Extramural Vascular Invasion at Rectal MRI: A Finding of Questionable Clinical Value

Poster No.: C-0444
Congress: ECR 2015
Type: Scientific Exhibit
Authors: M. J. Gollub\(^1\), V. Arora\(^2\), R. G. H. Beets-Tan\(^3\), M. Maas\(^3\), J. Zheng\(^1\), C. Moskowitz\(^1\), M. Sohn\(^4\), M. Weiser\(^1\), J. Shia\(^1\); \(^1\)New York City, NY/US, \(^2\)Merseyside/UK, \(^3\)Maastricht/NL, \(^4\)Princeton, NJ/US
Keywords: Gastrointestinal tract, Colon, Vascular, MR, Diagnostic procedure, Cancer
DOI: 10.1594/ecr2015/C-0444

Any information contained in this pdf file is automatically generated from digital material submitted to EPOS by third parties in the form of scientific presentations. References to any names, marks, products, or services of third parties or hypertext links to third-party sites or information are provided solely as a convenience to you and do not in any way constitute or imply ECR’s endorsement, sponsorship or recommendation of the third party, information, product or service. ECR is not responsible for the content of these pages and does not make any representations regarding the content or accuracy of material in this file.

As per copyright regulations, any unauthorised use of the material or parts thereof as well as commercial reproduction or multiple distribution by any traditional or electronically based reproduction/publication method is strictly prohibited.

You agree to defend, indemnify, and hold ECR harmless from and against any and all claims, damages, costs, and expenses, including attorneys’ fees, arising from or related to your use of these pages.

Please note: Links to movies, ppt slideshows and any other multimedia files are not available in the pdf version of presentations.

www.myESR.org
Aims and objectives

Extramural vascular invasion (EMVI), defined as the presence of malignant cells within endothelial cell-lined blood vessels beyond the muscularis propria [1], and reported to occur in as many as 52% of cases of colorectal cancer [1-4], is a known poor prognostic factor when seen at histopathological examination of rectal cancer specimens and has also been reported to be prognostic of poor outcomes when seen on high-resolution, thin section MRI. However, mostly single or paired observer studies, often limited to expert interpretations have formed the basis of this conclusion, which when tested with other readers, showed variable sensitivity for histopathological EMVI as well as variable, often low inter-observer agreement and lack of independence as a risk factor for clinical outcomes.

In the initial description, a single highly experienced observer had a sensitivity of 62% to predict EMVI in patients proceeding directly to surgery when compared to histopathology of the resected specimen (5). Patients with tumors exhibiting EMVI, a feature characteristic of T3 or deeper tumors by definition would ordinarily be subjected to preoperative chemoradiation in today's treatment paradigm, with some exceptions, and thus the results of that study, in which patients did not receive chemo-radiotherapy, cannot be generalized. A further study, performed by the MERCURY group, used paired observers and demonstrated poor interobserver agreement (kappa = 0.41) for the presence of EMVI (6). In neither of these studies was EMVI shown to be an independent risk factor for clinical outcomes. Although an earlier, smaller study did achieve a slightly higher kappa (7), uncertainty about the reproducibility and the prognostic importance of MRI-detected EMVI still remains, and further study is warranted by radiologists, with varying degrees of experience, in order to determine the reproducibility of this finding.

As such, the purpose of our study was to assess whether radiologists with different degrees of experience could agree that EMVI was present at MRI, and to determine if its presence at imaging conferred an independent risk for poor outcome when controlling for known risk factors such as nodal status and lymphovascular invasion.

Methods and materials

Patients and Methods:
Patients:

After IRB approval and in compliance with HIPAA, using our institutional surgery and radiology databases, we searched for all patients who underwent total mesorectal excision (TME) for primary rectal adenocarcinoma and had an available MRI between 2000-2010. Patients had to have undergone neoadjuvant chemoradiotherapy or chemotherapy alone, either because of clinical T3 or N+ disease according to our standard treatment, or T2 tumors in the lower 1/3 of the rectum to maximize the possibility of sphincter-sparing surgery. All scans and surgery were done at our institution. Patients going directly to surgery were excluded, as were those with recurrent disease or any histology other than adenocarcinoma. Exclusions included stage 4 disease at presentation, poor-quality scans, MRI exams with slice thickness greater than 4mm, and patients with recurrent disease. From 156 patients initially identified, this left a final study sample of 89 suitable patients. It should be noted that in the earlier years of the above date-range, endorectal ultrasound was the primary staging modality used, and MRI gradually gained traction with time.

Readers, Reader Strategy:

Three board-certified radiologists independently reviewed all cases blinded to the T-stage and other pathological information. Reader 1 is a GI-specialist radiologist with 10-years experience in rectal MRI. Reader 2 is a GI-specialist radiologist with PhD training in rectal MRI and 15 years experience. Reader 3 is an oncologic radiology fellow. Axial, oblique axial, sagittal, coronal oblique and coronal images could be used for determination of extramural vascular invasion (EMVI). Cross-referencing across image sets was also allowed. A previously described rating scale (5) was used to determine EMVI (Figure 1). Ten initial cases were reviewed in conference after independent assessments in order to establish consistent understanding of the rating system. These 10 cases were then re-evaluated with the other randomized cases after a 2-week interval and included in all analyses.

MRI technique

Using both 1.5 and 3.0 T magnets (Signa LX, GE Healthcare, Waukesha, WI), multiplanar T1 and T2 weighted sequences without fat saturation were obtained per institutional protocol as previously published (8). The median slice thickness was 4.0mm (n=30, 3mm; n=80, 4mm).

Clinical data collection:
For all patients, using the electronic medical records, we collected information on microscopic lymphovascular invasion (LVI), final pathologic stage (ypTNM; AJCC 7th edition), percent treatment response in the pathologic specimen, as well as survival and disease status.

**Biostatistical methods:**

Patient characteristics were summarized in median and range for continuous variables and with percentages for categorical variables. Separately, in patients with pre-treatment MRI and patients with post-treatment MRI, Fisher’s exact test was used to compare the characteristic (e.g. LVI, positive LN) between EMVI present (score 3-4) and EMVI absence (score 0-2) on MRI. The Kaplan-Meier method was used to estimate three-year DFS. The log-rank test was used to compare DFS between patients with EMVI present and absent on MRI. A permutation log-rank test [9] was applied when the number of events was less than five in either arm of the test. Multivariable Cox regression was used to assess the effect of the presence of EMVI present after controlling for LVI or N stage. Due to the number of deaths and the small number of LVI with EMVI or positive LN, we were not able to obtain reliable estimates of LVI in the multivariable analysis. Thus we only controlled for N stage in multivariable analysis of OS. N stage was not associated with DFS univariately, we thus only controlled for LVI in multivariable analysis of DFS.

The readings from three readers were examined separately. We used weighted kappa with quadratic weights to assess pair-wise inter-reader agreement. The Light's kappa [10] was estimated for three-reader agreement.

**Images for this section:**
Figure 1 - MR EMVI Scale

___ 0 T2: No vessels adjacent to areas of tumor penetration

___ 1 Minimal extramural stranding/nodular extension, but not in the vicinity of any vascular structure

___ 2 Stranding demonstrated in the vicinity of extramural vessels, but these vessels are of normal caliber, and there is no definite tumor signal within the vessel

___ 3 Intermediate signal intensity present within vessels, although the contour and caliber of these vessels is only slightly expanded

___ 4 Obvious irregular vessel contour or nodular expansion of vessel by definite tumor signal. Vessel interrupted as approaches wall OR caliber increases closer to wall.

**Fig. 1:** Figure 1. Schema from Smith NJ et al. BJS 2008; 95: 229-236.
Results

Patients (Table 1 [Figure 2]):

Eighty-nine patients are included in this study. Sixty-four patients underwent chemoradiotherapy (CRT; hereafter "CRT" refers to either chemoradiotherapy or chemotherapy alone) and 25 underwent chemotherapy alone. Among them, 56 patients had pre-CRT MRI, 54 patients had post-CRT MRI and 21 patients had both pre- and post-CRT MRIs. The median age was 56 (range: 25-89) years. Forty-four (49%) patients were male. The median follow-up was 40.7 (range: 0.5 - 149.0) months. Median DFS was 78.6 (95% CI: 59.6 - not reached) months. Median OS was 78.6 (95% CI: 58.4, not reached) months. There were 20 tumor recurrences and all but 3 recurrences were distant in location. There were 15 deaths.

Reader agreement (Table 2 [Figure 3], Figure 4-6):

Reader 1 found EMVI on pre- and post-CRT scans in 16/56 and 8/54 cases respectively. Reader 2 found EMVI on pre- and post-CRT scans in 20/56 and 21/54 cases respectively. Reader 3 found EMVI on pre- and post-CRT scans in 15/56 and 10/54 cases respectively. Pre-treatment MRI kappa ranged from 0.46-0.61. Post-treatment MRI kappa ranged from 0.30-0.43. The least agreement was between the two most experienced readers; 1 and 2 (0.12) and the greatest agreement was between readers 2 and 3. (0.45). Overall agreement was 0.46.

EMVI and associations with treatment response, LVI and ypN status (Table 3 [Figure 7]):

For non-paired MRI (patients that had only either pre- or post-CRT MRI), reader 3 found correlation between pre-CRT EMVI and percent treatment response, LVI and LN. For non-paired MRI, reader 3 found correlation between post-CRT EMVI and LVI. For all paired MRI, no associations on pre- or post-CRT MRI were noted with EMVI.

EMVI and survival - Univariate analysis (Table 4 [Figure 8])

Univariate analyses evaluating dichotomized EMVI readings (0-2 vs. 3-4) are summarized in Table 4 [Figure 8] for OS and DFS. For 1 of 3 readers (reader 3), EMVI seen on pre-CRT MRI was associated with DFS (p= 0.03) and OS (p= 0.02). For 2 of 3 readers (readers 2 and 3), the post-CRT finding of EMVI was significantly associated with DFS (p < 0.001 and p =0.01, respectively) and OS (p < 0.001 and p =0.006, respectively). Based on pathology, LVI was associated with both DFS (p=0.007) and OS (p < 0.001)
on univariate analysis. In contrast, LN status was significantly associated with OS (p = 0.02) but not DFS.

**EMVI and survival - Multivariate analysis (Table 5 [Figure 9]),**

Multivariable analysis controlling for lymphovascular invasion (LVI) or N stage is summarized in Table 5 for DFS and OS on patients' post-CRT MRI scans (no reference standard is generally available for pre-treatment LVI status or N-stage). Due to the small numbers, no multivariable analysis was performed for patients with both pre- and post-CRT MRI. The presence of EMVI on post-treatment MRI was not significantly associated with DFS for 3 readers. The presence of LVI at pathology was not associated with DFS in multivariable analysis. Nodal stage (yN) was associated with OS for reader 1 (HR = 3.96; 1.23 - 12.75, p = 0.02). For 2 of 3 readers, (readers 2 and 3, most and least experienced), EMVI was associated with OS (HR ranging from 3.6 [1.2 - 10.7] - 6.0 [1.6 - 22], p = 0.022 and 0.007 respectively). Kaplan Meier curves for the two most experienced readers are shown for post-CRT OS (Figure 10) and DFS (Figure 11).

**Images for this section:**
Fig. 2: Table 1. Patient Characteristics

| CR = chemoradiotherapy |

Table 2. Agreement on EMVI (weighted kappa with quadratic weights)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>R1 and R2</th>
<th>R1 and R3</th>
<th>R2 and R3</th>
<th>Overall Light's kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>pre CR MRI</td>
<td>56</td>
<td>0.468</td>
<td>0.613</td>
<td>0.478</td>
<td>0.520</td>
</tr>
<tr>
<td>post CR MRI</td>
<td>54</td>
<td>0.414</td>
<td>0.302</td>
<td>0.427</td>
<td>0.381</td>
</tr>
<tr>
<td>All MRI</td>
<td>105</td>
<td>0.117</td>
<td>0.475</td>
<td>0.454</td>
<td>0.459</td>
</tr>
</tbody>
</table>

Fig. 3: Table 2. Agreement on EMVI (weighted kappa with quadratic weights)

Table 3. Patient characteristics classified by EMVI

<table>
<thead>
<tr>
<th>Pre-CRT MRI</th>
<th>R1 EMVI -</th>
<th>EMVI +</th>
<th>p value</th>
<th>R2 EMVI -</th>
<th>EMVI +</th>
<th>p value</th>
<th>R3 EMVI -</th>
<th>EMVI +</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Response</td>
<td>10% - 85%</td>
<td>17 (46%)</td>
<td>5 (28%)</td>
<td>0.197</td>
<td>20 (45%)</td>
<td>10 (77%)</td>
<td>0.197</td>
<td>20 (45%)</td>
<td>14 (74%)</td>
</tr>
<tr>
<td></td>
<td>90% - 100%</td>
<td>17 (46%)</td>
<td>5 (28%)</td>
<td></td>
<td>19 (54%)</td>
<td>14 (93%)</td>
<td></td>
<td>19 (54%)</td>
<td>14 (93%)</td>
</tr>
<tr>
<td>LVI No</td>
<td>28 (70%)</td>
<td>10 (62%)</td>
<td>0.752</td>
<td></td>
<td>26 (72%)</td>
<td>12 (60%)</td>
<td>0.383</td>
<td>32 (78%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>4 (10%)</td>
<td>5 (13%)</td>
<td></td>
<td>5 (14%)</td>
<td>4 (20%)</td>
<td></td>
<td>3 (7%)</td>
<td>6 (40%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-CRT MRI</th>
<th>R1 EMVI -</th>
<th>EMVI +</th>
<th>p value</th>
<th>R2 EMVI -</th>
<th>EMVI +</th>
<th>p value</th>
<th>R3 EMVI -</th>
<th>EMVI +</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Response</td>
<td>10% - 85%</td>
<td>17 (46%)</td>
<td>5 (28%)</td>
<td>0.197</td>
<td>20 (45%)</td>
<td>10 (77%)</td>
<td>0.197</td>
<td>17 (46%)</td>
<td>14 (74%)</td>
</tr>
<tr>
<td></td>
<td>90% - 100%</td>
<td>17 (46%)</td>
<td>5 (28%)</td>
<td></td>
<td>19 (54%)</td>
<td>14 (93%)</td>
<td></td>
<td>19 (54%)</td>
<td>14 (93%)</td>
</tr>
<tr>
<td>LVI No</td>
<td>28 (70%)</td>
<td>10 (62%)</td>
<td>0.752</td>
<td></td>
<td>26 (72%)</td>
<td>12 (60%)</td>
<td>0.383</td>
<td>32 (78%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>4 (10%)</td>
<td>5 (13%)</td>
<td></td>
<td>5 (14%)</td>
<td>4 (20%)</td>
<td></td>
<td>3 (7%)</td>
<td>6 (40%)</td>
</tr>
</tbody>
</table>

* EMVI - when reader rated confidence 0-2
** EMVI + when reader rated confidence 3-4

Fig. 7: Table 3. Patient characteristics classified by EMVI
Table 4. Univariate analysis

<table>
<thead>
<tr>
<th></th>
<th>OS Pre CRT</th>
<th>OS Post CRT</th>
<th>DFS Pre CRT</th>
<th>DFS Post CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>36-Month OS Rate (95% CI)</td>
<td>Log-Rank Test p-Value</td>
<td>N</td>
</tr>
<tr>
<td>EMVI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R1</td>
<td>0-2</td>
<td>94.9% (88.2%, 100%)</td>
<td>0.098</td>
<td>88.2% (78.9%, 98.5%)</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>86.5% (70.7%, 100%)</td>
<td></td>
<td>71.4% (44.7%, 100%)</td>
</tr>
<tr>
<td>R2</td>
<td>0-2</td>
<td>94.4% (87.1%, 100%)</td>
<td>0.072</td>
<td>93.5% (85.3%, 100%)</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>89.2% (76%, 100%)</td>
<td></td>
<td>73.9% (56.6%, 96.5%)</td>
</tr>
<tr>
<td>R3</td>
<td>0-2</td>
<td>92.5% (84.7%, 100%)</td>
<td>0.025</td>
<td>90.3% (81.7%, 100%)</td>
</tr>
<tr>
<td></td>
<td>3-4</td>
<td>91.7% (77.3%, 100%)</td>
<td></td>
<td>62.5% (36.5%, 100%)</td>
</tr>
</tbody>
</table>

Other factors

<table>
<thead>
<tr>
<th></th>
<th>OS Pre CRT</th>
<th>OS Post CRT</th>
<th>DFS Pre CRT</th>
<th>DFS Post CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>36-Month OS Rate (95% CI)</td>
<td>Log-Rank Test p-Value</td>
<td>N</td>
</tr>
<tr>
<td>LVI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>47</td>
<td>90.9% (82.8%, &lt;.001)</td>
<td>99.8%</td>
<td>47</td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>(13.7%, 100%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive LN</td>
<td>No</td>
<td>38</td>
<td>89% (79.4%, 0.018)</td>
<td>99.8%</td>
</tr>
<tr>
<td>Yes</td>
<td>16</td>
<td>77.4% (57.8%, 100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 8: Table 4. Univariate analysis
Table 5. Multivariable analysis in patients with post CRT MRI

<table>
<thead>
<tr>
<th>post CRT factors</th>
<th>OS Multivariable Analysis*</th>
<th>DFS Multivariable Analysis</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>p-Value</td>
<td>HR (95%CI)</td>
</tr>
<tr>
<td>R1 EMVI</td>
<td>3.37 (0.87, 13.04)</td>
<td>0.078</td>
<td>1.13 (0.33, 3.92)</td>
</tr>
<tr>
<td>LVI</td>
<td>3.96 (1.23, 12.75)</td>
<td>0.021</td>
<td>1.89 (0.49, 7.32)</td>
</tr>
<tr>
<td>Positive LN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1/N2 vs N0 (ref)</td>
<td>5.93 (1.62, 21.77)</td>
<td>0.007</td>
<td>1.82 (0.58, 6.66)</td>
</tr>
<tr>
<td>R2 EMVI</td>
<td>2.97 (0.9, 9.77)</td>
<td>0.074</td>
<td>1.84 (0.50, 6.87)</td>
</tr>
<tr>
<td>LVI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive LN</td>
<td>3.57 (1.21, 10.57)</td>
<td>0.022</td>
<td>3.04 (0.90, 10.30)</td>
</tr>
<tr>
<td>N1/N2 vs N0 (ref)</td>
<td>3.31 (0.99, 11.03)</td>
<td>0.052</td>
<td>1.20 (0.29, 4.91)</td>
</tr>
</tbody>
</table>

Due to the number of deaths and the small number of LVI with EMVI or positive LN, we were not able to obtain reliable estimates of LVI in the multivariable analysis. Therefore, LVI was not included in the multivariable OS analysis.

Fig. 9: Table 5. Multivariable analysis
Figure 3. Post-CRT K-M EMVI and DFS (a) reader 1 (b) reader 2

DFS ~ Reader 1 without contrast

Prop. Surviving

Months

Prop. Surviving

Months

DFS ~ Reader 2 without contrast

Prop. Surviving

Months

0, n=46
1, n=8
p=0.583

0, n=33
1, n=21
p<0.001
Fig. 11: Figure 6. Post-CRT K-M EMVI and DFS (a) reader 1 (b) reader 2
Figure 6. Post-CRT K-M EMVI and OS (a) reader 1 (b) reader 2

OS ~ Reader 1 without contrast

Proportion Surviving

0.0 0.2 0.4 0.6 0.8 1.0

0, n=46
1, n=8
p = 0.083

Months

0 12 24 36 48 60 72 84 96 108 120 132 144 156

OS ~ Reader 2 without contrast

Proportion Surviving

0.0 0.2 0.4 0.6 0.8 1.0

0, n=33
1, n=21
p < .001

Months

0 12 24 36 48 60 72 84 96 108 120 132 144 156
**Fig. 10:** Figure 5. Post-CRT K-M EMVI and OS (a) reader 1 (b) reader 2

---

**Figure 1 - MR EMVI Scale**

---

0 T2: No vessels adjacent to areas of tumor penetration

1 Minimal extramural stranding/nodular extension, but not in the vicinity of any vascular structure

2 Stranding demonstrated in the vicinity of extramural vessels, but these vessels are of normal caliber and there is no definite tumor signal within the vessel

3 Intermediate signal intensity present within vessels, although the contour and caliber of these vessels is only slightly expanded

4 Obvious irregular vessel contour or nodular expansion of vessel by definite tumor signal. Vessel interrupted as approaches wall OR caliber increases closer to wall.

---

**Fig. 1:** Figure 1. Schema from Smith NJ et al. BJS 2008; 95: 229-236.
Fig. 4: Figure 2. All readers agreed strongly that EMVI was present posteriorly on sagittal T2W image.
Fig. 5: Figure 3. All readers agree that NO EMVI was present on axial T2W image.
Fig. 6: Figure 4. Complete disagreement among readers. One expert rated 3, another rate 1 and less experienced reader rated 2 on 0-4 scale of likelihood of EMVI on axial T2W image.
Conclusion

In this retrospective study of patients with locally advanced rectal cancer undergoing neoadjuvant treatment, three radiologists of differing experience assessed the presence and prognostic significance of extramural venous invasion (EMVI) detected at MRI. Our data show that the presence of EMVI on post-CRT MRI scans was a prognostic factor for DFS for only 1 reader, and for OS for only 2 of 3 readers, the least and the most experienced. Furthermore, the inter-reader agreement ranged from poor to moderate, and was overall only fair. These findings confirmed our hypotheses that MRI-based EMVI is neither reproducible, nor reliably prognostic as a risk factor for survival.

Although it is soundly proven that large venous invasion at histopathologic examination of rectal cancer specimens outcomes (histopathological EMVI) portends worse outcomes, our data suggest that detection of EMVI by MRI is not currently reliable or independently prognostic using a previously suggested rating system and furthermore, that the subjectivity of the interpretation of EMVI at MRI leads to a lot of variability between observers, further reducing its practical use as a predictive tool.

Our study is limited by its retrospective nature. Inclusion of MRI cases performed before 2011, when uniform pathologic reporting of large venous invasion at our institution began, limited our ability to report our actual histopathological rate of EMVI. A proportion of our cohort underwent imaging with 4mm instead of 3mm thick sections possibly limiting our detection of EMVI. Finally, our multivariable analysis would have been bolstered by a greater number of recurrences and deaths thereby giving us the ability to explore potential risk factors more thoroughly. As such, a larger study is warranted to confirm our findings.

In summary, our data indicate that the finding of EMVI on rectal MRI is not very reproducible between readers and cannot be relied upon to consistently indicate risk for disease-free survival or overall survival.

Personal information

1,2,4. Department of Radiology


9. Heller G, Venkatraman ES. Resampling procedures to compare two survival


