MANUSCRIPT TITLE PAGE

A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI detected extra-mural vascular invasion (mrEMVI) versus mrEMVI negative cases

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MINI-ABSTRACT

A meta-analysis of patients with rectal cancer, assessing the prevalence of MRI detected extra-mural vascular invasion (mrEMVI), of metastases at presentation and after surgery in mrEMVI positive versus negative tumours. mrEMVI positive tumours were prevalent in 34% of reported studies and were over five more likely to present with metastases and almost four times more likely to develop metastases after surgery compared with mrEMVI negative tumours.

STRUCTURED-ABSTRACT

Background: Pathologic extramural vascular invasion (EMVI) is an independent prognostic factor in rectal cancer but can also be identified on magnetic resonance imaging (mrEMVI). We perform a meta-analysis to determine the risk of metastatic disease at presentation and after surgery in mrEMVI positive patients compared with negative tumours.

Methods: Electronic databases were searched from January 1980 to March 2016. Conventional meta-analytical techniques were used to provide a summative outcome. Quality assessment of the studies was performed.

Results: Six articles reported on mrEMVI in 1262 patients. There were 403 patients in the mrEMVI positive group and 859 patients in the mrEMVI negative group. The combined prevalence of mrEMVI positive tumours was 0.346(Range=0.198-0.574). Patients with mrEMVI positive tumours presented more frequently with metastases compared to mrEMVI negative tumours [fixed effects model: OR=5.68, 95%CI(3.75,8.61), z=8.21, df=2, p<0.001]. Patients who were mrEMVI positive developed metastases more frequently during follow-up [random effects model:OR=3.91,95%CI(2.61,5.86),z=6.63,df=5,p<0.001].

Conclusions: mrEMVI is prevalent in one third of patients with rectal cancer. mrEMVI is a poor prognostic factor as evidenced by the five fold increased rate of synchronous metastases and almost four fold ongoing risk of developing metastases in follow up after surgery.

Key words: extramural vascular invasion, MRI, rectal cancer

INTRODUCTION:

The link between histopathologic vascular invasion (EMVI) in specimens and metastatic disease was first reported in 1938 by Brown and Warren (Gibson et al., 2014). Talbot and colleagues subsequently showed that tumor spread into “thick-walled vessels” was evident in almost 52% of 703 rectal cancer specimens. Follow-up of their series showed a significantly worse 5-year survival rate and an almost four fold risk of developing liver metastases (40%) in patients with EMVI compared to EMVI negative tumours (14%) (Talbot et al.). The prevalence of EMVI varies greatly and is under-reported on histopathologic specimens (Messenger et al., 2012, Quasar Collaborative et al., 2007). The reasons for this may include lack of specific definitions and inconsistent analysis techniques despite efforts to improve this (Messenger et al., 2011, Kirsch et al., 2013).

MRI is able to demonstrate normal veins within the mesorectum as distinctive low signal serpiginous structures and when disrupted or expanded by tumour signal this is strongly linked to the likelihood of pathologic EMVI being detected in the specimen. This led to the standardization of mrEMVI deifinitions in the preoperative assessment of rectal cancer as “serpiginous extension of tumour signal within a vascular structure – resulting in contiguous or discontinuous expansion of a vein by tumour signal” (supplementary figure 1) (Smith et al., 2008c, Brown et al., 2003, Shihab et al., 2011, Taylor et al., 2014a, Taylor et al., 2008, Nougaret et al., 2013, Chand et al., 2014b). By comparing pre and post treatment scans, MRI identifies the persistence of EMVI in a greater percentage of patients than histopathology (mrEMVI)(Chand et al., 2015a) and has a high sensitivity even when enhanced histopathologic techniques are used (Jhaveri et al., 2016). Several studies have reported the prevalence of mrEMVI and its correlation to the development of metastatic disease (Sohn et al., 2014, Chand et al., 2015a, Bugg et al., 2014, Smith et al., 2008c, Hunter et al., 2012, Seehaus et al., 2015, Kim et al., 2016). Given the standardised, reproducible and

prognostically validated methods of describing tumour using MRI~~,~~ it is considered a standard for preoperative risk-stratification and treatment decision-making (Network, NICE, Glimelius et al., Ernst-Stecken et al., 2004, Brown et al., 2003, Chand et al., 2015b, 2006, Battersby et al., 2015, Yu et al., 2014, Taylor et al., 2014b, Taylor et al., 2011, Smith et al., 2008a, Shihab et al., 2011). Despite this, patients presenting with the finding of mrEMVI are treated in different ways with a lack of consensus on the use of adjuvant therapy. In a recent survey, only 55% of surgeons and 57% of oncologists considered it when deciding on post-operative treatment; this may lead to under-estimation of the risks of metastatic disease and the consequent under-treatment of an MRI identified high-risk group (Chand et al., 2014a). Identifying the true overall prevalence of mrEMVI and the risk of metastatic disease will help in establishing the need, or lack thereof, for further treatment strategies and would certainly aid in patient discussions regarding the potential advantages or disadvantages of adjuvant therapy.

This meta-analyses aims to establish the true overall prevalence of rectal tumours with mrEMVI, its association with metastatic disease at the time of presentation and development of distant disease after surgery.

METHODS

Registration & protocol

This meta-analysis was registered on the PROSPERO database a priori with an outline of the proposed hypotheses and analysis (Siddiqui et al.).

Hypothesis

Tumours that are mrEMVI positive demonstrate a higher incidence of synchronous and metachronous metastases compared with mrEMVI negative tumours.

Searching and Selection

All studies examining the outcomes in patients with rectal cancer and MRI-detected

extramural vascular invasion (EMVI) from January 1980 (first human publications regarding MRI) to July 2016 were identified. The MEDLINE, EMBASE and CINAHL databases available through the United Kingdom's National Health Service National Library of Health website, the Cochrane library and PubMed available online. Text words “rectal cancer”, “vascular invasion”, “extramural”, “tumour in vessels”, “medical imaging”, “magnetic resonance”, “MRI” were used in combination with the medical subject heading “rectal cancers”. Irrelevant articles, reviews and meta-analyses evident from the titles and abstracts were excluded. Relevant articles referenced in these publications were obtained and the references of identified studies were searched to identify any further studies. No language restriction was applied. A flow chart of the literature search according to PRISMA guidelines (Liberati et al., 2009) is shown in supplementary figure 2. 171 articles were screened for relevance. Of the 171 papers initially detected there were 55 duplicates leaving 116 records. Of these 116 records that were screened, most were pathology based and were excluded. Some of the studies were reviews and some studies captured by our search strategy were on unrelated subjects. On further scrutiny 6 studies comparing outcomes of rectal tumours with and without mrEMVI were found to have useful data for the summative outcome.

Quality Assessment

The methodological quality of the trials included for meta-analysis is explained comprehensively in Table 3. Assessment was performed by 2 authors independently (M.R.S.S. & J.B) (Rangel et al., 2003, Chalmers et al., 1981, Jadad et al., 1996).

Data Extraction

Each included article according to our meta-analysis criteria (Supplemenary table 1) was reviewed by two researchers. This was performed independently and if any conflict arose resolution was through discussion prior to analysis. Only papers examining outcomes in rectal cancer with and without mrEMVI were included. Where more specific data was

required the authors of manuscripts were contacted. Our main outcome measures were synchronous and metachronous metastases. For the purposes of this meta-analysis, synchronous metastases were defined as the presence of metastatic disease prior to surgical intervention and metachronous disease was defined as the occurrence of metastases after surgery during the follow-up period.

Data Synthesis

Statistical analyses were performed using Comprehensive Meta-Analysis 2006 for Windows XP (Borenstein M, 2005). A value of $p<0.05$ was chosen as the significance level for outcome measures. Binary data (number of metastases) were summarized as risk ratios (OR) and combined using the Mantel-Haenszel method (Egger et al., 2006). Heterogeneity of the studies was assessed according to Q and I^2. A random and fixed effects method was used. Studies were excluded on an individual basis to assess for influence on heterogeneity. In a sensitivity analysis, 1 was added to each cell frequency for trials in which no event occurred, according to the method recommended by Deeks et al (Deeks et al., 2001). Forest plots were used for the graphical display.

RESULTS

Six articles (Sohn et al., 2014, Chand et al., 2015a, Bugg et al., 2014, Smith et al., 2008c, Hunter et al., 2012, Seehaus et al., 2015) reporting on metastatic disease in patients with rectal cancer and extramural vascular invasion were retrieved from the electronic databases met the inclusion criteria (Supplemenary table 1). Two studies were from the same center but evaluated different time cohorts (Chand et al., 2015a, Smith et al., 2008c). One study included a combination of synchronous and metachronous metastases (predominately synchronous) and was included in the analyses for both outcome measures, exclusion of this study did not alter the significance for both synchronous or metachronous metastases (Sohn et al., 2014). For one study, the mrEMVI status in a cohort of patients was obtained after

contacting the authors (Hunter et al., 2012). A further study evaluated persistent ymrEMVI status after preoperative chemoradiotherapy (Chand et al., 2015a). Characteristics of each article are given in Table 1 and 2. The methodological quality of the trials included for meta-analysis is shown in Table 3 (Rangel et al., 2003, Chalmers et al., 1981, Jadad et al., 1996).

Prevalence of MRI defined EMVI positive rectal tumours

The combined prevalence of mrEMVI positive tumours from the six studies (Sohn et al., 2014, Chand et al., 2015a, Bugg et al., 2014, Smith et al., 2008c, Hunter et al., 2012, Seehaus et al., 2015) was 0.346 (CI=0.237-0.474) and is graphically portrayed in figure 1.

Synchronous metastases

Three studies incorporating a total of 804 patients (Smith et al., 2008b, Sohn et al., 2014, Hunter et al., 2012) contributed towards a summative outcome. Seventy patients had metastases out of 212 patients with mrEMVI (33%). Fifty-two patients presented with metastases out of 592 patients without mrEMVI (9%).

Patients with mrEMVI positive tumours presented more frequently with metastases at presentation compared to mrEMVI negative tumours [fixed effects model: OR=5.68,95% CI(3.75,8.61),z=8.21,p<0.001; figure 2]. There was no significant heterogeneity among trials (Q=1.85,df=2,p=0.40,I^2=0) and the fixed effects model was used.

In a sensitivity analysis one study was excluded (Sohn et al., 2014) due to clinical heterogeneity (inclusion of synchronous and metachronous metastases) although the heterogeneity was not reduced and the outcome remained significant [fixed effects model: OR=4.60, 95% CI (2.34,9.07), z=4.41, p<0.001]. Thus patients with mrEMVI were over four times more likely to present with metastases compared to patients without mrEMVI.

Metachronous metastases

Six studies incorporating 1262 patients (Sohn et al., 2014, Chand et al., 2015a, Bugg et al., 2014, Smith et al., 2008c, Hunter et al., 2012, Stewart et al., 2007) contributed towards a

summative outcome. 159 out of 403 patients had metastases and were mrEMVI positive (39%). 125 out of 859 patients had metastases and were mrEMVI negative (15%).

Patients who had mrEMVI positive tumours more often had metastases during follow-up compared with mrEMVI negative tumours [fixed effects model: OR=4.02, 95%CI (2.99,5.39), z=9.26, p<0.001; random effects model: OR=3.91, 95%CI (2.61,5.86), z=6.63, p<0.001; figure 3]. There was no significant heterogeneity among trials (Q=8.53,df=5,p=0.129,I^2=41) and the fixed and random effects models were used.

One study was excluded (Sohn et al., 2014) due to clinical heterogeneity (inclusion of synchronous and metachronous metastases) and heterogeneity was reduced (Q=4.35,df=5,p=0.36,I^2=8) but the outcome remained significant [fixed effects model: OR=3.26, 95% CI (2.29,4.66), z=4.35, p<0.001]. Therefore patients with mrEMVI over three times more likely to develop metastases than mrEMVI negative tumours.

DISCUSSION

The present analysis has shown that mrEMVI indicates poorer disease free survival (DFS) (Chand et al., 2014b). Thus, identifying the burden of disease in the population and its almost 4 fold increased risk of further metastatic disease may in future influence the use of neoadjuvant and adjuvant treatment strategies and certainly warrants future trial designs that take into account the presence of mrEMVI as a risk factor.

Main findings

This analysis of 804 patients has shown that those with mrEMVI are five times more likely to have metastases at presentation compared to those without. Analysis of 1262 with mrEMVI positive tumours are almost four times more likely to develop metastases on follow-up. The meta-analysis has also shown that MRI detected prevalence of EMVI in rectal cancer is 34.6% (CI: 23.7-47.4%) and thus amounts to over a third of all rectal cancers. Although the link between pathologic EMVI and liver metastases is well established (Talbot et al., 1980),

its reporting by individual pathologists is highly variable with documented pathologic under-reporting of pEMVI resulting in rates of only 9-21% in published audits (Kirsch et al., Messenger et al., Messenger et al., Betge et al., 2012, Bhangu et al., 2013, Courtney et al., 2009, Gibson et al., 2014, Stewart et al., 2007). Furthermore pathologic EMVI status is only available after surgery thus limiting the ability to tailor preoperative therapy. Arguably, MRI assessment of EMVI can be justified as a gold standard as it has both a higher detection rate and represents an independent risk factor for recurrence.

Importance and clinical implications

mrEMVI positive tumours represent a large cohort (34.6%) within the rectal cancer population and carry a significantly high risk of metastatic disease. Its positive identification could lead to better surveillance of high risk patients as well as future improvements in therapeutic strategies (Hunter et al., 2012, Slesser et al.). This analysis has quantified the metastatic risk at presentation and after surgery following analysis of more than 800 patients who were identified as mrEMVI positive thus enabling important prognostic information from the preoperative MRI assessment to be shared with patients. This is relevant because the current TNM classification and treatment policies largely fail to account for this prognostic group(Bujko et al., 2010). Existing recommendations for patients with pEMVI are based on historical studies which were limited by the low prevalence and under-reporting of EMVI or misreporting vascular tumour deposits as "lymph nodes" (Ueno et al., 2007, Ueno et al., 2012) . Node negative tumours in such studies showed a far greater overall survival and disease free survival rates than those currently observed in mrEMVI positive node negative tumours (Quasar Collaborative et al., 2007). The potential benefit of adjuvant chemotherapy in this previously unidentified group consequently remains uncertain (Quasar Collaborative et al., 2007). The risk of metastatic disease associated with mrEMVI has implications for administration of long course chemoradiotherapy (LCRT) with additional preoperative

chemotherapy given either before or after LCRT and this is currently under investigation in a number of clinical trials (Nilsson et al., 2013, Slesser et al., 2015, Courtney et al.).

Appraisal of evidence and heterogeneity

The overall incidence of mrEMVI in the individual studies were similar except for two studies which showed a prevalence of 53% (Chand et al., 2015a) and 57% (Seehaus et al., 2015). One of these studies evaluated a population limited to advanced rectal tumours undergoing preoperative chemoradiotherapy which accounts for the higher prevalence (Chand et al., 2015a). The other studies included both earlier and locally advanced stage tumours (Smith et al., 2008b, Sohn et al., 2014, Thomson et al., 2015). In this meta-analysis one study included only mrEMVI positive patients at baseline and compared patients who were persistently positive with EMVI that regressed. In this paper, those tumours that regressed to ymrEMVI negative had similar low rates of metastatic disease as those who are mrEMVI negative on baseline scans (Chand et al., 2015a). The link between mrEMVI in metastatic disease has been further highlighted by studies showing that about 90% of patients with hepatic metastases are EMVI positive (Slesser et al., 2015). One limitation of this analysis is that the cohorts may not be truly comparable due to tumour related factors however most of our results did not identify significant heterogeneity between studies for the outcomes of interest, suggesting the cohorts are comparable. In the results where there was significant heterogeneity (clinical or statistical), it sets the stage for further research to identify the reasons for variability and inconsistency between studies. This meta-analysis has more power than individual studies to identify a true difference that exists between two groups, especially for outcomes that require larger sample sizes. In addition, our meta-analysis not only has more power to identify statistical difference, but also, increases the precision in estimating the size of the effects of difference between groups.

Quality assessment & Limitations

Quality assessment of the studies (retrospective reviews of databases) included in this meta-analysis is shown in table 3. It is too early to comment on publication bias.

The individual articles in our studies showed clinical heterogeneity when examining metastatic disease after surgery and this may be due to differing follow-up times. One study included synchronous and metachronous metastases (Sohn et al., 2014) and when excluded from our analysis reduced the heterogeneity. Some studies (such as Smith et al) included in our meta-analysis had small sample sizes that resulted in wide confidence intervals and caution should be used when drawing conclusions. Despite the lack of statistical heterogeneity, the clinical differences need to be borne in mind as well as the relatively small number of patients retrieved from the literature. The small numbers involved also has the potential for over-estimating the Odds Ratios of our overall outcome results and therefore although our results are strongly supportive of our conclusions caution should be maintained and further trials would certainly be warranted. One potential area is that of tumour related factors which may affect the results however all the pre-operative variables assessed were comparable in the studies and whilst contributing to heterogeneity and to some extent the overall odds ratios it is unlikely to affect the direction of the result. The MERCURY II study has also shown that nodal status did not predict for local or distant failure, in addition the mrEMVI positivity rate was greater than the CRM positive rate therefore making mrEMVI likely to be a more predictive factor (Battersby et al., 2015). Further studies should standardise follow up of cases to add further to the literature.

Future studies

Further prospective matched-cohort studies focusing on outcomes will help in risk stratification of mrEMVI positive tumours. The clear definitions of EMVI identified on MRI, and confirmed in this meta-analysis, means that this imaging modality should be adopted as the gold standard in assessment of this prognostic factor. This analysis has shown that

mrEMVI is a likely precursor to metastatic disease and will be formally tested in a prospective study . With its greater detection of patients who are at high risk of developing metastatic disease than current methods, treatment with systemic chemotherapy may, in future, reduce the risk of recurrent disease. Further research into the biological processes of development of metastases and mrEMVI may be facilitated by study into release of tumour cells and DNA into the circulation (Talbot et al., 1981).

CONCLUSION

EMVI is a poor prognostic factor in rectal cancer. It is now readily identified on MRI as an independent prognostic factor with a significant prevalence in rectal tumour population. This meta-analysis has shown that patients with mrEMVI positive tumours are over five times more likely to have synchronous metastases and over three times as likely to develop metastases after surgery.

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Table Legends

Table 1 – Outcome measures

Table 2 – Characteristics of included studies

Table 3 - Methodological qualities of comparative studies included

Figure legends

Figure 1 – The proportion of patients with rectal cancer who have extramural vascular invasion identified on MRI at the time of presentation

Figure 2 – The proportion of patients with metastases at the time of presentation who have mrEMVI positive tumours versus mrEMVI negative tumours

Figure 3 – The proportion of patients who develop metastases after surgery who had mrEMVI positive tumours before surgery versus mrEMVI negative tumours before surgery

Supplementary Table 1 – Inclusion Criteria

Supplementary Figure 1 – MRI features of EMVI

Supplementary Figure 2 – Search Strategy

Table 1: Outcome measures

	Smith et al 2008	*Hunter et al 2012*	*Bugg et al 2014*	*Sohn et al 2014*	*Chand et al 2015*	*Seehaus et al 2015*
Patients (n)						
EMVI +	24	90	53	98	99	39
EMVI -	97	146	149	349	89	29
Number with metachronous metastases						
EMVI +	18	35	13	42*	36	15
EMVI -	41	18	10	37*	14	5
Number of local recurrences						
EMVI +	ND	ND	ND	ND	5	ND
EMVI -	ND	ND	ND	ND	3	ND
Disease/Recurrence Free Survival (3yr)						
EMVI +	35% (sd=9.75)	ND	ND	ND	42.7% (sd=12.95)	ND
EMVI -	74.1% (sd=4.53)	ND	ND	ND	79.2 (sd=4.6)	ND
Number with synchronous metastases						
EMVI +	7	21	ND	42*	ND	ND
EMVI -	4	11	ND	37*	ND	ND
Site of metachronous metastases						
EMVI + (Lung/Liver/Multi/Other)	ND	4/15/12/4	ND	ND	5/4/4/23	ND/15/ND/ND
EMVI - (Lung/Liver/Multi/Other)	ND	1/6/11/0	ND	ND	7/1/2/4	ND/5/ND/ND
Site of synchronous metastases						
EMVI + (Lung/Liver/Multi/Other)	ND	2/12/3/4	ND	ND	ND	ND
EMVI - (Lung/Liver/Multi/Other)	ND	4/4/2/1	ND	ND	ND	ND

ND = No Data; *data was combined with synchronous and metachronous (6 months post surgery), most were synchronous but unable to extract breakdown.

Table 2: Characteristics of studies comparing patients with and without EMVI

	Smith et al 2008	*Hunter et al 2012*	*Bugg et al 2014*	*Sohn et al 2014*	*Chand et al 2015*	*Seehaus et al 2015*
Total Number of paients (n)	121	236	202	447	188	68
Age of patients (range)	ND	64.5 (sd=13)	66 (32-84)	61.0 (36.6-75.4)	ND	64.3 (sd=14)
Gender (m:f)	77:65	161:69 (ND=6)	123:79	291:156	121:67	44:24
Tumour (MRI)						
T-stage	T3	Overall Stage III&IV: 89	ND	T3	137 (Defined as >3c)	T3
Node positive	ND	ND	ND	286	123	ND
CRM positive	ND		ND	75	81	ND
Height	ND	Low – 100 Middle – 54 High – 76 ND - 6	ND	Below Peritoneal Reflection – 259 Above Peritoneal Reflection - 61	Low – 69 Middle – 62 High - 57	Low – 32 Middle – 36 High - 0
Neoadjuvant/Adjuvant Therapy	+/+ (M)	+/-	Primary Surgery Only	Primary Surgery/+ (M)	+/+	ND/ND
Follow up	36 months	36 months	12 months	6 months	36 months	12 months
Study methodology	UK cohort – London	Canadian Cohort	UK cohort – E.Anglia	Korean cohort	UK cohort - London	South American Cohort
Country						
Time period	2000-2004	2004-2008	2007-2012	2011-2012	2006-2013	2011-2012

ND = No Data; M = Mix of cases

Table 3. Methodological qualities of comparative studies included
(Adapted from the Scottish Intercollegiate Guidelines Network and Rangel et al

Quality measures	*Smith et al 2008*	*Hunter et al 2012*	*Bugg et al 2014*	*Sohn et al 2014*	*Chand et al 2015*	*Seehaus et al 2015*
Inclusion Criteria	1	1	1	1	1	0.5
Exclusion Criteria	1	1	1	1	1	1
Can the number of participating centers be determined	1	1	1	1	1	1
Can the number of radiologists who participated be determined	0	0	0	0	0	1
Can the reader determine where the authors are on the learning curve for the reported procedure	0	0	0	0	0	1
Are diagnostic criteria clearly stated for clinical outcomes if required	1	1	1	0	1	1
Is there any way that they have tried to standardize the radiological interpretation	1	1	1	0	1	1
Do authors address whether there is any missing data	1	1	1	1	1	1
Were patients in each group treated along similar timelines	1	1	1	1	1	1
Outcomes clearly defined?	1	1	1	0	1	1

Figure 1 – The proportion of patients with rectal cancer who have extramural vascular invasion identified on MRI at the time of presentation

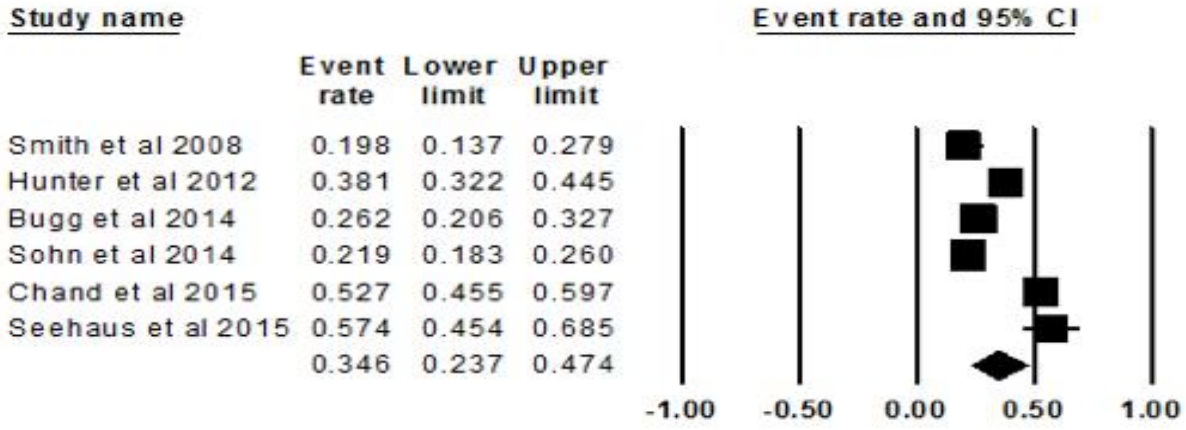

Figure 2 – The proportion of patients with metastases at the time of presentation who have mrEMVI positive tumours versus mrEMVI negative tumours

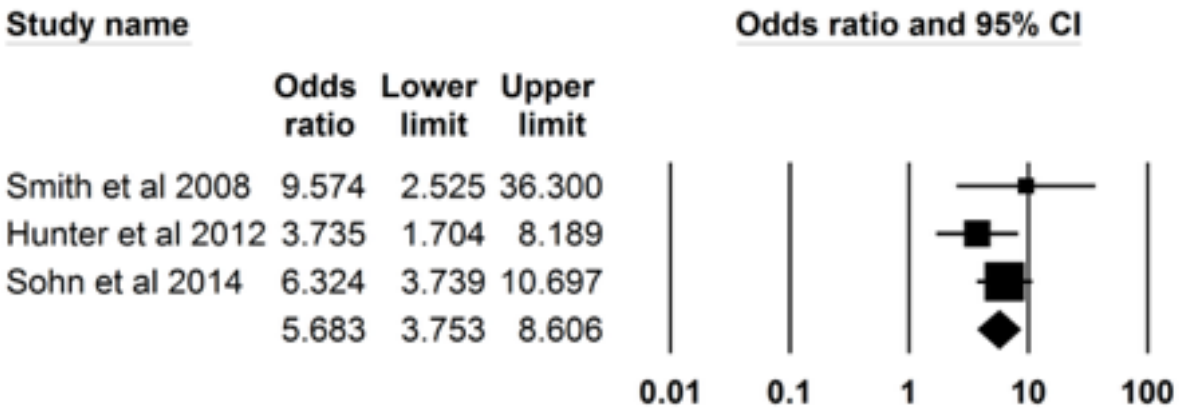

Figure 3 – The proportion of patients who develop metastases after surgery who had mrEMVI positive tumours before surgery versus mrEMVI negative tumours before surgery