ORIGINAL PAPER

MRI Evaluation of Extramural Venous Invasion (EMVI) with Rectal Carcinoma Using High Resolution T2 and Combination of High Resolution T2 and Contrast Enhanced T1 Weighted Imaging

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doi: 10.5455/aim.2021.29.113-117
ACTA INFORM MED. 2021 JUN 29(2): 113-117
Received: Apr 12, 2021
Accepted: Jun 17, 2021

ABSTRACT

Background: EMVI is a direct invasion of a vein by a tumor. As a predictor of hematogenous metastasis, it is a poor prognostic factor in rectal cancer and can be accurately identified on MRI prior to surgical procedure. **Objctive:** To evaluate the role of contrast-enhanced T1-weighted magnetic resonance imaging (CET1WI) in addition to high-resolution T2-weighted imaging (HRT2WI) in assessing extramural venous invasion (EMVI) of rectal cancer. **Methods:** In all 195 patients with rectal cancer, HRT2WI and CET1WI sequences were produced within pre-operative MRI for the purpose of assessing for the presence of EMVI (mrEMVI). CET1WI sequences were produced following administration of Gadolinium contrast medium. mrEMVI assessment results were classified into two groups. Group A consisted of mrEMVI assessment results obtained using HRT2WI sequences only. Group B consisted of mrEMVI assessment results obtained using a combination of HRT2WI + CET1WI sequences. Results obtained for each group (A and B) were correlated with a histopathological finding (pEMVI) as a reference standard. **Results:** Out of a total of 195 rectal cancer patients, mrEMVI was positive in 41 (21%) patients in group A, and in 45 (23%) patients in group B. Histopathological finding demonstrated pEMVI in 54 (27.7%) patients. A statistical analysis of group A (HRT2WI sequences) resulted in 75.9% sensitivity to mrEMVI and 96.4% specificity, Positive Predictive Value of 89.1% and Negative Predictive Value of 91.2% (95% confidence interval (CI), p< 0.05). Statistical analysis of group B (HRT2WI + CET1WI sequences) resulted in 83.3% sensitivity to mrEMVI and 98.5% specificity, Positive Predictive Value of 89.1% and Negative Predictive Value of 91.2% (CI 95%, p< 0.05). **Conclusion:** T1-weighted magnetic resonance imaging (CET1WI) in addition to high-resolution T2-weighted imaging (HRT2WI) increased evaluation of extramural venous invasion (EMVI) of rectal cancer.

Keywords: extramural venous invasion, EMVI, rectal carcinoma, MRI.

1. BACKGROUND

From the viewpoint of surgical oncology, rectal cancers are considered a particular problem amongst the colorectal malignancies (1). MRI is an important tool in pre-operative assessment of rectal carcinoma (2). MRI finding of rectal carcinoma includes the estimation of tumor size and location, and its relationship to the mesorectal fascia (MRF) and anal sphincters. MRI assessment also implies insight into extramural spread (T stage), peritoneal reflection, lymph node involvement, presence of bone metastases and extramural venous invasion (EMVI) (3, 4).

As a direct invasion by tumor, EMVI ought to be an integral part of every histopathology report (pEMVI), even though it is not included in TNM staging. It is defined as tumor lying within an endothelium-lined space that is either surrounded by a rim of muscle or contains red blood cells. If tumor has obliterated the lumen of a vein, an elastic stain may highlight the wall, confirming a rounded structure as a vein (5) (Figure 1 and Figure 2).

As a predictor of hematogenous metastasis, EMVI is a poor prognostic factor in rectal cancer and can be accurately identified on MRI, pre-operatively (6-9). mrEMVI is seen as tubular or serpiginous projections of intermediate signal intensity, which follows a

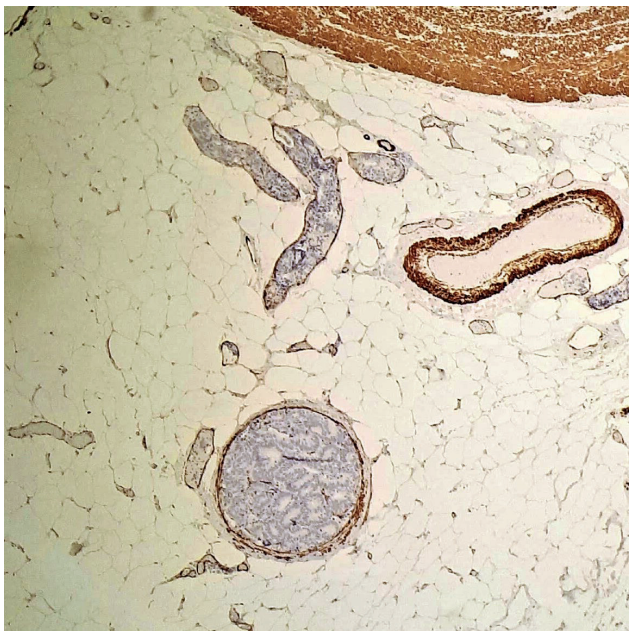

Figure 1. SMAx20: intestinal wall, empty artery of thicker wall, thin wall veins filled with tumor tissue.

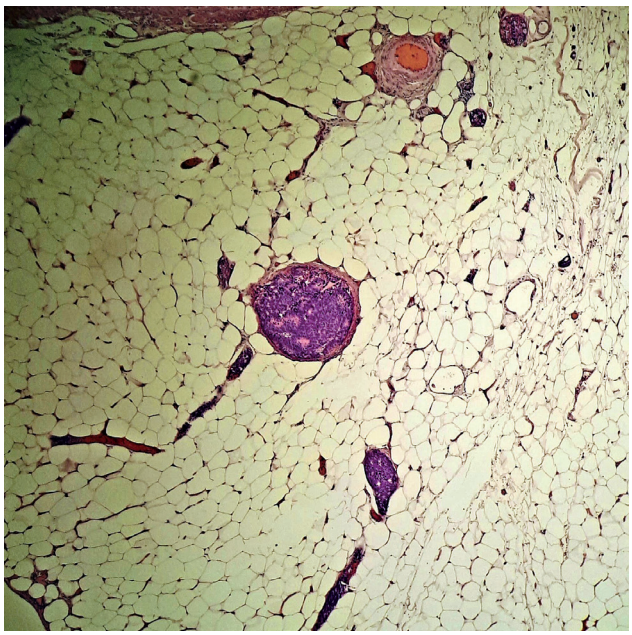

Figure 2. CD34x20–eosinophilic beads

course of a perirectal vein. It may be either directly contiguous with the tumor or non-contiguous. An initial mrEMVI is important in patient stratification for selection of an appropriate treatment, especially for administration of an adjuvant therapy (10). The presence of EMVI on pre-treatment MRI has been associated with a four-fold increase in risk of distant metastases, and a significant reduction in disease-free survival, from 74% to only 35% (11).

2. OBJECTIVE

The aim of this study was to evaluate the role of contrast-enhanced T1-weighted magnetic resonance imaging (CET1WI) in addition to high-resolution T2-weighted imaging (HRT2WI) in assessing extramural venous invasion (EMVI) of rectal cancer.

3. PATIENTS AND METHODS

Our study was designed as an analytical and comparative study involving 195 patients with rectal carcinoma verified on the basis of a histopathology biopsy specimen. The study was conducted from October 2012 to September 2020. All patients underwent pre-operative MRI for the purpose of surgical resection planning. Within this MRI protocol, HRT2WI and CET1WI sequences were produced in order to assess for the presence of mrEMVI. Contrast CET1WI sequences were produced following intravenous administration of a contrast medium, Magnevist® (gadopentetate dimeglumine), manufactured by Bayer. Examinations were carried out on 1.5 T MRI devices manufactured by General Electric and Siemens. Ultrasound gel was applied per rectum as a contrast medium for rectal lumen marking. Body matrix coil was used, placed on pelvis so that the lower edge of coil was below the pubic bone. The coil was attached with a belt, and the patient entered the machine head first. The protocol had the following sequences: T1Fl3D cor FS FOV400 slice thickness (sl.th.) 2 mm TR 3.25, TE 1.2, voxel size 1.7 x 1.6 x 2 mm; T2 TRUFI 3D cor FOV 450, sl.th.1 mm TR 4.09, TE 1.8 voxel size 1.6 x 1.4 x 1; T2TSE sag FOV 280 sl.th.4mm TR 3700, TE 101 voxel size 0.7 x 0.7 x 4; T2TSE tra FOV 210, sl.th. 4 mm TR 3730, Te101 voxel size 0.8 x 0.8 x 4; T2 cor FOV 300 sl.th. 4 mm, TR 5230, Te 99, voxel size 0.7 x 0.7 x 4; VIBE T1 FS tra FOV 450, TR 4.99, TE 2.61, sl.th. 2.5 mm voxel size 2.7 x 1.8 x 2.5; T1TSE tra FOV 210, sl.th. 4mm, TR 666, TE10, voxel size 0.8 x 0.8 x 4.1p2d; DWI FOV 380, TR 4600, TE 76, sl.th. 4mm, B value 50, 300, and 600 with ADC map.

An agreement test between two independent radiologists in evaluation of mrEMVI was performed. Parameters of mrEMVI evaluation were: serpent-like tubular tumor extensions of veins, varicose veins with an irregular contour, presence of intermediate signal intensity along the veins in the vicinity of rectal carcinoma. The results of mrEMVI evaluation were classified into two groups. Group A consisted of results of mrEMVI evaluation using HRT2WI sequences alone. Group B consisted of results of mrEMVI evaluation using a combination of HRT2WI + CET1WI sequences. The pathological status of EMVI (pEMVI) was used as a standard reference. A sensitivity and specificity test was performed, and PPV and NPV for the results of both groups (A and B) were determined. Statistical package MedCalc Statistical Software version 15.2 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2015) was used.

4. RESULTS

Out of a total of 195 patients in our study with histopathologically verified rectal carcinoma, 98 (50.25%) were male and 97 (49.75%) were female. Average age was 62 years ±10.41.

An agreement test between two independent radiologists in mrEMVI detection resulted in a significant statistical concordance, Kappa coefficient (Measure of Agreement Kappa) was 0.864 ($p<0.0005$).

Out of all 195 patients with rectal carcinoma, mrEMVI was positive in 41 (21%) patients in group A, and 45 (23%) patients in group B. A histopathological finding demonstrated pEMVI in 54 (27.7 %) patients. A statistical analysis of group A (HRT2WI sequences) revealed 75.9% sensitivity to mrEMVI and 96.4% specificity, Positive Predictive Value

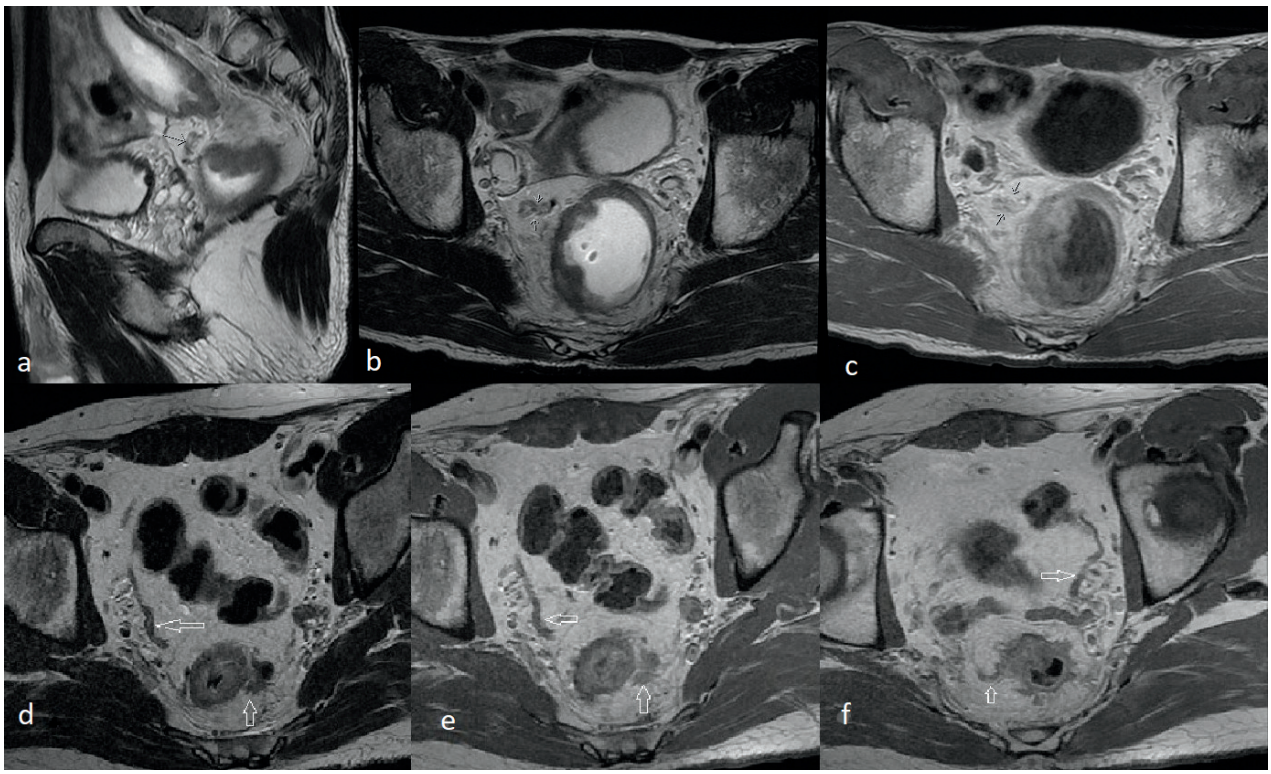

Figure 3 a,b,c dilates veins have the intensity of tumor tissue a.t2sag, b. t2tra nativ, c.t2 +CE d,e,f serpentine appearance of vein filld with a tumor in d.t1tra nativ; e,f t1 tra+CE

of 89.1% and Negative Predictive Value of 91.2% (CI 95%, p< 0.05).

A statistical analysis of group B (HRT2WI + CET1WI sequences) revealed 83.3% sensitivity to mrEMVI and 98.5% specificity, Positive Predictive Value of 89.1% and Negative Predictive Value of 91.2% (CI 95%, p< 0.05) (Table 1).

Stage II rectal carcinoma was present in 26.2% of the patients with EMVI, while stage III was present in 46.1%.

MRI HRT2WI * Histopathol. EMVI					
			PH EMVI		Total
			No	Yes	
MRI HRT2WI	No	N	136	13	149
		%	96.5	24.1	76.4
	Yes	N	5	41	46
		%	3.5	75.9	23.6
Total		N	141	54	195
		%	100.0	100.0	100.0
MRI HRT2WI + CET1WI * Histopathol. EMVI					
			PH EMVI		Total
			No	Yes	
MRI HRT2WI + CET1WI	No	N	139	9	148
		%	98.6	16.7	75.9
	Yes	N	2	45	47
		%	1.4	83.3	24.1
Total		N	141	54	195
		%	100.0	100.0	100.0

Table 1. HRT2WI in mrEMVI and HRT2WI + CET1WI in mrEMVI test results. MRI HRT2WI:, Sensitivity =0.7592592592592593, Specificity =0.9645390070921985, Positive Predictive Value =0.8913043478260869, Negative Predictive Value=0.912751677852349, MRI HRT2WI + CET1WI:, Sensitivity =0.8333333333333334, Specificity =0.9858156028368794, Positive Predictive Value =0.9574468085106383, Negative Predictive Value=0.9391891891891891

5. DISCUSSION

As a spread of rectal tumor to veins beyond muscularis propria, EMVI may be detected on MRI (mrEMVI). mrEMVI is present when veins in the vicinity of the tumor are noticeable and presented as obviously irregular, varicose and as having a modified tumor signal intensity. Thin section T2-weighted magnetic resonance imaging (MRI) can be used to demonstrate a number of adverse prognostic features for local rectal recurrence and survival in patients with rectal cancer. This implies an estimation of tumor extension to the lateral resection margin, the depth of extramural tumor extension and EMVI.

High-resolution T2-weighted imaging is the key sequence in the magnetic resonance (MR) imaging evaluation of primary rectal cancer. This sequence generally consists of thin-section (3-mm) axial images obtained orthogonal to the tumor plane, with an in-plane resolution of 0.5–0.8 mm. For a good assessment, HR T2-weighted images in three planes are used: sagittal plane, coronal plane and also in axial plane orthogonal to the tumor. This technique allows for a distinction between a T2 stage representing tumor restriction to the rectal wall only and a T3 stage when the tumor reaches beyond muscularis propria. Most importantly, the depth of invasion beyond muscularis propria may be evaluated with a high degree of accuracy (12). In addition, T2-weighted high-resolution images allow for evaluation of morphological appearance of pelvic lymph nodes. Differentiating between a tumor invasion of minor lymph nodes and the blood vessels may be a problem with MRI. It is established that Gadolinium contrast sequences are not particularly helpful in diagnosing TN stage of rectal

carcinoma. However, considering that administration of Gadolinium significantly enhances the visibility of blood vessels, it can be of great importance for EMVI demonstration (Figure 3).

Generally, small-vessel involvement is difficult to assess, and the involvement of larger vessels such as the midrectal or superior rectal arteries or veins is suggested by the visualization of tumor in the vessel lumen on contiguous sections (13). In 2008, Smith et al. highlighted the importance of future research in development of capabilities of recognizing EMVI in order to stratify patients for the purpose of administration of optimal neoadjuvant systemic chemotherapy so that emergence of remote relapses can be prevented (14). Chand et al. reported extramural venous invasion (EMVI) as a poor prognostic factor in rectal cancer (15). EMVI is associated with greater incidence of metastases, local relapse, poorer response to pre-operative chemoradiotherapy and an overall lower survival rate (16,17). Pre-operative chemoradiotherapy has no significant effect on the diagnostic performance of MRI. Currently, EMVI status does not directly influence the initial management of rectal carcinoma. This available and potentially prognostic feature could be used to guide treatment pathways to increase disease-free survival (18).

In our research, a histopathological finding confirmed pEMVI in 27.7 % of the patients with rectal carcinoma. A study by Jhaveri et al. resulted in a somewhat bigger proportion–pEMVI was present in 31% of the pathology specimens (19). Our pEMVI result most closely approximates a comprehensive study published by McClelland et al., where EMVI presence was reported in 27.9% of colorectal cancer excision specimens. The same authors stressed the importance of EMVI and other pathological factors in colorectal carcinoma and confirmed that in an individual center study EMVI is being detected at an appropriate rate and is of prognostic significance (20). In a study by W.G. Bugg et al., 26.2% of rectal carcinoma patients had positive EMVI. Of the patients with EMVI, 24.5% developed metastases at 1 year follow-up, compared to 6.7% of those without. Those with EMVI have 3.7 times increased relative risk of developing metachronous metastases within 1 year of diagnosis (18). Smith et al. published in a retrospective analysis that mrEMVI was present in a quarter of patients with rectal carcinoma (13). In our study, 21% of the patients had positive mrEMVI when HRT2WI sequences were employed, while 24% of the patients had positive mrEMVI when a combination of HRT2WI + CET1WI sequences was employed. In our research, when analyzing group A (HRT2WI sequence), 75.9% sensitivity and 96.4% specificity were established; when analyzing group B (HRT2WI + CET1WI sequences), 83.3% sensitivity and 98.5% specificity were established. These results show that even though HRT2WI yields good results, a combination of sequences (HRT2WI + CET1WI) is more successful in mEMVI detection in comparison with HRT2WI sequence alone (Figure 1). In their study, Liu et al. concluded that employment of Gadolinium contrast-enhanced T1-weighted magnetic resonance imaging improves EMVI evaluation. They reported 72.5% sensitivity to mrEMVI and 73.2% specificity when HRT2WI sequences alone were used in assessment, and presence of mrEMVI in 30.5% of the patients (21). Following administration of Gadolinium contrast medium with CET1WI, there was 83.3% sensitivity and 75.6% specificity. The authors concluded that the combination of HRT2WI + CET1WI sequences is more successful in the evaluation of mrEMVI than use of HRT2WI sequence alone. In comparison with their results, ours show similar sensitivity but a significantly better specificity. Koh et al. compared the sensitivity and specificity of mEMVI by means of analyzing T2-weighted magnetic resonance imaging MR score in relation to the vein size. For MR score of >2, they had 100% sensitivity and 89% specificity in identifying EMVI involving veins >3 mm in diameter. For EMVI score under 2, they obtained a sensitivity of 56% and specificity of 81% (22). In a recent study, Jhaveri concluded that MRI has high specificity and moderate sensitivity in detection of EMVI, and mrEMVI score (3-4) in veins 3mm and more in diameter showed 54% sensitivity and 96% specificity. In mEMVI score 2, sensitivity was increased to 79% but specificity was reduced to 74% (19).

Identification of vascular invasion is also associated with quality of pathology, i.e. number of examined tissue blocks. Betge concluded that diagnoses vary when routine pathological diagnosis is reviewed, thus stressing the need for standardized control of high quality of pathological reports (23). The development of high-resolution magnetic resonance imaging, where extramural venous invasion can be detected pre-operatively, may also influence the manner in which pathologists process specimens (24).

6. CONCLUSION

T1-weighted magnetic resonance imaging (CET1WI) in addition to high-resolution T2-weighted imaging (HRT2WI) increased evaluation of extramural venous invasion (EMVI) of rectal cancer. A reliable mrEMVI evaluation is very beneficial for a safer selection of optimal oncologic treatment and a more reliable prediction of rectal carcinoma prognosis.

- **Patient Consent Form:** All participants were informed about subject of the study.
- **Author's contribution:** All authors were involved in preparation of this article. Final proofreading was made by the fisrt author.
- **Conflict of interest:** The authors declare no conflict of interest.
- **Financial support and sponsorship:** None.

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