

REVIEW ARTICLE

Resection of colorectal liver metastases and extra-hepatic disease: a systematic review and proportional meta-analysis of survival outcomes

William J. Hadden¹, Philip R. de Reuver², Kai Brown^{1,2}, Anubhav Mittal^{1,2}, Jaswinder S. Samra^{1,2} & Thomas J. Hugh^{1,2}

¹Northern Clinical School, University of Sydney, and ²Upper GI Surgical Unit, Royal North Shore Hospital and North Shore Private Hospital, Sydney, New South Wales, Australia

Abstract

Background: Colorectal cancer (CRC) accounts for 9.7% of all cancers with 1.4 million new cases diagnosed each year. 19–31% of CRC patients develop colorectal liver metastases (CRLM), and 23–38% develop extra-hepatic disease (EHD). The aim of this systematic review was to determine overall survival (OS) in patients resected for CRLM and known EHD.

Methods: A systematic review was undertaken to identify studies reporting OS after resection for CRLM in the presence of EHD. Proportional meta-analyses and relative risk of death before five years were assessed between patient groups.

Results: A total of 15,144 patients with CRLM (2308 with EHD) from 52 studies were included. Three and 5-year OS were 58% and 26% for lung, 37% and 17% for peritoneum, and 35% and 15% for lymph nodes, respectively. The combined relative risk of death by five years was 1.49 (95% CI = 1.34–1.66) for lung, 1.59 (95% CI = 1.16–2.17) for peritoneal and 1.70 (95% CI = 1.57–1.84) for lymph node EHD, in favour of resection in the absence of EHD.

Conclusion: This review supports attempts at R0 resection in selected patients and rejects the notion that EHD is an absolute contraindication to resection.

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Correspondence

Thomas J. Hugh, Northern Upper GI Surgical Unit, Royal North Shore Hospital, St. Leonards NSW 2065, Australia. Tel: +61 2 9463 2899. Fax: +61 2 9463 2080. E-mail: tom.hugh@sydney.edu.au

Introduction

Colorectal cancer (CRC) is a major health burden with a world-wide estimate of 1.4 million new cases annually resulting in approximately 694,000 deaths.¹ Approximately 19–31% of all patients with CRC present with, or subsequently develop, liver metastases (CRLM). These are defined as either synchronous if found at the time of presentation of the primary tumour or metachronous if identified at a later date. At diagnosis, a further 23–38% of patients already have, or will develop extra-hepatic disease (EHD).^{2–4} EHD is defined as either synchronous or metachronous to the primary CRC and/or the CRLM.

Over the past 10 years widespread use of modern chemotherapeutic and biological agents, combined with careful case selection and improved surgical techniques, have markedly

improved outcomes in patients with metastatic CRC.^{5–8} The presence of limited EHD is no longer considered an absolute contra-indication to liver resection as long as the future remnant liver is of sufficient volume, the patient is fit for a major operation, and there is potential for an R0 resection at both sites.^{9–18}

The current literature is difficult to interpret in relation to the benefit of removing EHD due to selection variability, multimodal treatment regimens and the inherent subjectivity of the term ‘resectable’. Compounding this difficulty are the numerous permutations of possible presentations regarding the timing of both the CRLM and EHD. This ambiguity is reflected in numerous inconsistencies in consensus statements and guidelines regarding the value of resection of CRLM in the presence of EHD.^{19,20}

The aim of this systematic review was to determine overall survival (OS) in patients who underwent resection of CRLM and known EHD (synchronous or prior to the CRLM). Patients were stratified by site of EHD and then comparisons made between outcomes in this group and those who underwent resection of CRLM in the absence of EHD.

Materials and methods

The study protocol for this systematic review followed the PRISMA checklist (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and consulted the MOOSE checklist (Meta-analysis of Observational Studies in Epidemiology) for relevant additions.^{21,22}

Eligibility criteria

Full-text English language studies of adult human patients published between December 2004 and December 2014 were considered for this review. Case reports, systematic reviews, meta-analyses and studies of recurrence were excluded.

Search

A systematic search was applied to PubMed, Embase, Cinahl and Medline databases up to December 2014 to identify studies reporting resection of CRLM in the presence of known EHD with the terms referenced in Fig. 1. All articles were vetted by title then abstract, with the full text of the remaining articles examined for inclusion. Reference lists of all included articles were searched for further studies also meeting inclusion criteria.

Study selection

Selection criteria were predefined and applied to results of the search strategy. Original studies reporting OS in patients undergoing first-time curative liver resection for CRLM with known EHD were included in the systematic review. Studies were excluded if follow-up was less than three years, resection was undertaken for palliative purposes or if the study population was exclusive. All included patients had undergone prior curative resection of the primary tumour. Only patients undergoing resection of both CRLM and synchronous or previous EHD were included in these analyses; outcomes in patients whose EHD was detected after resection for CRLM were excluded.

Data collection

Reported survival, mortality, morbidity, demographic, peri-operative and chemotherapy (no stratification) data specific to patients resected for CRLM with EHD were extracted.

Level of evidence/risk of bias

Level of evidence for each study was assessed using the Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence.²³ The methodological tool described by Downs and Black

was modified for non-randomized studies by excluding the power calculation and applied to all included studies.²⁴

Outcomes

Primary outcome measures were proportionally-weighted OS by EHD site (lung, peritoneum and lymph nodes) for those patients undergoing both CRLM and EHD resection and relative risk (RR) of death before five years comparing those resected for CRLM and EHD to those resected for CRLM without EHD.

Statistical analysis

Freeman–Tukey transformations were used to obtain proportional OS, while the X^2 test with $k-1$ degrees of freedom was used to assess RR of death by five years.²⁵ Survival data were expressed as pooled OS or RR and because significant heterogeneity (I^2) was found, more conservative random-effects methods were used.²⁶ P values were calculated with the X^2 test or Freeman–Tukey transformation as appropriate; $P < 0.05$ was considered statistically significant. Data analysis was performed using Review Manager 5.0 software (Cochrane Collaboration, Oxford, UK) and MedCalc for Windows, version 12.5 (Ostend, Belgium).^{25–27}

Results

Selection

Constrained by year, language, study type and population this search returned 1470 unique articles. Vetting as per Appendix 1 yielded 45 studies whose reference lists were searched manually, identifying six further studies whose references were also manually examined. One study was identified while background-researching other reviews in this field. This process yielded 52 articles for inclusion in the systematic review, from which data were extracted.

Study characteristics

The 52 studies included in this review examined a total of 15,144 patients who had hepatic resection for CRLM. Of these 15,144 patients, 2308 presented with EHD known at hepatic resection. Three-hundred seventy-two of these patients with EHD did not progress to resection of both CRLM and EHD and were therefore excluded from further analysis. The remaining 1936 patients underwent hepatic resection plus resection of the EHD and comprise the population in the following analyses (Table 1).

Level of evidence/risk of bias

The studies in this review are comprised of level 2b (observational cohort) and 3b (case–control) as per the Oxford CEBM guideline.²³ Median modified Downs and Black methodology score for included studies is 15/26 (IQR = 14–17) (Supplementary Fig. 1).

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OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Evaluation
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Figure 1 Search strategy applied to PubMed database

Patient, disease, operative and post-operative characteristics

Twenty-one studies report patient characteristics specific to those resected for CRLM in the presence of EHD ([Supplementary Table 1a](#)). The median reported values for the number of liver lesions was two, and the median size of the largest lesion was 38 mm. Fifty-four percent of all patients in these studies were male. [Supplementary Table 1b](#) shows that in the 17 studies reporting characteristics of the primary tumour and liver metastases 75% of patients had a colon primary, 74% had primary

tumour lymph node involvement, 48% had CRLM's present synchronous to the primary tumour, and 42% had unilateral liver disease at the time of resection (all values median). Finally, in 13 studies reporting specific R0 resection rates for our cohort of interest, a median 85% of patients had an R0 resection ([Supplementary Table 1c](#)).

Morbidity and mortality

In patients who underwent resection of CRLM in the presence of EHD, 10 studies report a median mortality of 1.8% (range

Table 1 Characteristics of included studies reporting overall survival after resection in patients with CLM and EHD^{16,28–57,69–89}

First author	Year of publication	Study period start	Study period end	CLM patients (n)	CLM patients with EHD (n)	CLM resected, EHD not resected (n)	CLM and EHD resected (n)
<i>Elias</i>	2005	1987	2000	308	84		84
<i>Elias</i>	2006	1993	2003	24	24		24
<i>Minagawa</i>	2006	1980	2002	187	39		39
<i>Shah</i>	2006	1992	2002	39	12		12
<i>Tanaka</i>	2006	1992	2004	53	14		10
<i>Favero</i>	2007	1989	2005	5	5		5
<i>Figueras</i>	2007	1990	2004	501	73	7	66
<i>Kianmanesh</i>	2007	1996	2005	43	16		16
<i>Kornprat</i>	2007	1998	2002	98	18		18
<i>Miller</i>	2007	1981	2000	131	46		46
<i>Niu</i>	2007	1990	2006	402	63	63	
<i>Takahashi</i>	2007	1992	2005	30	12		11
<i>Tamandl</i>	2007	2001	2004	200	18	18	
<i>Tanaka</i>	2007	1985	1999	156	20		20
<i>Tsukioka</i>	2007	1990	2006	46	4		4
<i>Zakaria</i>	2007	1960	1995	662	35		35
<i>Adam</i>	2008	1992	2006	757	47		47
<i>Aoki</i>	2008	1988	2005	187	37		37
<i>Bennett</i>	2008	2002	2004	59	22	22	
<i>Rees</i>	2008	1987	2005	929	164		136
<i>Tanaka</i>	2008	1987	2006	85	14		14
<i>Wicherts</i>	2008	1992	2007	817	7		7
<i>Byam</i>	2009	1995	2008	383	39		39
<i>Carpizo</i>	2009	1992	2007	1369	127	10	117
<i>Chua</i>	2009	1997	2008	55	16		16
<i>Karanjia</i>	2009	1996	2006	283	12		12
<i>Lordan</i>	2009	1996	2006	285	4		4
<i>Marudanayagam</i>	2009	2000	2007	43	10		10
<i>Neeff</i>	2009	1987	2006	44	13		13
<i>Oussoultzoglou</i>	2009	2000	2006	45	45		45
<i>Reissfelder</i>	2009	2002	2008	281	40	40	
<i>Varban</i>	2009	1991	2007	142	14		14
<i>Elias</i>	2010	1990	2007	543	77		77
<i>Hemming</i>	2010	1996	2009	40	13		13
<i>House</i>	2010	1985	2004	1600	229		229
<i>Maithel</i>	2010	2004	2006	160	68	68	
<i>van der Pool</i>	2010	2000	2008	272	21		21
<i>Adam</i>	2011	1990	2006	186	186	59	127
<i>Pulitano</i>	2011	1996	2007	1629	171		171
<i>Beppu</i>	2012	2000	2004	727	82		82
<i>Gomez</i>	2012	2006	2010	184	30	30	
<i>Kawano</i>	2012	1997	2008	35	8		8
<i>Pulitano</i>	2012	1996	2007	61	61		61
<i>Allard</i>	2013	1985	2010	42	42		30

Table 1 (continued)

First author	Year of publication	Study period start	Study period end	CLM patients (n)	CLM patients with EHD (n)	CLM resected, EHD not resected (n)	CLM and EHD resected (n)
Edwards	2013	2002	2012	4	4		4
Hattori	2013	1999	2009	96	29		29
Ishibashi	2013	2000	2008	61	13		3
Maggiori ^a	2013	1993	2009	98	37		37
Marin	2013	1996	2010	44	21		21
Mavros	2013	1982	2011	97	97		97
Meimarakis ^a	2013	1981	2009	543	13		13
Liu	2014	2000	2012	73	12		12
Total				15,144	2308	317	1936
Median				136.5	23	30	21
Range				4–1629	4–229	7–68	3–229

^a Case control study, all others are observational.

0–8%), while 16 studies report a median morbidity of 30.5% (range 12.5–80%) (Supplementary Table 2).

Resection of liver & lung metastases

Twenty-three studies^{15,18–21,31,36,37,42,45–58} report survival after resection of CRLM in a total of 574 patients with lung metastases. This patient group accounts for 25% of all patients resected for CRLM and EHD, and 4% of all patients resected for CRLM (Supplementary Table 3). Proportional meta-analysis of survival data for those in whom both CRLM and known EHD was resected reveal three and 5-year OS of 58% (95% CI = 52–65%, $I^2 = 7\%$) and 26% (95% CI = 15–39%, $I^2 = 79\%$) (Fig. 2a), while brief quantitative analysis shows that this group has a relative risk (RR) of mortality by five years after resection of 1.49 (95% CI = 1.34–1.66) when compared to patients resected for CRLM without EHD (Fig. 3a). Reported median OS of this cohort is 42 months (Supplementary Table 4a).

Resection of liver & peritoneal metastases

Sixteen studies^{16,28–42} report survival after resection of CRLM in a total of 378 patients with peritoneal metastases, accounting for 17% of all patients resected for CRLM and EHD, and 3% of all patients resected for CRLM (Supplementary Table 3). Proportional meta-analysis of survival data for those in whom both CRLM and known EHD was resected show three and 5-year OS of 37% (95% CI = 31–43%, $I^2 = 0\%$) and 17% (95% CI = 9–25%, $I^2 = 65\%$) (Fig. 2b), while brief quantitative analysis shows a RR of mortality by five years for this group of 1.59 (95% CI = 1.16–2.17) compared to those resected for CRLM alone (Fig. 3b). Reported median OS of this cohort is 29 months (Supplementary Table 4b).

Resection of liver & nodal metastases

Twenty-one studies^{16,28,31,33,34,36,39,40,43–55} report survival after resection of CRLM in a total of 559 patients with nodal disease,

which accounts for 24% of all patients resected for CRLM and EHD, and 4% of all patients resected for CRLM (Supplementary Table 3). Proportional meta-analysis of survival data for those in whom both CRLM and known EHD was resected reveal three and 5-year OS of 35% (95% CI = 29–41%, $I^2 = 15\%$) and 15% (95% CI = 11–20%, $I^2 = 27\%$) (Fig. 2c), while brief quantitative analysis shows a RR of mortality by five years after resection for this group of 1.70 (95% CI = 1.57–1.84), compared to patients resected for CRLM without EHD (Fig. 3c). Reported median OS of this cohort is 25 months (Supplementary Table 4c).

Resection at other sites

In nine studies, a total of 175 patients were reported to have a locally invasive metastasis, accounting for 8% of all patient with EHD and 1% of all patients with CRLM in this review. Four studies explicitly state 3-year, 5-year and median survivals of 40%, 23% and 27 months in patients with metastatic spread to local structures – including the diaphragm, the inferior vena cava (IVC) or biliary tree. Eight studies totalling 98 patients (4% of those with EHD in this review) had EHD at rare sites (bone, brain, ovary, spleen, etc.), while three studies reported a median 5-year survival of 51% in patients grouped together by presentation at these rare metastatic locations (Supplementary Tables 3 & 4d–e).

Finally, 16 studies report 3-year, 5-year and median survivals of 43%, 26% and 32 months in patients where all EHD is lumped into one category and six studies report median 3-year, 5-year and median survivals of 26%, 14% and 17 months in patients with multiple sites of EHD (Supplementary Table 4f–g). Two studies report only that EHD of an unknown site has been resected.^{56,57}

R0 versus R1/2

Quantitative analysis of R0 versus R1/2 resection showed a relative risk of death by five years of 0.73 (95% CI = 0.60–0.90)

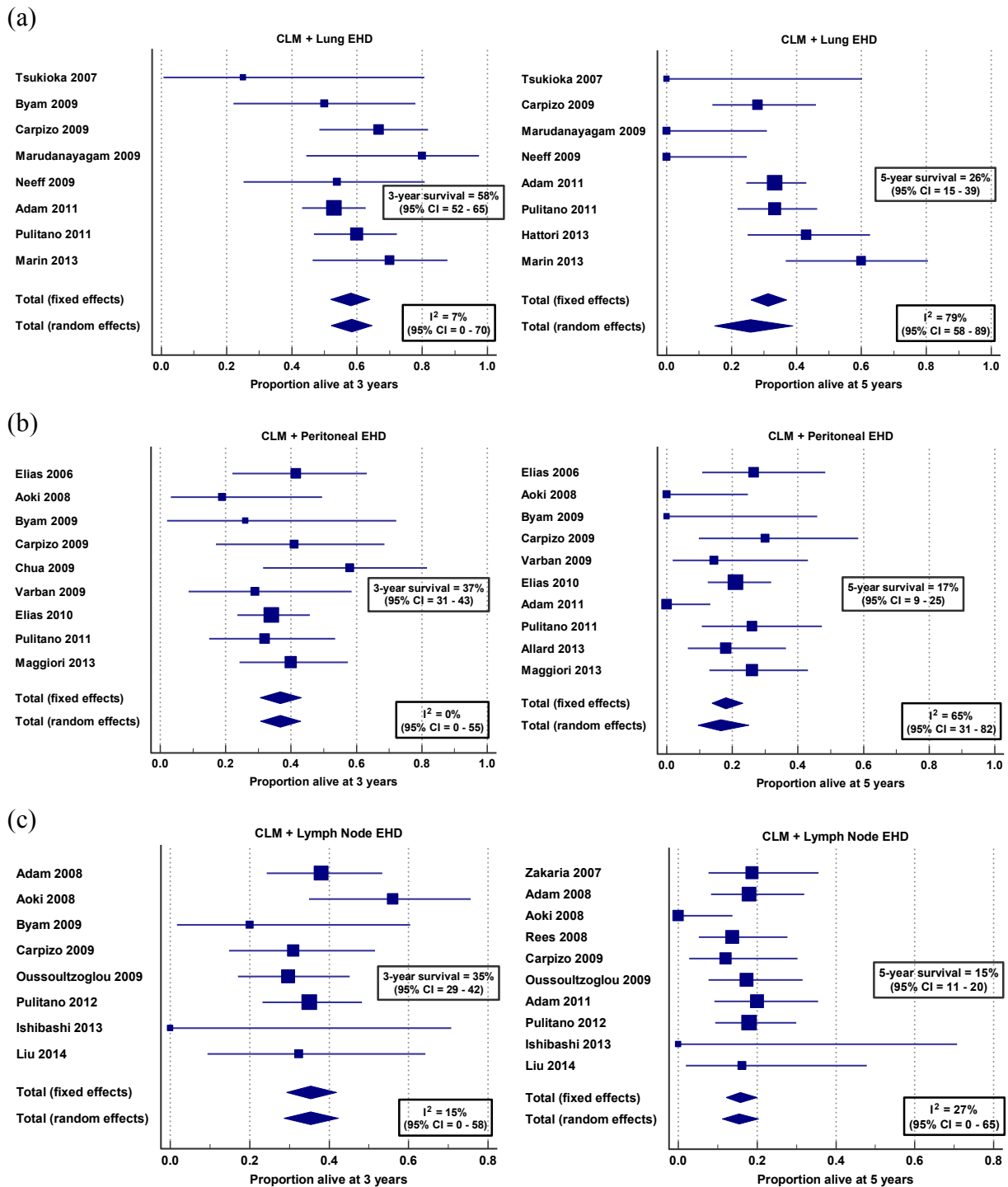


Figure 2 Proportional meta-analyses of three and 5-year overall survival in patients resected for CRLM and EHD in the (a) lung,^{16,34,39,40,72,77,78,81,87} (b) peritoneum^{16,29,33-35,37-42} and (c) lymph nodes^{16,33,34,36,39,47,48,50,52,53,55}

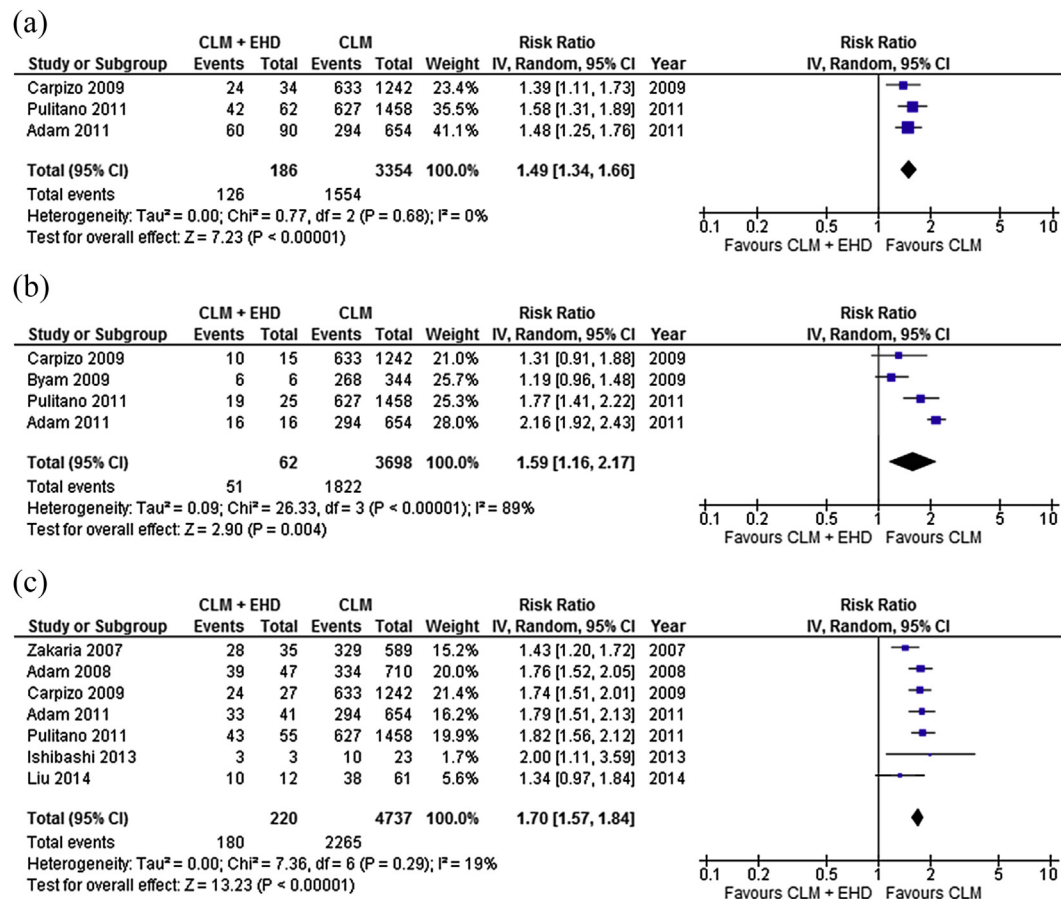


Figure 3 Forest plot comparing 5-year overall survival in patients resected for CRLM without EHD versus patients resected for both CRLM and EHD in the (a) lung,^{16,39,40} (b) peritoneum^{16,34,39,40} and (c) lymph nodes^{16,39,40,47,48,53,55}

in those for whom both CRLM and EHD achieved R0 resection (Supplementary Fig. 5).

Discussion

Without treatment the median survival and 5-year overall survival of patients with CRLM is eight months and 0%, respectively.^{58,59} The prognosis worsens when there are both liver and extra-hepatic metastases. Complete R0 resection of isolated CRLM offers 5-year survivals of up to 50%. However, if EHD is left in situ survival decreases dramatically to less than 20%.^{60,61} An R0 resection is an essential component for long-term survival and this was confirmed in the current systematic review. Although best available chemotherapy can prolong survival in patients with CRLM and EHD to as much as 12–13 months, and even provide a 1% 5-year survival, evidence from available cohorts shows that no treatment modality approaches outcomes offered by curative resection.^{34,62,63} This is the first review to use

a proportional meta-analysis of overall survival in patients presenting for CRLM and EHD resection. Although it is difficult to pool heterogeneous data from a group of observational studies, this method was chosen because it gives statistical weight to data based on cohort size, and therefore more accurately approximates true survival outcomes when compared to a median of values from multiple studies.

This study demonstrates that resection of CRLM and lung EHD, most often performed as staged procedures, is associated with a 42-month median survival and a 26% 5-year survival. When CRLM and EHD confined to the peritoneum (all volumes of disease were treated together in this review) are resected patients can expect a median 29-month survival and a 17% 5-year survival. Finally, when CRLM and lymph node metastases are resected, patients achieve a 25-month median survival and a 15% 5-year survival. It is worth noting that these studies include highly selected patients, most of whom are also treated with combination chemotherapy and/or biological agents.

Nevertheless, these survival data exceed the best outcomes in patients receiving systemic chemotherapy alone.^{60,62,63} In contrast, patients who undergo resection of EHD at multiple sites have a median survival of only 17 months which is similar to what can be expected with chemotherapy alone.⁶³ The worse outcomes with EHD at multiple sites may reflect the lower R0 resection rates achieved in these patients.

Mortality rates after resection of isolated CRLM in specialist centres are usually less than three percent.⁵⁹ Therefore, the median 1.8% mortality rate demonstrated in this review confirms that resection of CRLM + EHD can be done safely.

Reported median overall survivals for resection of CRLM and EHD in the lung, peritoneum and lymph nodes of 42, 29 and 25 months in this study are comparable to previous reviews. Hwang *et al.* reported 45-month, 29-month and 26-month median overall survivals while Chua *et al.* reported similar figures of 41, 25 and 25 months for these same disease sites.^{64,65} In contrast to these previous reviews, the present study extracted data specific to patients presenting with CRLM and known EHD from within cohorts that are often only investigating EHD as a prognostic factor in a larger cohort. Importantly, this review separated survival data from those patients whose EHD was either left in situ, of ambiguous fate, or was discovered after a previous liver resection. Furthermore, this review is the first to summarize OS after resection of CRLM and EHD as a proportional meta-analysis. This is a more representative measure of true outcome compared with using median overall survival figures alone. Unfortunately, it was not possible with the available data to present overall 5-year DFS figures which would give the best indication of possible cure after resection. We believe that future studies would benefit from a more concerted focus on 5-year DFS.

This review was limited by the available literature, specifically by the heterogeneity between observational studies and the lack of high-level evidence comparing similar patient groups. Expectedly, the data analysed show significant relative risks of death by 5-years after resection of CRLM and EHD in the lungs (RR = 1.49), peritoneum (RR = 1.59) and lymph nodes (RR = 1.70) compared with patients resected for CRLM in the absence of EHD. More interesting comparisons would involve patients with similar CRLM and EHD treated with resection of all metastases versus either resection of CRLM only or best medical therapy. However, there is a paucity of data available and therefore it was not possible to compare these cohorts.^{66,67} Level 2b and 3b evidence, coupled with a median methodological score of only 15/26 (Supplementary Fig. 1), indicates a strong selection bias in many of the studies, and poor overall quality of available evidence for analysis.

A further limitation of the data reported here was the fact that all lymph node metastases were combined together for the sake of simplifying the analysis. This is problematic as there may be

marked differences in survival depending on which lymph nodes are involved. Metastases in nodes at the hepatic pedicle confer a more favourable prognosis than metastases at more distant sites. This was demonstrated by Adam *et al.* who found a 25% 5-year survival in patients with involvement of the portal pedicle compared with a 0% 5-year survival when there were metastases in the para-aortic region.⁴⁸ These findings have been confirmed in other studies.^{36,52}

Another limitation of this review was the length of time over which the pooled patients were treated, and consequently the variation in the types and duration of chemotherapy and biological agents used. It was not possible in the analysis to tease out potential contributions of the evolving medical treatments to overall survival. This is an important area of future study to determine the true impact of resection of EHD on long-term outcomes.⁶⁸

The wide gap in survival outcomes reported for patients resected for CRLM and EHD compared with other treatment modalities supports attempts at R0 resection where appropriate, and in carefully selected patients. Specifically, CRLM resection should be considered even if EHD is present, as long as it is possible to achieve an R0 resection at both sites. This is especially the case for EHD confined to the lungs or when there is limited spread to the peritoneum. However, the exact number or extent of metastases that are appropriate for resection in the presence of resectable CRLM's is still unclear. With regard to lymph node metastases, there are insufficient data to make firm conclusions. Certainly, individual studies^{36,48,52} demonstrate reasonable outcomes after resection of nodes at the hepatic pedicle, albeit involving small numbers of patients. However, less favourable outcomes after resection of lymph nodes at distant sites must be weighed against the peri-operative risks.

Considering that the evidence generated in this review is limited by the non-randomized nature of the studies, the heterogeneity between those observational studies and the highly selected cohorts they present, it is impossible to make specific selection recommendations based on these findings. Instead, this review supports increased consideration of resection for patients presenting with CRLM and known EHD, rejects the notion that EHD is an absolute contraindication to liver resection and encourages further study of both OS and DFS to better elucidate the objective benefit conferred by resection of EHD.

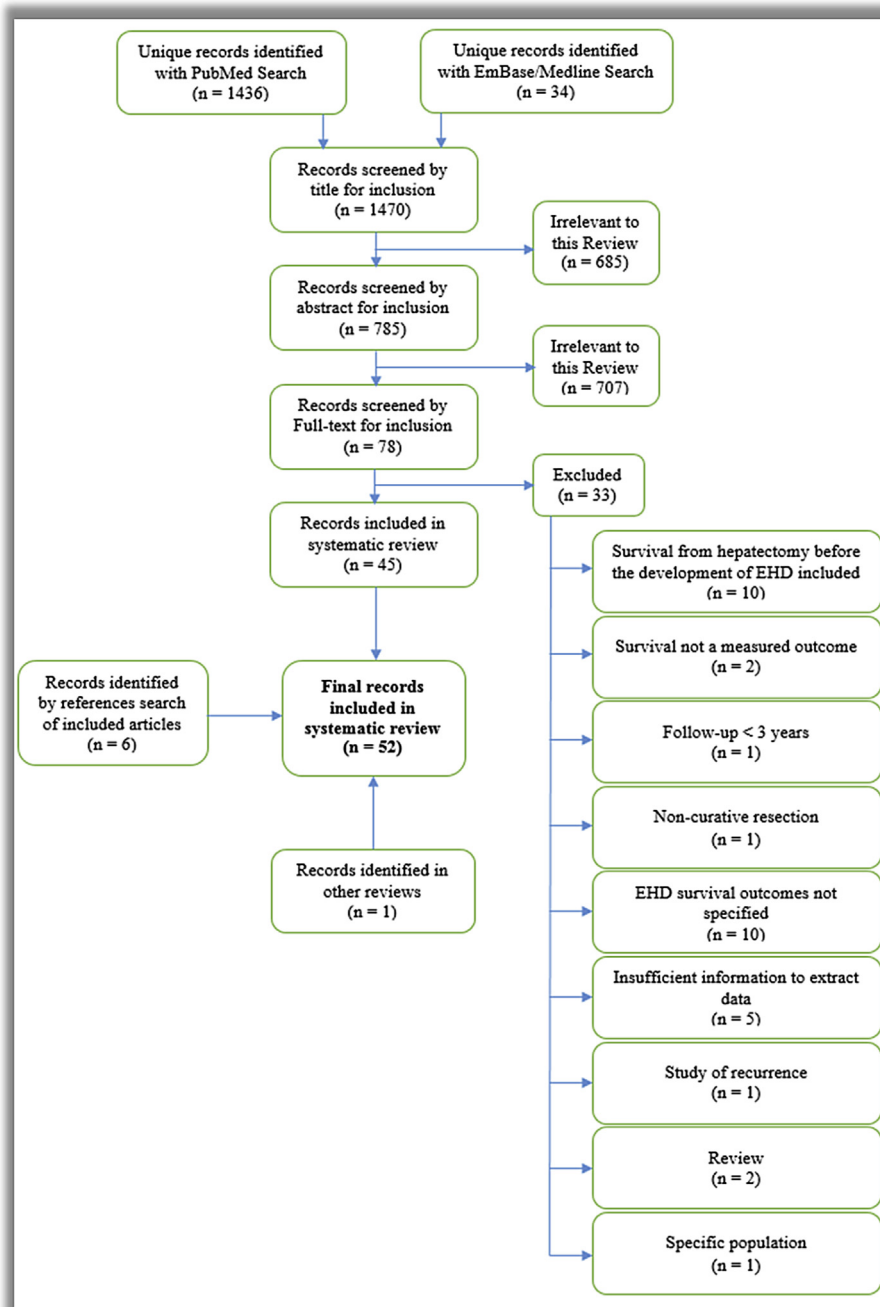
Funding sources

None.

Conflicts of interest

None to declare.

Appendix 1. Flow diagram depicting acquisition of reviewed articles.



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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.hpb.2015.12.004>.