

## 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<sup>[1-7]</sup> 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<sup>[8]</sup>. 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<sup>[9,10]</sup>. Furthermore, the reliance on pathology for identification of EMVI particularly after neoadjuvant treatment (CRT) may lead to under-detection<sup>[11]</sup>.

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<sup>[11]</sup>. These inconsistencies 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 (1965-2014), EMBASE (1980-2014), CINAHL (1982-2014) 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<sup>[12]</sup> 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<sup>[2,6,13-16]</sup>. There was clinical heterogeneity in the stains used, the common ones being used were H + E, Gieson's, elastin

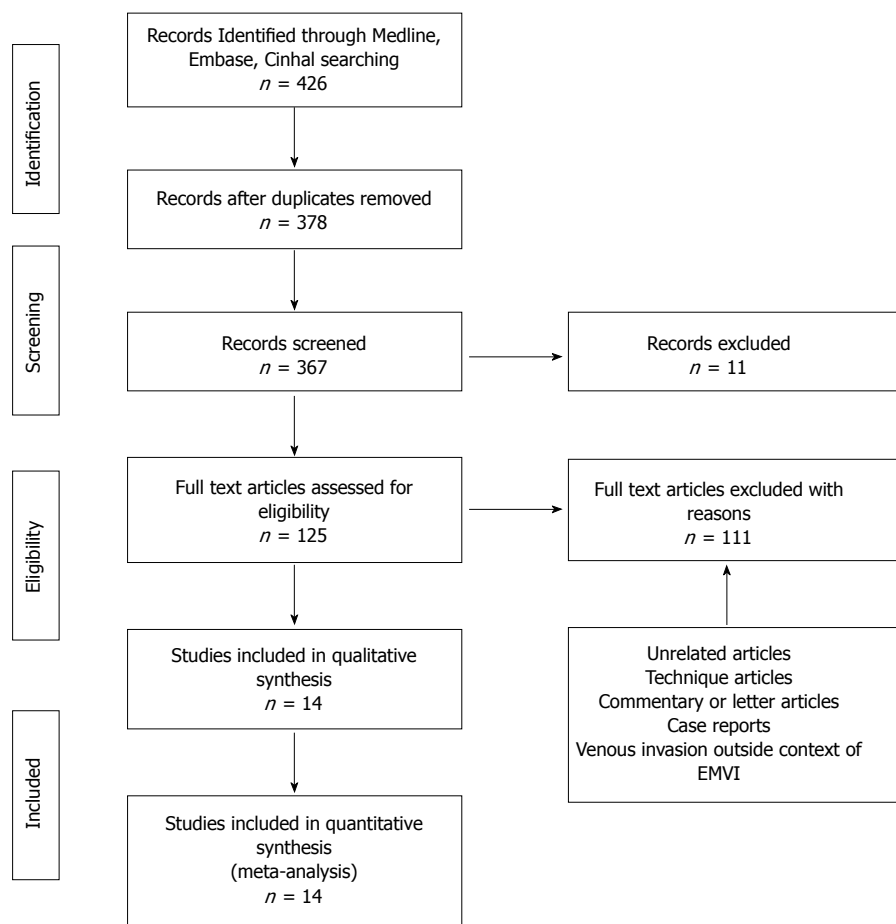


Figure 1 Flowchart showing search strategy for systematic review. EMVI: Extramural venous invasion.

**Table 1** The prevalence of vascular invasion in rectal cancer

Author	Year	No. patients	Study design	No. of pathologists, blinding	Stain	Tumour site	Elastin stain	No. EMVI +ve pts	Prev VI +ve	EMVI +ve 5 yr survival	Independent prognosticator
Brown <i>et al</i> <sup>[29]</sup>	1938	170	Retrospective	Unspecified	H + E	Rectum	Yes	104	61%	No 5 yr data	No comment
Dukes <i>et al</i> <sup>[30]</sup>	1941	689	Prospective	Unspecified	No stain	Rectum	No	107	17%	No 5 yr data	No comment
Seefeld <i>et al</i> <sup>[13]</sup>	1943	100	Prospective	1, blinded	H + E, Gieson's	Rectum	Yes	20	20%	5%	No comment
Madison <i>et al</i> <sup>[31]</sup>	1954	42	Prospective	Unspecified	Brominol, H + E, Gieson's	Rectum	Yes	19	43%	No 5 yr data	No comment
Carroll <sup>[17]</sup>	1963	1996	Retrospective	Unspecified	H + E	Rectum	No	240	11.8%	36%	No comment
Khankhania <i>et al</i> <sup>[32]</sup>	1977	143	Retrospective	Unspecified	Not stated	Rectum	No	70	19% (BVI + LVI)	Data not usable	EMVI is +ve IPS
Talbot <i>et al</i> <sup>[6]</sup>	1980	706	Prospective	2, blinded	H + E, elastin	Rectum	Yes	366	52%	33%	No comment
Rich <i>et al</i> <sup>[15]</sup>	1983	142	Prospective	1, blinded	H + E	RS/Rectum	No	23	17%	No 5 yr data	No comment
Freedman <i>et al</i> <sup>[4]</sup>	1984	494	Retrospective	Unspecified	No comment	Rectum	Yes	89	36%	31%	No comment
Jass <i>et al</i> <sup>[16]</sup>	1986	447	Prospective	1, blinded	H + E	Rectum	No	116	26%	41%	EMVI - No IPS
Sasaki <i>et al</i> <sup>[33]</sup>	1987	774	Retrospective	Unspecified	H + E	Rectum	No	163	21% (extramural only)	No 5 yr data	No comment
Minsky <i>et al</i> <sup>[14]</sup>	1988	168	Retrospective	1, blinded	H + E, elastin	RS/Rectum	Yes	81	48%	33%	EMVI - No IPS
Harrison <i>et al</i> <sup>[2]</sup>	1994	348	Retrospective	2, blinded	H + E, elastin	Rectum	Yes	74	21.2%	21%	EMVI has IPS
Ptok <i>et al</i> <sup>[18]</sup>	2006	1043	Retrospective	Unspecified	Not state	Rectum	No	75	9%	80.7% LVI +ve	EMVI - No IPS

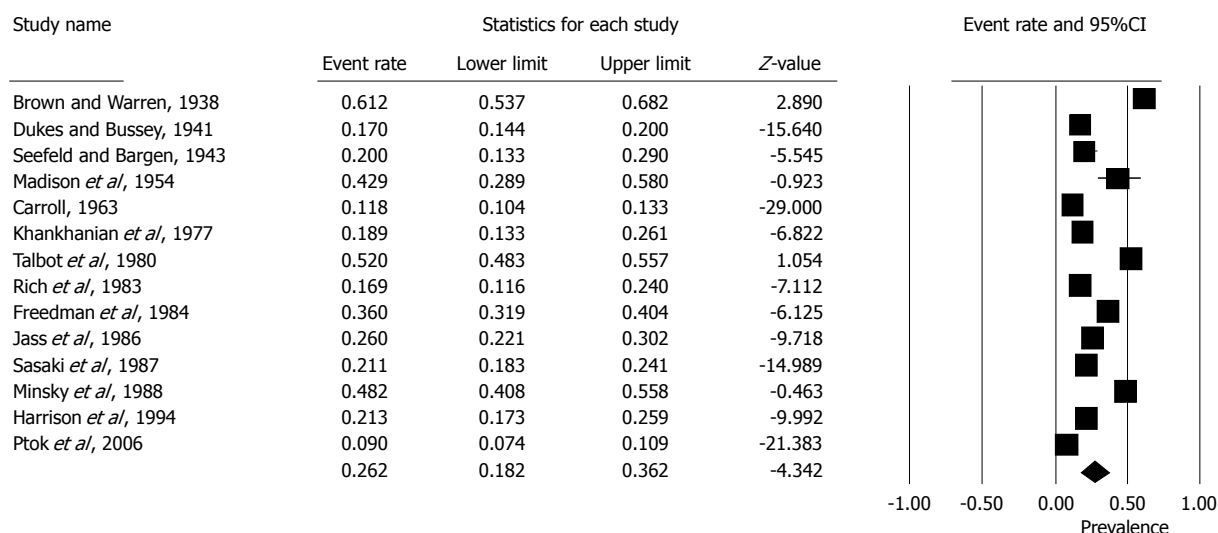


Figure 2 Forest plot for prevalence of extramural venous invasion.

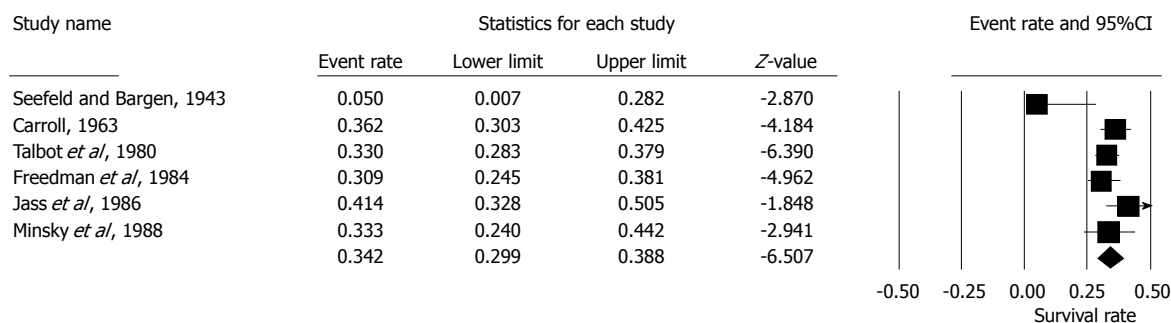


Figure 3 Forest plot for 5-year overall survival in extramural venous invasion positive rectal cancer.

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

**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, I<sup>2</sup> = 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<sup>[4,6,13,14,16-18]</sup>. The pooled overall survival was 39.5% [Random effects: Event rate 0.395 (0.29, 0.51), z = -1.9, Q = 58.06, I<sup>2</sup> = 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<sup>[19]</sup>. 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<sup>[20,21]</sup>. Further, in the presence of optimal TME surgery nodal disease may not be prognostic for local recurrence<sup>[22]</sup>. 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 pre-operative treatment. Another consideration is that stage II tumours are a heterogeneous group and it is those which demonstrate EMVI that have a much higher risk of disease recurrence and may ultimately benefit from adjuvant chemotherapy<sup>[23]</sup>.

The more consistent detection rates, found in more recent reports usually use the terminology of "extramural venous invasion". Messenger *et al*<sup>[24]</sup> 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<sup>[8,25,26]</sup>. It has also been shown to detect cases of EMVI which have been "missed" on routine pathology<sup>[25]</sup>. 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)<sup>[27]</sup> and MARVEL (Molecular And Radiological Evaluation of Extramural venous invasion in Rectal Cancer)<sup>[28]</sup>, 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 prognosis 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.

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