Systematic review of prognostic importance of extramural venous invasion in rectal cancer

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Abstract

AIM: To systematically review the survival outcomes relating to extramural venous invasion in rectal cancer.

METHODS: A systematic review was conducted using PRISMA guidelines. An electronic search was carried out using MEDLINE, EMBASE, CINAHL, Cochrane library databases, Google scholar and PubMed until October 2014. Search terms were used in combination to yield articles on extramural venous invasion in rectal cancer. Outcome measures included prevalence and 5-year survival rates. These were graphically displayed using Forest plots. Statistical analysis of the data was carried out.

RESULTS: Fourteen studies reported the prevalence of extramural venous invasion (EMVI) positive patients. Prevalence ranged from 9%-61%. The pooled prevalence of EMVI positivity was 26% [Random effects: Event rate 0.26 (0.18, 0.36)]. Most studies showed that EMVI related to worse oncological outcomes. The pooled overall survival was 39.5% [Random effects: Event rate 0.395 (0.29, 0.51)].

CONCLUSION: Historically, there has been huge variation in the prevalence of EMVI through inconsistent reporting. However the presence of EMVI clearly leads to worse survival outcomes. As detection rates become more consistent, EMVI may be considered as part of risk-stratification in rectal cancer. Standardised histopathological definitions and the use of magnetic resonance imaging to identify EMVI will improve detection rates in the future.

Key words: Extramural venous invasion; Rectal cancer; Overall survival; Pathology; Vascular invasion; Magnetic resonance imaging

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Core tip: Extramural venous invasion (EMVI) has been shown to be an adverse risk factor in rectal cancer. Historical studies have shown a wide range of...
prevalence which has made survival risk difficult to interpret. This has been due to lack of standardised
detection methods. As these methods improve, we
are more likely to be able to identify those patients
with evidence of EMVI and thus offer patients optimal
treatment.

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INTRODUCTION

Venous invasion is considered a prognostic factor in rectal cancer[1-7] however the exact effect on survival
outcomes and disease recurrence remains unknown. The current nomenclature refers to extramural venous
invasion (EMVI) and specifically describes tumour cells
within the veins outside the muscularis propria of the
bowel wall[8]. This distinction from other descriptions
of venous or vascular invasion is helpful in the modern
management of rectal cancer where risk of recurrence
needs to be accurately defined for individual patients,
to determine whether they would benefit from neo-
adjuvant and adjuvant therapies.

The existing literature generally examines venous
invasion based on pathology specimens and combine
colon and rectal cancer. There are only a limited
number of reports focusing on rectal cancer with clear
methods and definitions used for identification of EMVI.
As a result there is a large variation in reporting EMVI
between pathologists[9,10]. Furthermore, the reliance
on pathology for identification of EMVI particularly
after neoadjuvant treatment (CRT) may lead to under-

More recently, magnetic resonance imaging (MRI)
has been shown to accurately detect EMVI before
and after CRT and identify cases which are missed
on routine pathological assessment[12]. These inconsis-
tencies in the definition and specific histological
methods applied have led to challenging interpretation
of the true incidence and risk associated with EMVI;
leading to its lack of mandatory consideration for
oncological treatment. If EMVI is shown to have
prognostic implications but is being under-detected by
traditional histopathological methods alternatives such
as MRI may be considered to avoid the risk of disease
recurrence.

The aim of this review is to critically examine the
evidence for the prognostic importance of venous
invasion; specifically EMVI on histopathology, on the
survival outcomes of rectal cancer.

MATERIALS AND METHODS

An electronic search was carried out using MEDLINE
and the Cochrane library databases. Google scholar
and PubMed were used to search articles prior to 1965.
Medical subject heading terms and keywords were used: "rectal cancer"; "venous invasion"; "vascular
invasion"; "extramural"; and “EMVI". The "related
articles" function was used to broaden the search and
all abstracts, studies, and citations retrieved were
scanned for subject relevance. The latest date of this
search was October 2014. All potentially relevant
manuscripts were retrieved and evaluated for inclusion.
Reference lists of all relevant publications were hand-
searched for additional studies, and cross referenced
until no further relevant publications were identified.

Study methodology was carried out in accordance
with the “Preferred Reporting for Systematic Reviews
and Meta-Analyses” guidelines. We included all studies
in English reporting on outcomes of venous invasion
or EMVI in curative rectal cancer. Adult patients
over the age of 18 were included. Where multiple
studies describing the same patient population were
identified, the most recent publication was used. Case
reports were excluded. Studies of colorectal cancer
were included where data for rectal cancer could be
extracted. We included studies if they reported on
outcomes such as disease recurrence and overall
survival. Quality assessment of eligible studies was
carried out by two independent reviewers.

Pooling of prevalence rates was performed using
Comprehensive Meta-Analysis[12] and forest plots were
used as a graphical display.

RESULTS

Literature search and description of studies

Three hundred and sixty-four publications were initially
identified with potential relevance (Figure 1). Thirty-
two articles included patients who did not undergo
surgery; 30 articles described techniques only; 25
articles were case reports; 24 articles described
venous invasion outside the context of cancer. Further
screening identified 14 studies published between
1935 and 2014 which were included in this review.
This is shown in Table 1.

Study characteristics

A total of 7262 patients in 14 studies were involved in
this review. The patient cohort spanned 1938-2006.
Six studies were retrospective. Only 6 studies commented
on number of pathologists and blinding status[22A,13-16].
There was clinical heterogeneity in the stains used, the
common ones being used were H + E, Gieson’s, elastin
Records Identified through Medline, Embase, Cinhal searching
\(n = 426\)

Records after duplicates removed
\(n = 378\)

Records screened
\(n = 367\)

Full text articles assessed for eligibility
\(n = 125\)

Studies included in qualitative synthesis
\(n = 14\)

Studies included in quantitative synthesis (meta-analysis)
\(n = 14\)

Records excluded
\(n = 11\)

Full text articles excluded with reasons
\(n = 111\)

Unrelated articles
Technique articles
Commentary or letter articles
Case reports
Venous invasion outside context of EMVI

Figure 1 Flowchart showing search strategy for systematic review. EMVI: Extramural venous invasion.

Table 1 The prevalence of vascular invasion in rectal cancer

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. patients</th>
<th>Study design</th>
<th>No. of pathologists, blinding</th>
<th>Stain</th>
<th>Tumour site</th>
<th>Elastin stain</th>
<th>No. EMVI +ve pts</th>
<th>Prev VI +ve</th>
<th>5 yr survival</th>
<th>EMVI +ve</th>
<th>Independent prognosticator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al</td>
<td>1938</td>
<td>170</td>
<td>Retrospective</td>
<td>Unspecified</td>
<td>H + E</td>
<td>Rectum</td>
<td>Yes</td>
<td>104</td>
<td>61%</td>
<td>No 5 yr data</td>
<td>No comment</td>
<td>EMVI is +ve</td>
</tr>
<tr>
<td>Dukes et al</td>
<td>1941</td>
<td>689</td>
<td>Prospective</td>
<td>Unspecified</td>
<td>No stain</td>
<td>Rectum</td>
<td>No</td>
<td>107</td>
<td>17%</td>
<td>No 5 yr data</td>
<td>No comment</td>
<td>EMVI is +ve</td>
</tr>
<tr>
<td>Seefeld et al</td>
<td>1943</td>
<td>100</td>
<td>Prospective</td>
<td>1, blinded</td>
<td>H + E, Gieson’s</td>
<td>Rectum</td>
<td>Yes</td>
<td>20</td>
<td>20%</td>
<td>No 5 yr data</td>
<td>No comment</td>
<td>EMVI is +ve</td>
</tr>
<tr>
<td>Madison et al</td>
<td>1954</td>
<td>42</td>
<td>Prospective</td>
<td>Unspecified</td>
<td>Gieson’s</td>
<td>Rectum</td>
<td>Yes</td>
<td>19</td>
<td>43%</td>
<td>No 5 yr data</td>
<td>No comment</td>
<td>EMVI is +ve</td>
</tr>
<tr>
<td>Carroll et al</td>
<td>1963</td>
<td>1996</td>
<td>Retrospective</td>
<td>Unspecified</td>
<td>H + E</td>
<td>Rectum</td>
<td>No</td>
<td>240</td>
<td>11.8%</td>
<td>Data not usable</td>
<td>No comment</td>
<td>EMVI is +ve</td>
</tr>
<tr>
<td>Khankhanian et al</td>
<td>1977</td>
<td>143</td>
<td>Retrospective</td>
<td>Unspecified</td>
<td>Not stated</td>
<td>Rectum</td>
<td>No</td>
<td>70</td>
<td>19% (BVI + LVI)</td>
<td>52%</td>
<td>No 5 yr data</td>
<td>No comment</td>
</tr>
<tr>
<td>Talbot et al</td>
<td>1980</td>
<td>706</td>
<td>Prospective</td>
<td>2, blinded</td>
<td>H + E, elastin</td>
<td>Rectum</td>
<td>Yes</td>
<td>366</td>
<td>36%</td>
<td>No 5 yr data</td>
<td>No comment</td>
<td>EMVI is +ve</td>
</tr>
<tr>
<td>Rich et al</td>
<td>1983</td>
<td>142</td>
<td>Prospective</td>
<td>1, blinded</td>
<td>H + E</td>
<td>RS/Rectum</td>
<td>No</td>
<td>23</td>
<td>17%</td>
<td>No 5 yr data</td>
<td>No comment</td>
<td>EMVI is +ve</td>
</tr>
<tr>
<td>Freedman et al</td>
<td>1984</td>
<td>494</td>
<td>Retrospective</td>
<td>Unspecified</td>
<td>No comment</td>
<td>Rectum</td>
<td>Yes</td>
<td>89</td>
<td>36%</td>
<td>No 5 yr data</td>
<td>No comment</td>
<td>EMVI is +ve</td>
</tr>
<tr>
<td>Jass et al</td>
<td>1986</td>
<td>447</td>
<td>Prospective</td>
<td>1, blinded</td>
<td>H + E</td>
<td>Rectum</td>
<td>No</td>
<td>116</td>
<td>26% (extramural only)</td>
<td>41%</td>
<td>EMVI - No IPS</td>
<td>EMVI - No IPS</td>
</tr>
<tr>
<td>Sasaki et al</td>
<td>1987</td>
<td>774</td>
<td>Retrospective</td>
<td>Unspecified</td>
<td>H + E</td>
<td>Rectum</td>
<td>No</td>
<td>163</td>
<td>21% (extramural only)</td>
<td>No 5 yr data</td>
<td>No comment</td>
<td>EMVI - No IPS</td>
</tr>
<tr>
<td>Minsky et al</td>
<td>1988</td>
<td>168</td>
<td>Retrospective</td>
<td>1, blinded</td>
<td>H + E, elastin</td>
<td>RS/Rectum</td>
<td>Yes</td>
<td>81</td>
<td>48%</td>
<td>No 5 yr data</td>
<td>EMVI - No IPS</td>
<td>EMVI - No IPS</td>
</tr>
<tr>
<td>Harrison et al</td>
<td>1994</td>
<td>348</td>
<td>Retrospective</td>
<td>2, blinded</td>
<td>H + E, elastin</td>
<td>Rectum</td>
<td>Yes</td>
<td>74</td>
<td>21.2%</td>
<td>EMVI - No IPS</td>
<td>EMVI has IPS</td>
<td></td>
</tr>
<tr>
<td>Ptok et al</td>
<td>2006</td>
<td>1043</td>
<td>Retrospective</td>
<td>Unspecified</td>
<td>Not stated</td>
<td>Rectum</td>
<td>No</td>
<td>75</td>
<td>9%</td>
<td>EMVI - No IPS</td>
<td>EMVI - No IPS</td>
<td>80.7% LVI +ve</td>
</tr>
</tbody>
</table>

Chand M et al. EMVI in rectal cancer
detection rates. The prevalence ranges from 9%-61% reflecting the inconsistent nature of recognition and detection. The overall prevalence is around 25% which is consistent with guidance from the Royal College of Pathologists.

The present study has shown that venous invasion generally, and EMVI more specifically, is associated with worse survival outcomes. Despite this, EMVI is not considered a mandatory factor for the use of adjuvant treatment. Indeed the current position on EMVI is variable and has been recently investigated [19]. Many clinicians rely on the EMVI status to make decisions on treatment and it has become a mandatory part of the pathology reporting dataset in the United Kingdom. The reasons behind this variability on behalf of clinicians are unknown. This may be due to inconsistent detection rates shown above or may be that it is rare to find EMVI without the association of more traditional adverse features such as nodal disease or increased T-stage. However, the evolution of rectal cancer management may lead to a change in attitude towards EMVI if a more selective approach is taken to neoadjuvant treatment in the light of clinical trial evidence. For example, the universal policy of irradiating all T3 tumours or any tumour that has

and Brominol. All the studies we included examined rectal tumours however 2 papers also incorporated rectosigmoid tumours [14,15].

**Prevalence**

Prevalence of EMVI positive patients ranged from 9%-61% in the studies. The pooled overall prevalence from fourteen studies was 26% [Random effects: Event rate 0.26 (0.18, 0.36), z = -4.3, Q = 787, I² = 98%] (Figure 2).

**Survival outcomes in the presence of venous invasion**

Seven studies reported on 5 year survival rates in patients with EMVI positive histology [4,6,13,14,16-18]. The pooled overall survival was 39.5% [Random effects: Event rate 0.395 (0.29, 0.51), z = -1.9, Q = 58.06, I² = 90%] (Figure 3).

**DISCUSSION**

The results of the present study have shown an association between venous invasion and poor prognosis. Patients that demonstrate evidence of venous invasion have worse overall survival. However the most striking finding is the variation in histopathological detection rates. The prevalence ranges from 9%-61% reflecting the inconsistent nature of recognition and detection. The overall prevalence is around 25% which is consistent with guidance from the Royal College of Pathologists.

The present study has shown that venous invasion generally, and EMVI more specifically, is associated with worse survival outcomes. Despite this, EMVI is not considered a mandatory factor for the use of adjuvant treatment. Indeed the current position on EMVI is variable and has been recently investigated [19]. Many clinicians rely on the EMVI status to make decisions on treatment and it has become a mandatory part of the pathology reporting dataset in the United Kingdom. The reasons behind this variability on behalf of clinicians are unknown. This may be due to inconsistent detection rates shown above or may be that it is rare to find EMVI without the association of more traditional adverse features such as nodal disease or increased T-stage. However, the evolution of rectal cancer management may lead to a change in attitude towards EMVI if a more selective approach is taken to neoadjuvant treatment in the light of clinical trial evidence. For example, the universal policy of irradiating all T3 tumours or any tumour that has
local nodal disease may be over-treating a proportion of patients. There is accumulating evidence that not all T3 tumours behave the same and that it is depth of penetration through the mesorectum (T3 sub-stage) that is prognostic\cite{20,21}. Further, in the presence of optimal TME surgery nodal disease may not be prognostic for local recurrence\cite{22}. In these situations whereby early T3 tumours or those with N1 disease may not benefit from neoadjuvant chemoradiotherapy, it may be EMVI which tips the balance towards preoperative treatment. Another consideration is that stage II tumours are a heterogenous group and it is those which demonstrate EMVI that have a much higher risk of disease recurrence and may ultimately benefit from adjuvant chemotherapy\cite{23}. The more consistent detection rates, found in more recent reports usually use the terminology of "extramural venous invasion". Messenger et al\cite{24} have offered suggestions which may help pathologists improve detection rates - the use of elastin stains to identify cases where there is uncertainty; and to reference imaging studies such as MRI to guide sampling.

MRI can accurately identify EMVI both before and after CRT\cite{18,25,26}. It has also been shown to detect cases of EMVI which have been “missed” on routine pathology\cite{25}. A further benefit of MRI is that it is able to visualise the entire rectum in-situ whereas the analysis of a small sample of the tumour is dependent on macroscopic assessment by the pathologist in the first instance, to ensure a representative area has been evaluated.

Current multicentre studies such as BACCHUS (Bevacizumab And Combination Chemotherapy in rectal cancer Until Surgery)\cite{27} and MARVEL (Molecular And Radiological Evaluation of Extramural venous invasion in RectaL Cancer)\cite{28}, may help in resolving some of these issues and future results will be highly anticipated.

In conclusion, the presence of EMVI leads to worse survival outcomes. As detection rates become more consistent, EMVI may be considered as part of risk-stratification in rectal cancer. Standardised histopathological definitions and MRI may improve detection rates in the future.

**COMMENTS**

**Background**

Extramural venous invasion is a poor prognostic factor in rectal cancer. Many of the historical studies investigating extramural venous invasion (EMVI) did not use a standardised method of detection. With modern techniques in both pathology and radiology we have been able to identify EMVI more consistently and confidently. This has helped clinicians to offer patients optimal treatment.

**Research frontiers**

Despite good historical evidence EMVI remains a contentious prognostic factor with many clinicians outside Europe.

**Innovations and breakthroughs**

This systematic review adds further high-quality evidence to the clinical importance of EMVI in rectal cancer and may influence future treatment decision making.

**Applications**

EMVI should be specifically sought by radiologists and pathologists to offer patients a more accurate prognostic of rectal cancer and aid clinicians in treatment decision making, specifically for adjuvant chemotherapy.

**Peer-review**

This manuscript is good paper, well written and well presented.

**REFERENCES**


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Chand M et al. EMVI in rectal cancer

2013; 6192900 DOI: 10.1002/1097-0142(19831001)52[16]


Dukes CE, Bussey HJ. Venous Spread in Rectal Cancer: (Section of Proctology). *Proc R Soc Med* 1941; 34: 571-573 [PMID: 19992363]


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