tumor margins could be delineated, tumor size was measured, in 3 axes if possible. The non-tumoral portion of cervix was not included in the diameter measurements. Mean tumor diameter was calculated for tumors when two or 3 diameter axes were measured. Tumors not seen were considered smaller than 1 cm.

Statistical Analysis

Three categories of histologic lymph node involvement were considered: negative (no involvement), low pelvic (not involving common iliac or above), and common iliac (with or without para-aortic). Additionally, binary responses were considered for common iliac histologic lymph node involvement (vs. low pelvic or no involvement), and any histologic lymph node involvement (vs. no involvement).

The association of histologic lymph node involvement and each clinical, pathological or imaging feature, was examined by means of Cochran-Mantel Haenszel (CMH) Statistics, employing the non-zero correlation statistic or the row mean score statistic, as appropriate, on the full ordinal scale. When possible exact p-values were computed and reported, otherwise the asymptotic chi-square approximation was used. These statistics are similar to the well-known chi-square test, but can have greater power to detect certain departures from the null hypothesis of row and column independence for ordinal variables. The Bonferroni procedure was used to account for the 36 multiple comparisons in the association analysis (12 prospective and 24 retrospective), with a P value of 0.0014 or less considered to indicate statistical significance. Additionally the strength and direction of the association was examined using univariate logistic regression models for the above described binary responses of general histologic lymph node involvement and histologic lymph node involvement specific to common iliac nodes, reporting odds ratios and associated 95% confidence intervals. Generalized estimating equations (GEE) were used for the multi-observer re-reads to account for the correlation induced by multiple readings of each case. For the multi-observer re-reads, agreement among readers for each feature was examined on the respective ordinal scale using the multi-rater kappa statistic [33]. Kappa (κ) values can be assessed as follows: $0.00 \leq \kappa < 0.40$ indicates poor agreement; $0.40 \leq \kappa \leq 0.75$, fair to good agreement; and $\kappa > 0.75$, excellent agreement [33].

A significant statistical association between a marker and the outcome of interest, as measured by the above statistics, does not always translate into high discrimination, or classification, accuracy [34]. Therefore, each feature's ability to predict histologic lymph node involvement was also examined by means of the diagnostic probabilities of sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV), as well as by the area under the receiver operating characteristic (ROC) curve (AUC). In calculating ROC AUC, the full respective ordinal scale was employed for each predictor. For the retrospective reads, the average AUC for MRI and CT was compared using the method of DeLong et al. [35], and the

Bonferroni procedure was used to account for the 4 multiple comparisons in this analysis, with a P value of 0.0125 or less considered to indicate statistical significance.

Lastly, a multivariate logistic regression model was employed based on the prospective readings to assess the additive predictive value of MRI and CT findings compared to the clinical assessment and biopsy alone, as follows: First, based on available clinical and biopsy predictors, selection procedures (forward, backward, and stepwise) were employed to help arrive at a parsimonious multivariate logistic regression model which adequately fit and explained the data. Goodness of fit was assessed via the Hosmer-Lemeshow test and adequacy of the reduced model was assessed via an appropriate likelihood ratio test. Once the baseline clinical model was determined, the MRI predictors of parametrial invasion, uterine involvement and average tumor size were added to the baseline clinical model and their joint significance tested via a likelihood ratio test. This step was then repeated separately for the CT predictors. For each modality, a formal comparison of the C-statistic (which is equivalent to the AUC derived using the predicted values from the model) between the baseline clinical model and the baseline clinical model plus imaging was also performed using the test statistic proposed by DeLong et al. [35]

RESULTS

A more detailed description of this patient cohort and multiobserver analysis is described in prior publications [18-20], and summarized in Appendix 1. Surgical and pathological tumor characteristics are summarized in Table 1. A representative case is illustrated in Figure 1.

Surgico-Pathologic Lymph Node Data and Patient Outcome

Surgical and pathological data regarding histologic lymph node involvement were missing or incomplete in 11 of the 172 women, including the 3 who had aborted hysterectomy. Lymph node involvement was found pathologically in 55 of the remaining 161 women (34%). Of these 55 women with histologic lymph node involvement, 14 (25%) had common iliac and para-aortic involvement, 7 (13%) had common iliac but not paraortic involvement (high pelvis), and 34 (62%) had metastases restricted to the low pelvis.

N-staging by prospective imaging, scored as presence or absence of metastases at any site, showed 37% and 31% sensitivity, respectively, for both MRI and CT (not significantly different). Specificity was significantly higher for MRI (94%) than CT (86%), with a difference contrast of 0.09 (95% CI: 0.02, 0.15).

Tumor Size

Prospective readings—Average tumor diameter by pathology was less than 1 cm in 33 women (19%), 1-2 cm in 47 (27%), 2-3 cm in 32 (19%), 3-4 cm in 11 (6%), greater than 4 cm in 11 (6%), and unresolved or unavailable in 38 women (22%); these 38 women were excluded from analysis of tumor size by exam and imaging.

Tumor size could be measured by MRI in 153 (89%) women, compared with 126 (73%) by CT. Considering only cases where measurements were recorded, significant associations were detected between histologic lymph node involvement and average tumor size for MRI ($p=0.0001$) and clinical assessment ($p=0.0002$). After adjusting for multiple comparisons, no significant association was found for CT ($p=0.007$) or pathology ($p=0.01$). Estimated odds ratios, diagnostic probabilities and ROC AUCs are shown in Table 2.

Retrospective multi-observer readings—The multirater kappa statistic for CT was 0.35, and for MRI was 0.46. All data for the multi-observer readings are summarized in Table 3.

There was no significant association between histologic lymph node involvement and average tumor size for any of the 4 CT readers (p=0.07, 0.50, 0.55, 0.73), and odds ratios were near unity for both general lymph node involvement and lymph node involvement specific to the common iliac nodes. After adjusting for multiple comparisons, one of the four MRI multi-observer re-readers demonstrated a significant association between histologic lymph node involvement and average tumor size (p=0.0005; 0.005, 0.01, 0.02). Odds ratios for average tumor size and corresponding 95% confidence intervals, along with average ROC AUC, for both MRI and CT are shown in table 3. Average AUC was higher for MRI than for CT (table 3), but could not be compared statistically because too few CT readers recorded measurements. [19]

Parametrial Extent

Prospective readings—By pathology, parametrial extent was bilateral in 6 (3%), unilateral in 9 (5%), absent in 123 (72%), and unknown or data unavailable by pathology in 34 (20%) women. A significant association was detected between histologic lymph node involvement and parametrial invasion, as detected by pathology (p=0.0011). After adjusting for multiple comparisons, the corresponding associations for MRI (p=0.02), CT (p=0.01) and clinical assessment (p=0.05) were not significant. Estimated odds ratios, accuracy statistics and ROC AUC were similar for each method for unilateral/bilateral invasion versus no invasion (Table 4), as well as for bilateral parametrial involvement versus unilateral or no parametrial involvement (results not shown).

Retrospective multi-observer readings—The multirater kappa statistic, averaged over left and right sides, was -0.04 for CT and 0.11 for MRI.[20] After adjusting for multiple comparisons, no significant associations between presence of histologic lymph node involvement and parametrial invasion (as determined by imaging) were detected for any of the 4 CT readers (p=0.006, 0.51, 0.71, 0.94). For MRI, a significant association was detected for 1 of the 4 readers (p=0.0002; 0.01, 0.05, 0.12). Odds ratios for parametrial invasion and corresponding 95% confidence intervals, along with average ROC AUC, for both MRI and CT are shown in Table 3. There was no significant difference in average AUC between MRI and CT for detection of histologic lymph node involvement specific to the common iliac nodes (p=0.10). Average AUC of parametrial involvement for detection of general histologic lymph node involvement was not significantly different for MRI versus CT, after adjusting for multiple comparisons (p=0.04).

Uterine Involvement

Prospective readings—Uterine involvement (lower uterine segment or higher) was present pathologically in 32 (19%), absent in 101 (59%), and unknown or data unavailable by pathology in 39 (23%) women. Histology was squamous in 19 of the 32 (59%) women with uterine involvement, compared with 73 of 101 (72%) without uterine involvement (p=0.17). Among tumors with available nonzero measurements, mean tumor size by pathology was 2.6 +/- 1.3 cm for the 28 tumors with versus 1.8 +/- 0.9 cm for the 82 tumors without uterine involvement (p=0.0046). The 32 women exhibiting uterine involvement included 7 of the 10 who had histologically involved common iliac nodes and available pathologic data (4/4 common iliac and paraaortic, 3/6 common iliac only). A significant association existed between histologic lymph node involvement and uterine involvement, as determined both by pathology (p=0.0001) and clinical assessment (p=0.0002).

Among women with available pathological material, prospective MRI readers considered the uterus definitely involved in 16, including 7 (50%) of the 14 women with histologically involved common iliac nodes, compared with 9 (6%) of the 147 who did not have involved common iliac nodes. CT prospective readers considered the uterus definitely involved in only

7 women overall, including 2 (14%) of 14 with involved common iliac nodes and 5 (3%) of 146 who did not have involved common iliac nodes. For both, MRI (p<0.0001) and CT (p=0.0004), a significant association was detected between histologic lymph node involvement and uterine involvement.

Estimated odds ratios, accuracy statistics and ROC AUC are shown in Table 5. The largest odds ratios for histologically involved common iliac nodes were observed for MRI and pathologic assessment, and the lowest for clinical assessment. The AUCs were similar for all modalities.

Retrospective multi-observer re-reads—The multirater kappa statistic was -0.09 for CT and 0.10 for MRI. After adjusting for multiple comparisons, there was no significant association between histologic lymph node involvement and uterine involvement for any of the 4 CT readers (p=0.009, 0.01, 0.13, 0.90). A significant association was demonstrated for 1 of the 4 MRI readers (p=<0.0001, p=0.003, p=0.03, p=0.05). Odds ratios for uterine involvement and corresponding 95% confidence intervals, along with average ROC AUC, for both MRI and CT are shown in Table 3. None of the CT readers recorded a maximum grade of 5 (definitely present) for uterine involvement for any women with histologically involved common iliac nodes, and thus odds ratios could not be computed. The odds ratio for CT for general histologic lymph node involvement was close to unity. For MRI, women with a maximum grade of 5 for uterine involvement by MRI had an almost 6-fold increase in the odds of histologically involved common iliac nodes, and a more than 3-fold increase in the odds of histologic lymph node involvement in general (Table 3). However, there was no significant difference in average AUC between MRI and CT for detection of histologic lymph node involvement, either in general (p=0.63), or specific to the common iliac nodes (p=0.16).

Multi-variate analysis

The multivariate analysis of histologic lymph node involvement utilized the 161 cases with available lympadenopathy status. Histologically involved common iliac nodes could not be separately analyzed, as too few events resulted in model non-convergence.

The final baseline clinical model included the following covariates: tumor size by clinical exam, stromal invasion and cell type by histology, age, and race; as well as the following interactions: Age by race, age by clinical tumor size, and age by cell type. The likelihood ratio test compared with the full model was not significant at the 0.05 level (p=0.51), arguing for adequacy of the reduced model. Also, there was no demonstrable lack of fit at the 0.05 level (p=0.73). Thus, this was considered to be a parsimonious model based only on biopsy and clinical predictors which adequately fit and explained the data.

Adding the desired CT predictors of tumor size (>3 cm, <=3 cm), parametrial invasion (absent, unilateral/bilateral), and uterine involvement (5:Definitely present, <5) to the baseline clinical model demonstrated no improvement in model fit based on the likelihood ratio test (p=0.60), and no significant difference in the C-statistic (p=0.94).

Adding the same predictors as determined by MRI to the baseline clinical model did demonstrate a significant improvement in model fit based on the likelihood ratio test (p=0.01). Therefore, a multivariate logistic regression model consisting of biopsy and clinical plus MRI predictors was developed. The sole significant MRI predictor was tumor size, where women with average size >3 cm demonstrated greater odds of histologic lymph node involvement versus those with size <=3 cm, even after adjusting for biopsy and clinical predictors (OR 4.4; 95% CI: 1.8, 11.2). Additionally, the final model including clinical and MRI predictors showed good discriminatory ability (AUC=0.82; 95% CI: 0.75, 0.88). However, the increase in the C-statistic when MRI was added to the baseline clinical model was not significant (AUC increased

from 0.79 to 0.82; p=0.21). These results show that the final model including MRI predictors leads to improved model fit, yet these MRI predictors were not shown to significantly increase the ability of the model to classify participants with or without the outcome compared to the clinical and biopsy predictors alone. However, given the improved model fit, of the two models in question, preference would be given to the final model including MRI predictors.

COMMENT

Most evaluations of cross-sectional imaging have assessed its accuracy compared with a pathologic reference standard. However, the radical surgical specimen is not available for preoperative clinical decision making, and the pathological findings are far from perfect in predicting clinical outcome. [2,4,6] It is therefore important to study diagnostic methods that can be utilized prior to and during clinical treatment, and to verify these methods based on clinical outcome whenever possible. For cervical cancer, predictors of lymphatic involvement are particularly important with regard to eventual outcome.

The ACRIN-6651/GOG-183 multicenter trial showed that MRI had higher agreement with pathology than CT or clinical examination for delineating tumor margins and measuring tumor size.[19] This trial also provides an opportunity to use histologic lymph node involvement as determined by radical hysterectomy and retroperitoneal lymphadenectomy tissue as an indicator of unexpected adverse clinical outcome. Of the 161 women with invasive cervical carcinoma treated for cure with radical hysterectomy and lymphadenectomy, unsuspected histologic lymph node involvement was found in 55 (34%); 21 (13%) had common iliac nodal metastases, and 14 (9%) had paraortic nodal metastases. Unfortunately, incomplete follow-up limited the value of our data regarding disease recurrence.

We found that pathology and MRI had similar ability to predict lymphatic metastases based on measurement of tumor size and uterine involvement. Our finding that less than half of tumors could be measured by CT retrospective readers due to poor delineation limits the potential utility of CT for measuring tumor size. The predictive ability of clinical exam for histologic lymph node involvement based on tumor size and parametrial involvement was similar to that of MRI, but MRI agrees more with pathologic measurement of tumor size, suggesting that MRI may have more potential value for treatment planning. [19] MRI is also more effective for determining uterine involvement [19]; evaluation of uterine extent may be a particular additive benefit of MRI. Analysis of these benefits of MRI versus its additive cost relative to clinical exam alone is beyond the scope of this investigation.

For MRI and CT, we were able to obtain multi-observer data in addition to the primary prospective readings, but could only evaluate the primary single-observer data for clinical and pathological assessment. Another important limitation was enrollment of women based on the expected availability of hysterectomy specimens for pathologic confirmation. This selection bias reduced the number of large or advanced tumors included, but our population of early cervical cancer is clinically important. Our ability to evaluate the association between parametrial involvement and histologic lymph node involvement was limited, since only 15 (9%) of women selected had parametrial involvement.

In conclusion, the ACRIN-6651/GOG-183 intergroup multicenter trial in women with early invasive cervical carcinoma showed unsuspected histologic lymph node involvement in 34% of radical hysterectomy specimens. Based on the retrospective multi-observer re-reads, after adjusting for multiple comparisons, there was no difference in average AUC for detection of histologic lymph node involvement between MRI and CT for parametrial invasion or uterine involvement. For tumor size, the estimates of average AUC were higher for MRI versus CT, although formal statistic comparisons could not be conducted. Lastly, we found improved

model fit incorporating MRI predictors, but not CT, over and above the initial clinical and biopsy predictors. Our final multivariate model including MRI predictors demonstrated good discriminatory ability (AUC = 0.82), although the increase in discriminatory ability was not statistically significant (p=0.21). This may suggest that future studies to determine how imaging features could best be used to alter patient management based solely on FIGO criteria may be useful.

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Appendix 1

Patient Cohort and Data Related to the Primary Aim

Of the 208 participants enrolled, 9 (4%) were deemed ineligible because of enrollment disqualifications. Of the remaining 199 participants, 27 (14%) were excluded because of missing or incomplete data; thus 172 (83%) participants were included in the final analysis of prospective readings. Hysterectomy was abandoned in three of the 172 women, but detailed descriptions of surgical findings were provided. Lymphadenectomy was performed for 91% of women on the right, and for 92% on the left. There were no significant differences between the eligible and analysis sets of patients regarding demographics or clinical characteristics (data not shown).

Data Related to the Blinded Multi-observer Study

Separate analysis sets were defined for MRI and CT to maximize the sample size for each modality. For CT, 29 cases from the primary analysis set were excluded from the retrospective multi-observer study because of incomplete submission of digital image data. However, 3 cases excluded from the primary analysis set, due to lack of MRI imaging (n=2) or non-submission of local site CT interpretation data (n=1), had pathology reference standard information and could be included in the CT multi-observer analysis set, thus arriving at 73% (146/199) analyzable cases.

For MRI, 22 cases from the primary analysis set similarly were excluded in the multi-observer study, but 2 cases excluded in the primary analysis set could be included in the MRI multi-observer analysis set, thus arriving at 76% (152/199) analyzable cases.

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Figure 1.

Grade 3 poorly differentiated adenosquamous carcinoma with deep cervical invasion, left parametrial invasion, invasion of lower uterine segment, and positive paraaortic lymphadenopathy. Clinical assessment was FIGO stage IIA with estimated tumor diameter of 3.5 cm, and no involvement of uterus or parametrium. Average size by CT was 2.8 cm. Lower uterine segment was considered not involved by 3 CT readers, and possibly involved by one CT reader; parametrium was considered not involved by all CT readers. By MRI, tumor size was 3.7 cm; parametrial and uterine involvement were both considered definite by 3 MRI readers, and indeterminate by one. Lymph nodes were considered involved by 3 MRI readers but by no CT readers.

A. Transverse CT image shows tumor in cervix, without visible parametrial extent.

B. Transverse T2-weighted MR image shows tumor in cervix. Low signal stroma is intact surrounding most of tumor, but there is some indistinctness at the left anterior margin (arrow) suggesting parametrial spread.

C. Sagittal T2-weighted MR image shows tumor extension into lower uterine segment (arrows).

Table 1

Summary of Histological and Surgical Findings

	Count	Percent
Histologic Type		
Squamous	124	72%
Adenocarcinoma	38	22%
Other	10	6%
Histologic Differentiation		
Well	23	13%
Moderate	52	30%
Poor	63	37%
Unknown	34	20%
Pathologic average tumor size		
Data unavailable	38	22%
<1 cm (or tumor not seen)	33	19%
[1,2] cm	47	27%
(2,3] cm	32	19%
(3,4] cm	11	6%
>4 cm	11	6%
Pathologic parametrial invasion		
Unknown or data unavailable	34	20%
Absent	123	72%
Unilaterally positive	9	5%
Bilaterally positive	6	3%
Pathologic uterine involvement		
Unknown or data unavailable	39	23%
Negative	101	59%
Positive	32	19%
Histologic lymph node involvement		
Data unavailable	11	6%
Positive para-aortic	14	8%
Positive common iliac nodes (without para-aortic)	7	4%
Positive other nodes (without para-aortic or common iliac)	34	20%
Negative	106	62%
Total	**172**	**100%**

Table 2

Odds ratios from univariate logistic regression models for average tumor size, using a threshold of >3 cm versus <=3 cm, by modality based on the prospective reads, along with the estimated diagnostic probabilities and ROC AUC for detection of histologic lymph node involvement

Response	Modality	Odds ratio (95% CI)	NPV	PPV	Sensitivity	Specificity	AUC (SE)
Histologic lymph node involvement specific to common iliac (with or without paraaortic nodes	MRI	4.1 (1.5, 11.5)	0.93	0.22	0.61	0.72	0.70 (0.06)
	CT	2.7 (1.1, 7.0)	0.91	0.22	0.57	0.67	0.63 (0.07)
	Clinical	7.4 (2.5, 21.6)	0.95	0.27	0.75	0.71	0.73 (0.06)
	Pathologic	1.4 (0.3, 7.4)	0.93	0.09	0.22	0.83	0.64 (0.08)
General histologic lymph node involvement (Any positive node)	MRI	4.6 (2.2, 9.5)	0.78	0.57	0.54	0.80	0.68 (0.04)
	CT	2.3 (1.2, 4.7)	0.72	0.48	0.49	0.71	0.63 (0.05)
	Clinical	4.0 (2.0, 8.0)	0.77	0.55	0.56	0.76	0.64 (0.05)
	Pathologic	3.0 (1.2, 7.6)	0.75	0.50	0.29	0.88	0.62 (0.05)

Table 3

Odds ratios from univariate logistic regressions models employing generalized estimating equations for the features of average tumor size, parametrial invasion and uterine involvement by modality based on the retrospective multi-observer readings, along with average ROC AUC and range over the readers for detection of histologic lymph node involvement. Thresholds used were for average tumor size >3cm versus <=3cm; for parametrial invasion bilateral or unilateral invasion versus no invasion; for uterine involvement 5:Definitely present versus <5

Response	Modality	Tumor size		Parametrial involvement		Uterine involvement	
		Odds ratio (95% CI)	Average ROC AUC (range)	Odds ratio (95% CI)	Average ROC AUC (range)	Odds ratio (95% CI)	Average ROC AUC (range)
Histologic lymph node involvement specific to common iliac nodes	MRI	2.8 (1.2, 6.5)	0.66 (0.63 - 0.69)	2.7 (1.2, 6.1)	0.60 (0.54 - 0.70)	5.7 (2.0, 16.6)	0.66 (0.58 - .79)
	CT	1.1 (0.3, 3.3)	0.54 (0.42 - 0.64)	1.4 (0.5, 4.0)	0.51 (0.49 - 0.55)	None recorded[1]	0.57 (0.46 - .66)
General histologic lymph node involvement (Any positive node)	MRI	2.5 (1.3, 4.7)	0.63 (0.61 - 0.65)	2.5 (1.3, 4.7)	0.58 (0.54 - 0.62)	3.1 (1.2, 8.3)	0.57 (0.54 - .60)
	CT	1.1 (0.6, 2.3)	0.55 (0.50 - 0.61)	1.5 (0.7, 3.2)	0.52 (0.50 - 0.54)	1.1 (0.2, 6.1)	0.58 (0.54 - .63)

[1] Odds ratio could not be estimated as none of the cases which had para-aortic or common iliac metastases were coded as uterine involvement definitely present by any of the CT readers.

Table 4

Odds ratios from univariate logistic regression models for parametrial invasion by modality based on the prospective reads, along with the estimated diagnostic probabilities and ROC AUC for detection of histologic lymph node involvement. Threshold was bilateral or unilateral invasion versus no invasion

Response	Modality	Odds ratio (95% CI)	NPV	PPV	Sensitivity	Specificity	AUC (SE)
Histologic lymph node involvement specific to the common iliac nodes	MRI	1.9 (0.7, 5.0)	0.89	0.19	0.38	0.76	0.58 (0.06)
	CT	3.9 (1.4, 11.0)	0.90	0.29	0.35	0.88	0.61 (0.06)
	Clinical	3.7 (0.6, 21.8)	0.88	0.33	0.1	0.97	0.54 (0.04)
	Pathologic	7.6 (1.8, 31.5)	0.95	0.29	0.40	0.92	0.66 (0.08)
General histologic lymph node involvement (Any positive node)	MRI	2.9 (1.4, 5.9)	0.72	0.52	0.40	0.81	0.61 (0.04)
	CT	2.7 (1.1, 6.5)	0.70	0.54	0.24	0.90	0.57 (0.03)
	Clinical	4.2 (0.7, 23.7)	0.68	0.67	0.08	0.98	0.53 (0.02)
	Pathologic	9.5 (2.7, 32.8)	0.79	0.71	0.29	0.96	0.62 (0.04)

Table 5

Odds ratios from univariate logistic regression models for uterine involvement by modality based on the prospective reads, along with the estimated diagnostic probabilities and ROC AUC for detection of histologic lymph node involvement, using a threshold of 5:Definitely present versus <5

Response	Modality	Odds ratio (95% CI)	NPV	PPV	Sensitivity	Specificity	AUC (SE)
Histologically involved common iliac nodes	MRI	10.2 (3.3, 31.5)	0.91	0.50	0.38	0.94	0.71 (0.07)
	CT	6.0 (1.2, 29.1)	0.89	0.43	0.15	0.97	0.71 (0.06)
	Clinical	3.4 (0.3, 39.3)	0.87	0.33	0.05	0.98	0.71 (0.07)
	Pathologic[1]	8.7 (2.1, 36.0)	0.97	0.22	0.7	0.79	-
General histologic lymph node involvement (Any positive node)	MRI	2.8 (0.97, 7.9)	0.68	0.56	0.16	0.93	0.60 (0.05)
	CT	2.7 (0.6, 12.7)	0.67	0.57	0.07	0.97	0.63 (0.05)
	Clinical	0.9 (0.1, 10.4)	0.65	0.33	0.02	0.98	0.60 (0.05)
	Pathologic[1]	3.4 (1.4, 8.0)	0.81	0.44	0.44	0.81	-

[1]For Pathology, the odds ratio is computed as those women with uterine involvement as determined by pathology versus those women without.