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Original Article

Correlation of MRI-detected extramural vascular invasion with regional lymph node metastasis in rectal cancer☆,☆☆

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ABSTRACT

Aim: To evaluate the value of magnetic resonance imaging-detected extramural vascular invasion (MR-EMVI) in predicting regional lymph node metastasis (RLNM) in patients with rectal cancer.
Methods: A total of 183 patients were included. A set of clinical and imaging factors including MR-EMVI were evaluated using univariate and multivariate analyses to determine the risk factors for RLNM.
Results: Among the clinical and imaging factors evaluated, MR-EMVI, pathologic EMVI, nodal size, and diffusion-weighted imaging-detected positive nodes were independent predictors of RLNM.
Conclusions: MR-EMVI may be an independent predictor of RLNM in patients with rectal cancer.

1. Introduction

Approximately 50% of patients with rectal cancer will have regional lymph node metastasis (RLNM) at the time of surgery [1–3], and the challenge in these cases is the high local regional recurrence rate after resection [4]. Randomized trials have proven that preoperative neoadjuvant therapy (NAT) for patients with RLNM reduced the risk of local and regional recurrence by 50% [5,6]. However, NAT is associated with serious side effects, such as drug toxicity, encopresis, and sexual dysfunction [7–9]. Therefore, accurate evaluation of nodal status is vital for selecting patients who would benefit most from NAT and simultaneously excluding ineligible cases to avoid the unnecessary side effects.

Unfortunately, there is no reliable imaging technique to detect RLNM for treatment decision making [10]. Although nodal size is the most frequently used criterion for the prediction of nodal status, its performance has been unsatisfactory with reported overall accuracy of only 50%–70% [10–12]. In addition, some researchers attempted to predict nodal status by evaluating a spectrum of functional magnetic resonance imaging (MRI) parameters, from diffusion-weighted imaging (DWI) to dynamic-enhanced imaging; however, these studies did not achieve improved results due to the small size of positive lymph nodes and the low spatial resolution of the images [13–16]. Therefore, new methods and factors that can detect or predict RLNM before surgery need to be studied.

Extramural vascular invasion (EMVI) in rectal cancer is pathologically defined as active invasion by tumor cells of blood vessels beyond the outer limits of the muscularis propria [17,18]. Recently, some studies have shown that EMVI could be evaluated using high-resolution MRI before surgery [17,19]. In addition, pathologic EMVI (P-EMVI), T stage, and differentiation were considered as potential risk factors for RLNM [20,21]. However, the value of MRI-detected EMVI (MR-EMVI) as a predictor of RLNM has not been determined. If proven so, MR-EMVI may serve as a preoperative marker that could influence selection of patients for NAT. Therefore, we retrospectively analyzed the MR images and clinical data of a group of patients with rectal cancer to evaluate whether MR-EMVI could independently predict RLNM.

2. Materials and methods

2.1. Patients

The institutional review board of our hospital approved the protocols for data collection and analysis; informed consent was waived because this was a retrospective study. A search of the electronic patient record system of our hospital was performed. From December 2011 to December 2014, 243 rectal cancer patients underwent resection without NAT in the hospital. Among them, patients with rectal mucinous carcinoma were excluded ($n = 17$) because of its different biologic behavior. Other exclusion criteria were previous history of malignancy ($n = 8$), palliative surgery ($n = 19$), incomplete pathologic data

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($n=5$), and missing MR images ($n=11$). Finally, 183 rectal cancer patients (115 men and 68 women) were included in this study population.

2.2. MR scan protocol

MRI was performed using a 3.0-T system (Signa Excite HD 3.0 T; GE Healthcare, Milwaukee, WI, USA) that was used with phased-array surface coil. Bowel preparation, intravenous contrast enhancement, and intravenous antispasmodic agents were not mandatory. The following pulse sequences were observed in this study: (1) fast spin-echo sagittal high-resolution T_2-weighted imaging (HRT2WI) with a thickness of 4 mm, intersection gap of 1 mm, repetition time/echo time (TR/TE) of 4000 ms/102 ms, matrix size of 320×256, echo train length (ETL) of 16, number of excitation (NEX) of 4, and without fat saturation; (2) axial (perpendicular to the long axis of the rectum) HRT2WI with 3-mm contiguous section thickness, TR/TE of 4000 ms/102 ms, field of view (FOV) of 16×16 cm, matrix size of 320×256, ETL of 16, NEX of 4, and without fat saturation; and (3) axial DWI with a thickness of 5 mm, interval of 10%, TR/TE of 4000 ms/90 ms, matrix size of 128×128, FOV of 35×35 cm, NEX of 4–8, direction all, $b=0$, and 1000 s/mm^2.

2.3. Imaging interpretation

To detect EMVI, the images from HRT2WI were mainly reviewed by two radiologists with 6 and 8 years of experience, respectively, in abdominopelvic MRI diagnosis. When there were inconsistencies in their diagnoses, a third radiologist with >15 years of experience in gastrointestinal imaging decided on the final diagnosis. Measurement of nodal size on HRT2WI and prediction of nodal status on DWI were performed by the third radiologist. All radiologists knew the entry criteria for this study, but they were blinded to the pathologic stage or P-EMVI status of the patients. Before the review, the radiologists were trained together to familiarize them with the diagnostic imaging criteria of EMVI and lymph node involvement.

2.3.1. EMVI detection on HRT2WI

MR-EMVI was considered to be present when any one of the following imaging features was noted: (1) the tumor penetrated the rectal wall and invaded at least one extramural vascular structure or (2) the tumor signal, apart from the primary lesion, appeared within an extramural vascular structure. The method described by Smith et al. [17,19] was used to evaluate the likelihood of EMVI on MRI.

2.3.2. Measurement of nodal size

To determine nodal size, the radiologist measured the short axis of the largest visible mesorectal lymph node on axial HRT2WI. The short axis was measured to the nearest millimeter. If no visible node was observed, nodal size was recorded as zero.

2.3.3. DWI detection of positive node (DWI-LN)

A positive lymph node status was defined as at least one node with high-signal intensity on the b1000 images, similar to the signal of the primary tumor. If no high-signal intensity lymph node was detected, nodal status was recorded as negative.

2.4. Surgery and clinicopathologic assessment

Radical surgery, according to the principles of total mesorectal excision, was performed within 1 month after MRI scan. The specimens were fixed in formalin solution for at least 48 h after operation before transversely slicing (i.e., perpendicular to the long axis of the rectum) at 3-μm thickness. Clinicopathologic factors, including T stage (behalf of local invasion depth), nodal status, differentiation, tumor size, and P-EMVI, were examined and recorded. Tumors were staged according to the seventh edition of the TNM system [22] and were classified as well differentiated, moderately differentiated, or poorly differentiated. Tumor size was recorded as the longest diameter of the whole specimen. The presence of EMVI was confirmed when tumor tissue was present within an extramural space or within a tubular structure that was lined by endothelial cells, smooth muscles, or elastic fibers [23]. All histopathologic examinations were performed by a pathologist with 17 years of experience in colorectal pathology.

2.5. Statistical analysis

The diagnostic accuracy of HRT2WI for preoperative EMVI detection was measured by comparison with P-EMVI. Interobserver agreement for evaluating the likelihood of EMVI was evaluated using kappa calculation ($\kappa<0.40$, poor agreement; $\kappa=0.40$–0.60, moderate agreement; $\kappa=0.60$–0.80, good agreement; and $\kappa>0.80$, perfect agreement). Next, patients were classified into node-negative and node-positive groups, according to the histopathologic results. Correlations of clinical factors (age, gender, T stage, differentiation, tumor size, and P-EMVI) and imaging features (MR-EMVI, nodal size, and DWI-LN) with RLNM were calculated using chi-square test or t test. Statistically significant variables from the univariate analysis were evaluated using multivariate logistic regression to identify independent predictors for RLNM. Receiver operating characteristics (ROC) curve analyses were performed to determine the diagnostic performance of MR-EMVI, nodal size, and DWI-LN for predicting RLNM. Corresponding areas under the ROC curve (A_Z), sensitivities, specificities, and overall accuracies with 95% confidence intervals (CIs) were calculated. Differences in diagnostic performance between MR-EMVI and nodal size, as well as between MR-EMVI and DWI-LN, were assessed by comparing the A_Z values with a method described by Hanley and McNeil [24].

Statistical significance was set at $P<0.05$. All statistical analyses were performed using MedCalc 12.0 (MedCalc Inc., Ostend, Belgium).

Table 1
Patients' characteristics and correlations of clinic pathological factors and imaging features with nodal metastasis

	Total ($n=183$)	Nodal metastasis		P value
		Negative ($n=105$; 57.4%), n (%)	Positive ($n=78$; 42.6%), n (%)	
Age (year)[a]	57.0±10.4	58.3±10.2	55.2±10.5	0.798
Gender				0.056
Male	115 (62.8)	65 (56.5)	50 (43.5)	
Female	68 (37.2)	40 (58.8)	28 (41.2)	
T stage				0.001
T1	15 (8.2)	15 (100)	0 (0)	
T2	41 (22.4)	27 (65.8)	14 (34.2)	
T3	108 (59.0)	56 (51.9)	52 (48.1)	
T4	19 (10.4)	7 (36.8)	12 (63.2)	
Tumor size (cm)[a]	3.92±1.75	3.71±1.63	4.19±1.88	0.077
P-EMVI				<0.001
Negative	136 (74.3)	95 (69.9)	41 (30.1)	
Positive	47 (25.7)	10 (21.3)	37 (78.7)	
Differentiation				0.044
Well	24 (13.1)	12 (50.0)	12 (50.0)	
Moderately	134 (73.2)	73 (54.8)	61 (45.2)	
Poorly	25 (13.7)	20 (80.0)	5 (20.0)	
MR-EMVI				<0.001
Negative	130 (71.0)	92 (70.8)	38 (29.2)	
Positive	53 (29.0)	13 (24.6)	40 (75.4)	
Nodal size (mm)[a]	5.08±3.76	3.86±3.13	6.73±3.92	<0.001
DWI				<0.001
Negative	91 (49.7)	65 (71.4)	26 (28.6)	
Positive	92 (50.3)	40 (43.5)	52 (56.5)	

Data in parentheses: percentage; P-EMVI: pathologic extramural vascular invasion; MR-EMVI: magnetic resonance imaging-detected extramural vascular invasion; DWI: diffusion-weighted imaging.

[a] Data are mean±standard deviation.