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Histopathological prognostic factors for colorectal liver metastases: A systematic review and meta-analysis of observational studies

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Summary. Introduction. Resection is the mainstay of treatment for colorectal liver metastases (CRLMs). Many different histopathological factors related to the primary colorectal tumour have been well studied; however, histopathological prognostic factors related to CRLMs are still under evaluation. Objective. To identify histopathological factors related to overall survival (OS) and disease-free survival (DFS) in patients with resected CRLMs.

Methods. A systematic review was performed with the following databases up to August 2020: PubMed, EMBASE, Web of Science, SciELO, and LILACS. The GRADE approach was used to rate the overall certainty of evidence by outcome.

Results. Thirty-three studies including 4,641 patients were eligible. We found very low certainty evidence that the following histopathological prognostic factors are associated with a statistically significant decrease in OS: presence of portal vein invasion (HR, 410.50 [95% CI, 0.37 to 0.68]; I^2=0%), presence of perineural invasion (HR, 0.55 [95% CI, 420.36 to 0.83]; I^2=0%), absence of pseudocapsule (HR, 0.41 [CI 95%, 0.29 to 0.57], p<0.00001; I^2=0%), presence of satellite nodules (OR, 0.45 [95% CI, 0.26 to 0.80]; I^2=0%), and the absence of peritumoural inflammatory infiltrate (OR, 0.20 [95% CI, 0.08 to 0.54]; I^2=0%). Outcome data on DFS were scarce, except for tumour borders, which did not present a significant impact, precluding the meta-analysis.

Conclusion. Of the histopathological prognostic factors studied, low- to moderate-certainty evidence shows that vascular invasion, perineural invasion, absence of pseudocapsule, presence of satellite nodules, and absence of peritumoral inflammatory infiltrate are associated with shorter overall survival in CRLMs.

Key words: Colorectal cancer, Metastasis, Hepatectomy, Pathology, Prognosis, Surrogate markers, Systematic review, GRADE

Introduction

Colorectal cancer is the third most common cancer among men and the second among women (World Cancer Research Fund, 2018). The liver is the main site of haematogenous metastasis, occurring in approximately 50% of cases during the evolution of the disease (Manfredi et al., 2006). Among all colorectal carcinomas, approximately 15% have already developed synchronic liver metastases at the time of the primary tumour diagnosis (Bengmark and Hafstrom, 1969).

Metastatic involvement of the liver is directly related to the prognosis of the disease (Bengmark and Hafstrom, 1969; Wood et al., 1976; Bengtsson et al., 1981; Krüger et al., 2018). In the first series reporting the surgical treatment of colorectal cancer liver metastases (CRLMs), only 5.7% of patients with multifocal hepatic disease, 27% of patients with metastases located in a single segment or hepatic lobe, and 60% of patients with solitary metastases had a one-year survival rate if resection was not performed (Bengmark and Hafstrom, 1969; Krüger et al., 2018).

With the development of new surgical techniques, anaesthesia, diagnostic methods, chemotherapeutic management, and pre- and postoperative care, surgical

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indications have become increasingly frequent, with lower morbidity and mortality rates. It has been established that with the resection of metastases with free margins, maintaining an adequate liver remnant volume with satisfactory afferent and efferent blood flow and biliary drainage and the resection of all extrahepatic lesions, survival rates between 30% and 50% in five years can be reached (Adam et al., 2004; Mutsaerts et al., 2005; Vassiliou et al., 2007; Abdalla, 2011). However, approximately two-thirds of resected patients will develop recurrence of the disease within 16 months (de Jong et al., 2009).

In contrast to the primary tumour, where histopathological prognostic factors are well established, there are a limited number of publications and an unknown impact regarding liver metastases. The knowledge of the prognostic impact of histopathological factors on survival in patients with resected hepatic metastases from colorectal cancer is therefore lacking. The ability to predict precisely which surrogate marker is the ideal prognostic tool for patients with CRLMs would enable clinical oncologists and surgeons to select the most appropriate treatment and provide a better understanding of the patient's condition as well as assist pathologists in issuing a more detailed report.

Our group recently published a review (Fonseca et al., 2018a) narratively describing some prognostic factors of resected CRC liver metastases, such as the number and size of liver metastases, the presence of lymphatic, vascular, perineural and biliary invasion. We noted that knowledge of the evaluated prognostic factors is useful information that should be included in the pathological report of colorectal liver metastasis specimens, and emerging data from the histopathological aspect of CRLMs have added important information for predicting the long-term prognosis. Another systematic review (Knijn et al., 2013) assessed the histological prognostic factors in CRLMs, and although the authors did not explicitly describe the search strategy, the searched databases, or the methods of synthesis used, they performed a meta-analysis demonstrating a strong correlation between 5-year overall survival (OS) and both portal vein and lymphatic invasion. A more recent review (Barresi et al., 2019) summarized the prognostic relevance of gross and microscopic pathological characteristics in resected liver metastases, and the authors suggested that the pathologic report should not be limited to the confirmation of malignant disease but also include the histopathological prognostic factors evaluation we aimed to study in the present review.

Previous reviews were limited because they did not include all studies in this rapidly evolving field. Additionally, regarding methodology, the authors did not use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rate the certainty of evidence.

We therefore conducted an updated systematic review with explicit methodology to identify the histopathological prognostic factors of resected CRLMs as surrogate markers for OS and disease-free survival (DFS).

Materials and methods

Our study was performed in accordance with the methodology (Altman, 2001; Peat et al., 2014) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement (Stroup et al., 2000). This systematic review was registered in the PROSPERO (International Prospective Register of Systematic Reviews) database under number CRD42018106224.

We performed a systematic review of clinical observational studies and a meta-analysis of the impact of histopathological factors on the prognosis of patients with hepatic metastases of colorectal carcinoma (CRC).

Eligibility criteria

Any observational study (i.e., cohort, case-control, comparative cross-sectional study, case series) in adults (>18 years of age) that evaluated at least one of the following specified prognostic factors of colorectal liver metastases (CRLMs): the degree of tumour differentiation; lymphatic, vascular (hepatic and/or portal), perineural, and/or biliary invasion; tumour border type (expansive or infiltrative); and the presence of: tumour budding (TB), a tumour capsule or pseudocapsule, satellite nodules, peritumoural inflammatory infiltrate, and poorly differentiated clusters was included.

These chosen parameters were selected based on available data concerning the prognostic impact. As possible poor prognostic factors, we evaluated a low degree of differentiation (Beaton et al., 2013; Bosh et al., 2013; Mogoantă et al., 2014); the invasion of lymphatic vessels, blood vessels, and the neural and biliary tracts (Shirabe et al., 1997; Compton, 2007; Beaton et al., 2013; Bosh et al., 2013; Schneider and Langner, 2014; Fernández-Aceñero et al., 2015); and the presence of tumour budding (Bosh et al., 2013), poorly differentiated clusters (Fonseca et al., 2018b), satellite nodules (Fonseca et al., 2018b), and an infiltrative tumour border (Fernández-Aceñero et al., 2015). On the other hand, possible favourable parameters evaluated were the presence of a pseudocapsule (Yamamoto et al., 1999; Knijn et al., 2013; Fonseca et al., 2018b) and peritumoural inflammatory infiltrate (Fonseca et al., 2018b).

The outcomes of interest were OS, defined as the interval from resection until death from any cause, and DFS, defined as the interval from resection to evidence of colorectal liver metastases relapse or death from any cause. When an article reported data on either OS or DFS in different time frames (e.g., 1 year, 3 years, and 5 years), the longest one was chosen.

Data sources and searches

Medical Subject Headings (MeSH) was used based on the terms "hepatic metastases," "liver metastases,"

"colorectal carcinoma," and "histological prognosis" (S1 table). PubMed (Ovid) (1948 to August 2020), EMBASE (Ovid) (1980 to August 2020), Web of Science (ISI) (August 2020), Scientific Electronic Library Online (SCIELO, 1997 to August 2020), and the Latin American and Caribbean Health Sciences Literature Database (Literatura Latino-Americana e do Caribe em Ciências de Saúde, LILACS, 1982 to August 2020) were also searched. The date of the last search was August 11, 2020.

Furthermore, the reference lists of relevant review articles (Knijn et al., 2013; Fonseca et al., 2018b; Barresi et al., 2019) and primary studies were searched manually. We also contacted the corresponding authors to search for additional unpublished data. No language restrictions were imposed, and the search strategy was adapted for each database to achieve satisfactory sensitivity.

Selection of studies

Reviewers independently screened all titles and abstracts identified by the literature search, obtained full-text articles of all potentially relevant studies, and evaluated them against the eligibility criteria. Disagreement between reviewers was solved by discussion or, if necessary, with third party adjudication. Studies reported only as conference abstracts were also considered.

Data extraction

Two authors (CVCO and GMF) independently extracted the following data using a prestandardized data extraction form: characteristics of the study design, number of participants, histopathological prognostic factors, outcome event rates, and follow-up.

Tumours reported as having a mixed tumour border type were considered tumours with infiltrative borders. Regarding the degree of tumour differentiation, well and moderate differentiation or G1 and G2 were considered good prognostic factors, while G3 and G4 were considered poor prognostic factors. The presence of a thin or thick pseudocapsule was classified as a good prognostic factor. Regarding lymphatic invasion, moderate invasion accounted for severe outcomes, and no invasion accounted for mild outcomes, serving as poor or good prognostic factors, respectively. The presence of tumour budding was related to a worse prognosis when compared to absence of budding. Finally, regarding the number of poorly differentiated clusters (PDCs), G3 (more clusters) were considered worse prognostic factors when compared to G1.

When the article reported more than one hepatectomy in the same patient, data were extracted from the first operation. When available, data were extracted separately regarding portal and hepatic vein invasion.

Double counting of participants was avoided when multiple publications with the same population were found. If there was more than one published report on the same group of patients, the articles were analysed to verify whether they reported different outcomes. If they presented the same outcomes, data were extracted from the most recent or most complete article. We referred to "group of studies" in the results section when there were multiple publications of the same study.

Risk of bias assessment

Reviewers independently assessed risk of bias with a modified version of the Ottawa-Newcastle instrument (Guyatt and Busse) that includes confidence in assessment of exposure and outcome, adjusted analysis for differences between groups in prognostic characteristics, and missing data (Guyatt and Busse). For incomplete outcome data in individual studies we stipulated as low risk of bias for loss to follow-up of less than 10% and a difference of less than 5% in missing data between intervention/exposure and control groups (Guyatt and Busse). The answers were categorized as "definitely low," "probably low," "probably high," or "definitely high" for each domain.

Certainty of evidence

The reviewers used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the certainty of evidence for each outcome as high, moderate, low, or very low (Guyatt et al., 2008). Detailed GRADE guidance was used to assess overall risk of bias (Guyatt et al., 2011a), imprecision (Guyatt et al., 2011b), inconsistency (Guyatt et al., 2011c), indirectness (Guyatt et al., 2011d) and publication bias (Guyatt et al., 2011e), and the results are summarized in an evidence profile. To assess the association between any prognostic factors, cohort studies were considered high certainty evidence, while case-control and case series studies were considered low evidence.

For decisions regarding eligibility, risk of bias assessment, and data abstraction, reviewers resolved disagreement through discussion with third-party adjudication if necessary.

Data synthesis and statistical analysis

Our primary analysis was the generic inverse-variance method that pools hazard ratios (HRs) and the associated 95% confidential intervals (CIs) using random-effects models. For outcomes where there was not enough data to allow the primary analysis, pooled odds ratios (ORs) with the Mantel-Haenszel test was the chosen statistical method along with the 95% CIs using random-effects models. Absolute effects and 95% CIs were calculated by multiplying the pooled HRs or ORs and 95% CIs by baseline risk estimates derived from the

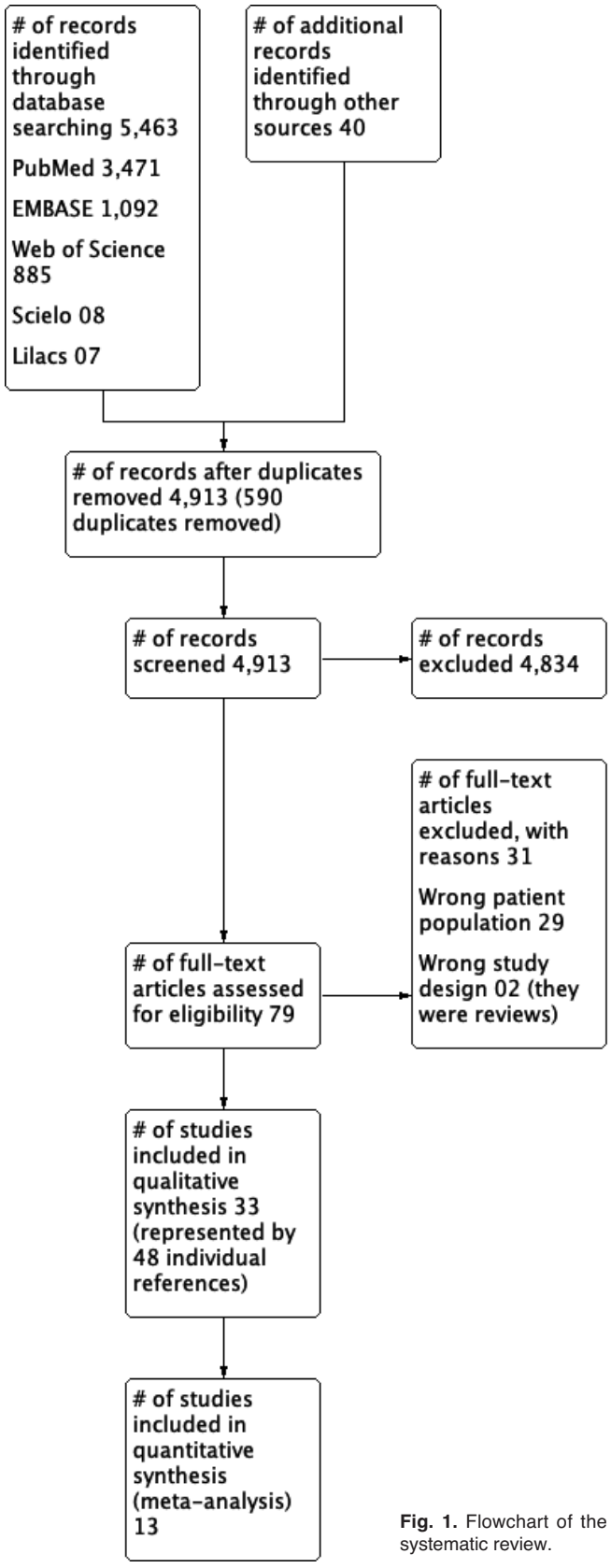

Fig. 1. Flowchart of the systematic review.

study that presented greater weight in the meta-analysis. Specific calculations to arrive at risk differences (RD) from different point estimates (i.e., HRs and ORs) were used. When necessary, we reversed the reported effect size values and the odds ratio outcome measures from primary studies to allow the comparison of worse versus better prognostic variables. When studies provided both adjusted and non adjusted HRs, data from the former were used.

When authors reported data on portal and hepatic vein invasion separately, a subgroup analysis to test the robustness of the findings was performed. We planned to perform a subgroup analysis on the size of the largest metastatic lesion (<or≥4 cm), the use (or not) of systemic chemotherapy, and the presence or absence of cointerventions.

Heterogeneity was evaluated using the chi-square test and the I^2 statistic (Higgins et al., 2003). An I^2 value of 0–40%, 30–60%, 50–90% and 75–100% was interpreted as not important, moderate, substantial or considerable heterogeneity, respectively, and significance was assumed when I^2 was higher than 50% with a P value <0.1.

Publication bias was assessed through the visual inspection of funnel plots for outcomes addressed in 10 or more studies. Review Manager (RevMan) provided the software for all analyses (version 5.3; Nordic Cochrane Centre, Cochrane) [(The Nordic Cochrane Centre, 2011)].

Results

Study selection

Figure 1 presents the process of identifying eligible studies, including publications from systematic reviews (Knijn et al., 2013; Fonseca et al., 2018b; Barresi et al., 2019) and citations identified by a search of electronic databases. A total of 4,080 citations were identified after duplicates were removed. Based on title and abstract screening, 79 full texts were assessed, of which 33 studies were included (represented by 48 individual references – please see supplemental material for references of included studies) involving 4,641 analysed patients in a recruitment period between 1960 (Zakaria et al., 2007) and 2015 (Reijonen et al., 2018) and published in the period between 1991 (Morino et al., 1991) and 2019 (Yonemura et al., 2019). All included studies were available as full-text articles and classified as cohort studies.

We contacted the authors of all included studies to request additional information related to clinical and/or methodological aspects, but only six groups of studies (Murad et al., 2007; Abengózar et al., 2012; Borrego-Estella et al., 2012; John et al., 2013; Lupinacci et al., 2014a,b; Pinheiro et al., 2014; Fernández-Aceñero et al., 2015; Serrablo et al., 2016; Fonseca et al., 2018b; Lionti et al., 2018; Stift et al., 2018) responded and provided the requested information.

Table 1. Study characteristics related to the country, setting, period of study, eligibility criteria, number of participants analysed, mean age, chemotherapy, and duration of follow-up.

Author, year	Country	Setting	Period of study	Inclusion criteria	Exclusion criteria	No. of patients analysed	Age, mean (SD), y	Male, %	Chemotherapy, %	Mean duration of follow-up (months)
Ambiru et al., 1999	Japan	Chiba University Hospital, Chiba	April 1984 to September 1997	Patients underwent curative hepatic resection for colorectal metastases. Criteria for the resection of hepatic metastases from CRC were as follows: good control of the primary tumour, no signs on the preoperative imaging of disseminated disease, and the complete resection of hepatic metastases with acceptable postoperative hepatic function.	NR	168	62[£] (NR)	61.9	Post, 61.9 (adjuvant regional chemotherapy via the hepatic artery or the portal vein)	23[£]
Bockhorn et al., 2009	Germany	NR	April 1998 to December 2006	Patients with CLM presented with the intent of curative liver resections undergoing initial resections for CLM.	Patients with repeat hepatectomies.	332	NR	NR	Pre, 13	60[£]
Bouviez et al., 2014	France	Liver Transplantation and Digestive Surgery Unit of Besançon University Hospital, Besançon	January 1990 to December 2000	Clinical data of patients with CLM who had undergone their first liver resection. All study patients had initially resectable tumours.	NR	86	64 (10)	64	Pre, peri, and post, 37	120[¢]
Brachet et al., 2009	France	Department of Surgery, University Hospital of Angers, Angers	January 1992 to August 2007	Patients who underwent repeat liver resection for metastases of CRC.	Extrahepatic metastases; medical contraindication to hepatic surgery; and unresectable extrahepatic disease.	62	62.2 (9.7)	63	Pre, 22.6 Post, 72.6	NR
Brunner et al., 2014	Germany	University Medical Centre of Regensburg, Regensburg	2004 to 2010	Patients with CLM (confirmed by histology) who underwent liver surgery. Only patients who had surgery with curative intent.	Not enough tissue for a histological evaluation.	201	62[£] (NR)	58.7	Pre, 44.8	37[£]
de Ridder et al., 2015	Netherlands	Tertiary referral hospital	1992 to 2011	Patients who underwent complete liver resection for a solitary CLM were identified.	Patients who were treated with neoadjuvant systemic therapy; and patients who died from postoperative complications, defined as within 30 days after liver resection.	124	64[£] (NR)	61.3	Pre, 14.5	41[£]
Falcão et al., 2018	Portugal	NR	2010 to 2013	Patients who underwent hepatic resection for CLM.	Patients undergoing rehepatectomies, patients who had insufficient clinical data, and those with inadequate histological material.	110	63 (10)	73.6	Pre, 47.3	31.7[£]
Fernández-Aceñero et al., 2015; Abengózar et al., 2012	Spain	Fundación Jiménez Díaz Hospital, Madrid	NR	Patients with CRC with initially resectable hepatic metastasis that received NAC and were subsequently operated on with disease-free margins.	NR	50	62.3 (11.3)	54	Pre, 100	55[£]
Fonseca et al., 2018b; Lupinacci et al., 2014a; Lupinacci et al., 2014b; Pinheiro et al., 2014; Murad et al., 2007	Brazil	University of São Paulo Medical School, São Paulo	1992 to July 2014	Patients who underwent their first resection of CLM.	Patients with incomplete macroscopic resection, postoperative death within 90 days, a pathological complete response, and an inability to access pathological specimens due to technical problems with the slides.	229	60.1 (11.2)	58.1	Pre and post, NR	43.2

Table 1. (continued).

Gomez et al., 2014	UK	Nottingham University Hospitals National Health Service (NHS) Trust, Nottingham	January 2005 to December 2011	Patients undergoing CLM resection. All patients who underwent primary hepatic resection with curative intent were included in the analysis.	NR	259	NR	63.6	Pre, 4.21	28
Hayashi et al., 2010	Japan	Osaka Medical College Hospital, Osaka	1995 to 2008	Patients undergoing initial hepatectomy for CRCLM; an ECOG performance status of 0-2; and adequate haematologic parameters (WBC > 4.0 × 103/L, platelet count > 100 × 109/L), renal function (serum creatinine ≤ 1.2 mg/dL or calculated creatinine clearance by the Cockroft formula ≥ 50 mL/min), or hepatic functions (total bilirubin < 2.0 mg/dL and aspartate aminotransferase, alanine aminotransferase < 100 IU/L).	Patients had to have no serious or uncontrolled concurrent medical illness; and no active infection.	83	66.5 (10.4)	66.3	Pre, 42.2 Post, 71.8	62
John et al., 2013	UK	Hepatobiliary unit in the Freeman Hospital, Newcastle upon Tyne	January 2000 to December 2010	Patients having liver resection for CLM; accepted adequate FLR at least 30% in those considered to have normal liver parenchyma and 40% in those with evidence of parenchymal liver disease. If less than 30%, FLR was measured on CTV, and PVE was routinely considered, and patient fitness was assessed by cardiopulmonary exercise testing.	No signs of disseminated disease on preoperative imaging, nonprogressive disease whilst on chemotherapy based on tumour size measurements on serial CT/MRI scan images; and any concurrent extrahepatic metastases.	432	64.5[£] (NR)	67	Pre, 60	27[£]
Korita et al., 2007; Wakai et al., 2008	Japan	Division of Digestive and General Surgery of Niigata University Medical and Dental Hospital, Niigata	January 1989 to December 2004	Patients with CLM.	Repeat hepatectomy for intrahepatic recurrences.	105	64[£] (NR)	69.5	Post, 64.7	124[£]
Lionti et al., 2018	Italy	Tumor Registry of Colorectal Cancer of the University of Modena and Reggio Emilia, Modena	2007 to 2013	Pathological tumour-node-metastasis stage IV CRC with surgically resected LNs; patients had received surgery for the primary tumour and CLM at the same time to reduce the hospital stay.	Patients who received NAC.	63	64[£] (10.7)	71.4	Post, 100	40[£]
Lunevicius et al., 2001; Koike et al., 2000	Japan	Aichi Cancer Center Hospital, Nagoya	1983 to 1997	Colorectal cancer patients who underwent radical hepatectomy due to liver metastases.	Patients with cirrhotic livers or focal nodular hyperplasia.	69	NR	NR	NR	60[¢]
Mańin Hernández et al., 2009	Spain	Transplantation and Liver Hepatic Unit, Surgery Department, Hospital Universitario Virgen de la Arrixaca, Murcia	September 1996 to December 2006	Patients undergoing surgery for CLM in whom pre-, intra-, and postoperative factors of survival were analysed.	NR	207	61 (12)	66.6	NR, 87.4	55
Minagawa et al., 2007; Kubo et al., 2002; Yamamoto et al., 1995; Yamamoto et al., 1999; Okano et al., 1999, 2000	Japan	Tertiary referral centers. The Department of Surgery, National Cancer Center, Tokyo, and the First Department of Surgery, Shinshu, Matsumoto	January 1980 to December 2002	Patients who underwent curative resection for CLM. Selection criteria for surgery were the possibility of the complete removal of all hepatic and extrahepatic lesions and the possibility of preserving at least 40% of the normal hepatic parenchyma.	The total number of hepatic metastases, their unilateral or bilateral presentation, and the existence of extrahepatic metastasis were not considered exclusion criteria.	369	NR	62.6	NR	49

Table 1. (continued).

Morino et al., 1991	Japan	1st Department of Surgery, University Hospital, Kyoto	1980 to 1986	Patients with liver metastases from CRC underwent hepatic resection. All patients were considered to have had curative resection of the primary tumour according the General Rules for the Clinical and Pathological Study of Colorectal Cancer.	NR	29	64[£] (NR)	55.2	NR	NR
Nagashima et al., 1999	Japan	First Department of Surgery, University Hospital Tokyo	January 1981 to December 1994	Patients with hepatic metastatic tumours from colorectal carcinoma underwent partial hepatectomy.	NR	63	NR	76.2	NR	18[£]
Okano et al., 2003	Japan	First Department of Surgery, Kagawa Medical University, Kagawa	1986 to 2001	Patients who underwent initial hepatic resection for liver metastases from CRC.	NR	41	60[£] (NR)	61	NR	72[£]
Park et al., 2014	Korea	NR	January 2003 to December 2008	Patients who underwent curative resection and a precise histologic evaluation of metastatic lesions.	NR	117	64 (NR)	62.4	Pre, 9.4 Post, 100	34.2
Rajaganeshan et al., 2007	UK	St James's University Hospital, Leeds and the Royal Liverpool University Hospital, Liverpool	June 1994 to June 2000	Patients included had primary CRC resected and were either diagnosed with synchronous liver metastases and underwent resection or developed metachronous liver disease on follow-up surveillance and underwent resection.	Patients with conditions known to predispose to CRC (e.g., inflammatory bowel disease, familial adenomatous polyposis) and those who had undergone preoperative chemoradiotherapy. Additionally, patients who died as a complication of their surgery were excluded.	55	63 (NR)	47.3	Pre, 100.0	47.0
Reijonen et al., 2018	Finland	Transplantation and Liver Surgery Unit at Helsinki University Central Hospital (HUCH), Helsinki	January 2009 to March 2015	Patients who had histologically verified biliary invasion in CLM and were resected with curative intent.	NR	109	65.7 (8.2)	84	Pre and post, 83.9	32[£]
Sasaki et al., 2002	Japan	Department of Surgery I, Oita Medical University, Oita	September 1982 to September 2000	Patients who underwent hepatectomy for liver metastasis from colorectal carcinoma.	NR	65	63.1 (NR)	53.7	NR	37
Serrablo et al., 2016; Borrego-Estella et al. 2012	Spain, Italy	Miguel Servet General University Hospital, Saragossa	January 2004 to April 2010	Patients who underwent 183 hepatic resections for metastatic CRC. All patients had a histological diagnosis of CRC and resectable synchronous or metachronous liver metastasis.	NR	150	NR	NR	Pre, 49.3	43.8
Shirabe et al., 1997	Japan	Second Department of Surgery, Faculty of Medicine, Kyushu University, Fukuoka	April 1985 to April 1995	Patients underwent hepatic resection for metastatic CRC. These were all attempts at curative resection with no residual tumour.	NR	31	65 (NR)	54.8	NR	NR
Siriwardana et al., 2016	UK	Royal Free Hospital NHS Foundation Trust, London	1998 to 2008	Patients who had not undergone NAC prior to potentially curative hepatectomy for CLM.	NR	26	NR	69.2	NA	115[£]
Stift et al., 2018	Austria	Medical University, Vienna	2005 to 2011	Patients with resectable or borderline resectable CLM who underwent three months of neoadjuvant and adjuvant bevacizumab-based chemotherapy and liver resection with curative intent.	No exclusion criteria defineda.	141	63.1[£] (9.6)	58.2	Pre, 100	36[£]
Tanaka et al., 2005	Japan	Department of Gastroenterological Surgery, Yokohama City University Graduate School of Medicine	1992 to 2003	Patients with ≥5 bilobar liver metastases from colorectal cancer who underwent hepatectomy.	NR	37	60.4 (9.6)	62.2	40.5	27

Study characteristics

The cohort studies' sample size ranged from 26 (Siriwardana et al., 2016) to 662 (Zakaria et al., 2007) patients. Typical participants were males in their 60s, with a mean follow-up period ranging from 27 (Tanaka et al., 2005) to 62 (Hayashi et al., 2010) months (Table 1).

There were more studies evaluating vascular invasion (78.8%, n=26), followed by the degree of tumour differentiation (69.7%, n=23), and biliary invasion (54.5%, n=18). Only % (n=2) of the included studies evaluated tumour budding (Table 2).

Risk of bias assessment

The overall methodological quality of the included studies showed a tendency to low risk of bias. However, the main issue was the risk of bias related to the lack of adjustments in the statistical analysis of most included studies. In addition, of the 33 included studies, 28 (84.8%) reported neither the definition nor the assessment of OS and DFS outcomes, and they were classified as probably with high risk of bias (S2 table 2 and S1 figure).

Outcomes

Overall survival

Degree of tumour differentiation. Three groups of studies (Koike et al., 2000; Lunevicius et al., 2001; Korita et al., 2007; Wakai et al., 2008; Brachet et al., 2009) (221 participants) addressed the degree of tumour differentiation. No significant decrease in OS was observed in undifferentiated tumours (HR, 0.61 [95% CI, 0.37 to 1.01], p=0.06; I^2=36%, p=0.21; risk difference (RD) 330/1,000) (Fig 2, panel A). The certainty of evidence was downgraded to low certainty due to risk of bias and imprecision (Table 3).

Lymphatic invasion. Two groups of studies (Sasaki et al., 2002; Murad et al., 2007; Lupinacci et al., 2014a,b; Pinheiro et al, 2014; Fonseca et al., 2018b) (183 participants) addressed lymphatic invasion, suggesting no association between the studied factor and OS (OR, 0.28 [95% CI, 0.05 to 1.63], p=0.16; I^2=44%, p=0.18; RD 46/1,000) (Fig 3, panel A). The certainty of evidence was downgraded to low certainty due to risk of bias, inconsistency, and imprecision (Table 3).

Vascular invasion. The presence of portal invasion was associated with a statistically significant decrease in OS (HR, 0.50 [95% CI, 0.36 to 0.69], p<0.0001; I^2=0%, p=0.90; RD 170/1,000) (Fig 2, panel B) according to three groups of studies (Yamamoto et al., 1995, 1999; Okano et al., 1999, 2000; Koike et al., 2000; Lunevicius et al., 2001; Kubo et al., 2002; Minagawa et al., 2007; Murad et al., 2007; Lupinacci et al., 2014a; Pinheiro et al, 2014; Fonseca et al., 2018b) (504 participants); however, there was no statistically significant decrease

Table 1. (continued).

Wiggans et al., 2013	UK	Histopathology Department at Derriford Hospital, Plymouth	March 2010 to May 2011	Patients undergoing resection for CLM and had been followed up for a minimum of 1 year.	NR	65	65[£] (NR)	60.6	Pre, 100	NR
Yamaguchi et al., 2002; Nanashima et al., 2009	Japan	Department of Surgery II, Nagasaki University School of Medicine, Nagasaki	1981 to 1998	Curative hepatic resections (no microscopic cancer cells at the surgical liver margin) in patients with isolated liver metastases.	NR	37	NR	NR	NR	24[¢]
Yonemura et al., 2019	Japan	Department of Surgery, National Defense Medical College, Saitama	1997 to 2014	CRC patients with liver metastases who underwent R0 resection for synchronous or metachronous liver metastases. Patients with other organ metastases at liver recurrence who underwent curative therapy concurrently with hepatic resection or shortly after resection were included.	Patients who had short follow-up periods after hepatectomy (less than a month) and those who had multiple or double cancers.	204	64.3 (NR)	68.1	Pre, 49.5	NR
Zakaria et al., 2007	USA	Mayo Clinic, Minnesota	1960 to 1995	Patients who underwent resection of CLM.	Patients who had initial hepatic resection elsewhere or had only local ablative therapy.	662	60 (11)	61	Post, 33.3	36

CLM: colorectal liver metastases; CRC: colorectal cancer; CRCLM: hepatectomy for liver metastasis from colorectal cancer; CTV: computed tomography volumetry; ECOG: Eastern Cooperative Oncology Group; FLR: functional liver remnant; IU/L: international units per litre; L: litre; mg/dL: milligrams per decilitre; min.: minutes; MRI: magnetic resonance imaging; no.: number; NA: not applied; NAC: neoadjuvant chemotherapy; NR: not reported; Peri: perioperative; Post; postoperative; Pre: preoperative; PVE: portal vein embolisation; SD: standard deviation; St.: Saint; UK: United Kingdom; USA: United States of America; WBC: whole body cryostimulation. α: As per e-mail contact with the author. [£]: Median. [¢]: Absolute no.

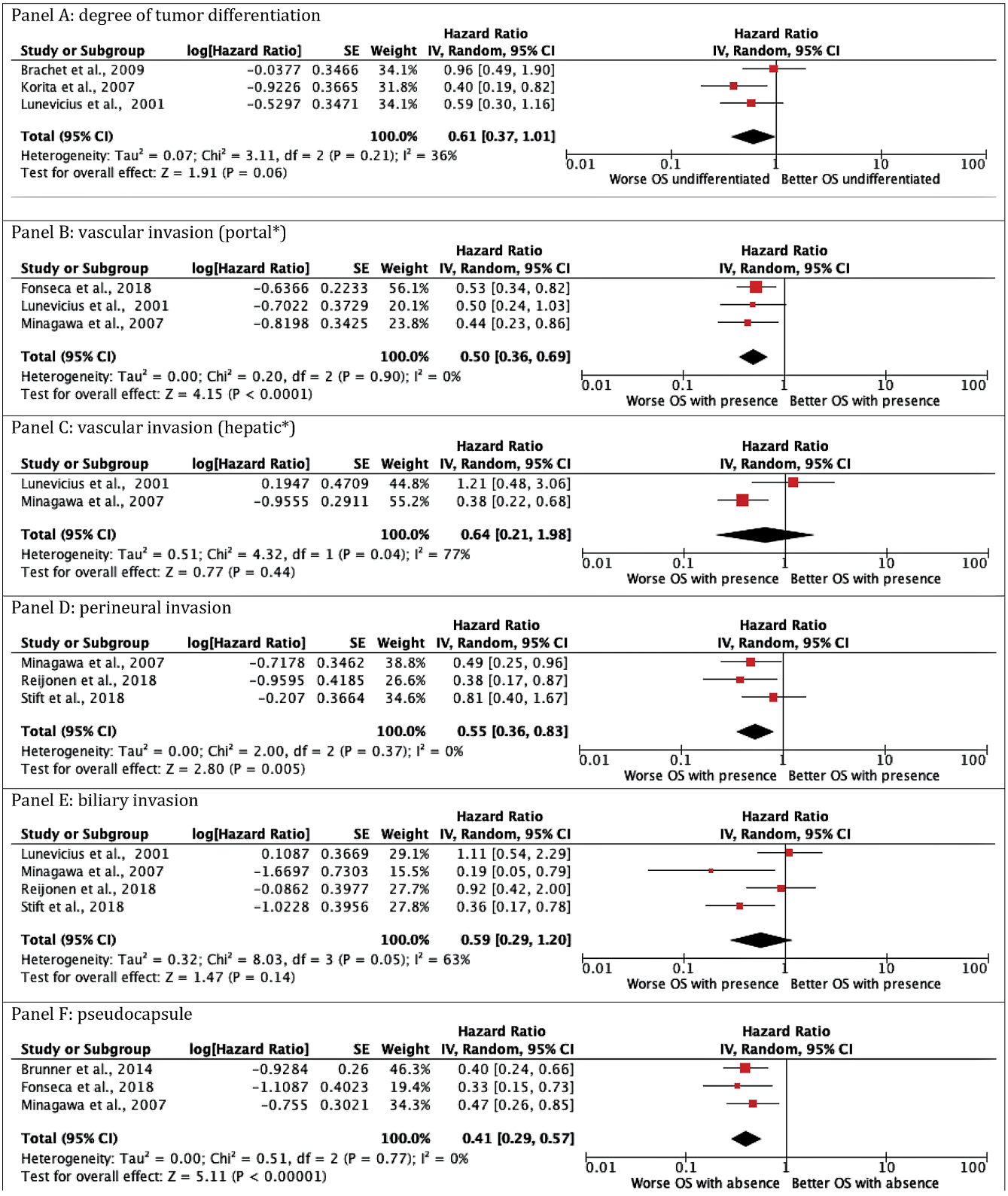

Fig. 2. Meta-analysis of hazard ratios on histopathological prognostic factors and overall survival.

Table 2. Histopathological prognostic factors, criteria, number of patients presenting prognostic factors, and definitions of overall survival and disease-free survival per the included studies.

Author, year	Histopathological prognostic factors analysed in each included study	Criteria used in each included study	No. of patients with the prognostic factor in the studied group	Definition of OS in each included study	OS (mo)	Definition of DFS in each included study	DFS (mo)	Reasons why the study was excluded from the analysis
Ambiru et al., 1999	Pseudocapsule	Fibrous tissue between the hepatic tumour and surrounding hepatic parenchyma.	Absence (NE): 95 Presence (E): 38	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel F. Although the study reported RR, our primary analysis was HR.
Bockhorn et al., 2009	Lymphatic invasion	NR	Presence (E): 312 Absence (NE): 20	NR	NR	NR	NR	Did not report absolute events for either OS or DFS to be plotted in Fig. 3, panel B.
	Vascular invasion	NR	Presence (E): 19 Absence (NE): 313	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel B.
Bouviez et al., 2014	Lymphatic invasion; peritumoural carcinomatous lymphangitis	NR	Presence (E): 9 Absence (NE): 77	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
Brachet et al., 2009	Degree of tumour differentiation	NR	Poorly ifferentiated (E): 27 Well or moderately differentiated (NE): 35	NR	NR	NR	NR	Plotted in Fig. 2, panel A.
Brunner et al., 2014	Pseudocapsule	Specimens were evaluated for a fibrotic capsule around tumours using haematoxylin and eosin, Masson trichrome and α-SMA staining.	Absence (E): 125 Presence (NE): 76	NR	E: 31[£] NE: 64[£]	NR	NR	Plotted in Fig. 2, panel F.
de Ridder et al., 2015	Lymphatic invasion	Single tumour cells or cell clusters visible within vessels that showed immunoreactivity for D2-40 but not CD31.	Presence (E): 33 Absence (NE): 91	Interval (in months) between liver resection and death or the date of the last follow-up.	E: 41.9[£] NE: 61.0[£]	Interval (in months) between liver resection and disease recurrence, death, or the last follow-up.	E: 19.4[£] NE: 29.2[£]	Did not report any data related to either OS or DFS.
	Vascular invasion	Single tumour cells or cell clusters visible within vessels that showed immunoreactivity for CD31 but not D2-40.	Presence (E): 46 Absence (NE): 78		E: 48.8[£] NE: 58.2[£]		E: 18[£] NE: 40.8[£]	
	Perineural invasion	Defined as a nerve, identified by S-100 staining, being surrounded by tumour cells for at least three-quarters of the circumference.	Presence (E): 11 Absence (NE): 113		E: 109.3[£] NE: 55.9[£]		E: 50.2[£] NE: 27.5[£]	
	Biliary invasion	Single tumour cells or cell clusters (CK7-negative) visible within bile ducts that showed immunoreactivity for CK7.	Presence (E): 11 Absence (NE): 113		E: 76.7[£] NE: 55.9[£]		E: 27.8[£] NE: 27.5[£]	
	Pseudocapsule	Fibrous tissue between the tumour and liver parenchyma.	Absence (E): 81 Presence (NE): 43		E: 56.7[£] NE: 109.3[£]		E: 25.8[£] NE: 27.8[£]	
Falcão et al., 2018	Tumour border	According to Vermeulen et al., if more than one group was observed and each group was present in up to 25% of tumor liver parenchyma interface, the growth pattern was described as mixed.	Desmoplastic (E): 19 Pushing (NE): 27	NR	NR	NR	NR	Single study reporting HR for tumour border related to OS.
Fernández-Aceñero et al., 2015; Abengózar et al., 2012	Degree of tumour differentiation	NR	Poorly differentiated (E): 5 Well or moderately differentiated (NE): 45	Time to death secondary to the tumour.	NR	Time to recurrence.	NR	Did not report any data related to either OS or DFS.
	Vascular invasion	Presence of tumour cells inside the lumen of a vessel and attached to the vessel wall. No distinction was made between lymph and systemic vessels.	Presence (E): 15 Absence (NE): 35		NR		NR	
	Perineural invasion	Presence of tumour cells beneath the fibrous capsule of a nerve.	Presence (E): 2 Absence (NE): 48		NR		NR	
	Biliary invasion	NR	Presence (E): 0 Absence (NE): 50		NR		NR	
	Satellite nodules	Metastatic nodule separated more than 1 mm from the main nodule.	Presence (E): 27 Absence (NE): 23		NR		NR	
	Tumour border	NR	Infiltrative (E): 16 Expansive (NE): 34		NR		NR	
	Peritumoural inflammation	NR	Presence (E): 16 Absence (NE): 34[¢]		NR		NR	

Table 2. (continued).

	Degree of tumour differentiation	NR	Poorly differentiated (E): 3[§] Well or moderately differentiated (NE): 88[§]		NR		NR	Did not report any data related to either OS or DFS.
	Lymphatic invasion	Positive when either single tumour cells or cell clusters were clearly visible within an endothelium-lined vessel-like structure demonstrating immunoreactivity for the D2-40 or CD34 antibody, respectively, beyond the metastasis border.	Presence (E): 38 Absence (NE): 191		E: 85 NE: 35		E: 49.4 NE: 46.4	Plotted in Fig. 3, panels A and B.
	Vascular invasion (portal)	Positive when either single tumour cells or cell clusters were clearly visible within an endothelium-lined vessel-like structure demonstrating immunoreactivity for the D2-40 or CD34 antibody, respectively, beyond the metastasis border.	Presence (E): 70 Absence (NE): 159		E: 66.7 NE: 91.1		E: 41.8 NE: 49.7	Plotted in Fig. 2, panels B and C.
Fonseca et al., 2018b; Lupinacci et al., 2014a,b; Pinheiro et al., 2014; Murad et al., 2007	Biliary invasion	Positive when either single tumour cells or cell clusters were clearly visible within an epithelium-lined structure that showed immunoreactivity for CK-7.	Presence (E): 20 Absence (NE): 93	Time interval between the date of liver resection to the date of death or the most recent follow-up if the patient was alive. Deaths from other causes were treated as censored events.	NR	Time interval between the date of liver resection to the date of the first documented recurrence at any site.	NR	Did not report any data related to either OS or DFS.
	Tumour budding	Isolated single cancer cell or a cluster composed of less than five cancer cells at the border edge of the tumour.	Presence (E): 112 Absence (NE): 117		E: 64.5 NE: 94.5		E: 32.6 NE: 64.1	Single study reporting HR.
	Pseudocapsule	Present when there was fibrous tissue between the tumour and liver parenchyma.	Absence (E): 172 Presence (NE): 57[€]		E: 72.7 NE: 98.9[⌘] and 106.5[]		E: 38.4 NE: 65.4[⌘] and 85.6[]	Plotted in Fig. 2, panel F.
	Tumour border	Defined according to the Jass[Δ] classification as either infiltrative (when the tumour spreads freely through the surrounding tissue, dissecting between normal hepatocytes) or expansive (when the tumour edges expand in a well-delineated fashion, pushing the adjacent liver tissue).	Infiltrative (E): 169 Expansive (NE): 60		E: 71.8 NE: 112.1		E: 38.3 NE: 74.6	Plotted in Appendix Figure 2.
	Peritumoural inflammation	Presence of lymphocytes in the tumour periphery and tumour infiltrating lymphocytes, being classified as mild, moderate or severe.	Presence (E): 65[ç] Absence (NE): 164[ç]		E: 80.4 NE: 111.8		E: 49.2 NE: 64.2	Plotted in Fig. 3, panel D.
	PDCs	Cancer clusters of five or more cancer cells in the stroma and/or tumoural border.	Presence, G1 or G2 (E): 113 Absence or G3 (NE): 116		E: 88.0 (G1) e 70.1 (G2) NE: 35.0		E: 56.4 (G1) e 35.1 (G2) NE: 10.1	Single study reporting HR.
Gomez et al., 2014	Lymphatic invasion	Presence of adenocarcinoma cells within the lumen of the lymphatic space.	Presence (E): 42 Absence (NE): 217	Time between the dates of primary hepatic resection and death or the most recent follow-up if the patient was still alive.	E: 24[£] NE: 25[£]	Time from primary hepatic resection to the first documented disease recurrence on imaging.	E: 14[£] NE: 17[£]	Did not report any data related to either OS or DFS.
	Vascular invasion	Adenocarcinoma cells within the lumen of the vascular channel.	Presence (E): 115 Absence (NE): 144		E: 24[£] NE: 28[£]		E: 15[£] NE: 18[£]	Did not report any data related to either OS or DFS.
	Perineural invasion	Tumour cells within any layer of the nerve sheath or tumour in the perineural space.	Presence (E): 13 Absence (NE): 246		E: 19[£] NE: 26[£]		E: 6[£] NE: 18[£]	Did not report HR to be plotted in Fig. 2, panel D. Single study reporting RR.
	Biliary invasion	Presence of adenocarcinoma cells infiltrating through part of or completely replacing the bile duct epithelium in large, medium or small intrahepatic bile ducts.	Presence (E): 94 Absence (NE): 165		E: 24[£] NE: 26[£]		E: 18[£] NE: 16[£]	Did not report any data related to either OS or DFS.
Hayashi et al., 2010	Vascular invasion (portal)	NR	Presence (E): 8 Absence (NE): 74	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panels B and C. Although the study reported the number of events, our primary analysis was HR.

Table 2. (continued).

John et al., 2013	Degree of tumour differentiation	NR	Poorly differentiated (E): 83 Well or moderately differentiated (NE): 317	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel A. Although the study reported OR, our primary analysis was HR.
	Vascular invasion	Authors followed the UK Royal College of Pathologist guidelines.	Presence (E): 137 Absence (NE): 292	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panels B and C. Although the study reported OR, our primary analysis was HR.
	Biliary invasion	NR	Presence (E): 70 Absence (NE): 357	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel E. Although the study reported OR, our primary analysis was HR.
Korita et al., 2007, Wakai et al., 2008	Degree of tumour differentiation	NR	Poorly differentiated (E): NR Well or moderately differentiated (NE): NR	NR	NR	NR	NR	Plotted in Fig. 2, panel A.
	Lymphatic invasion	Single tumour cells or cell clusters were clearly visible within vessels that showed immunoreactivity for the D2-40 monoclonal antibody.	Presence (E): 13 Absence (NE): 92	NR	NR	NR	NR	Did not report the number of events to be plotted in Fig. 3, panels A and B. Single study reporting RR.
	Vascular invasion (portal)	NR	Presence (E): 38 Absence (NE): 67	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
	Vascular invasion (hepatic)	NR	Presence (E): 18 Absence (NE): 87	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
	Biliary invasion	NR	Presence (E): 14 Absence (NE): 91	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
Lionti et al., 2018	Tumour border	Histological grading was assessed according to the WHO criteria.	Infiltrative (E): 39 Expansive (NE): 24	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
	PDCs	Defined according to the original definition provided by Ueno et al., 2012¥.	Presence, G1 or G2 (E): 51 Absence or G3 (NE): 12	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
Lunevicius et al., 2001; Koike et al., 2000	Degree of tumour differentiation	NR	Poorly differentiated (E): 24 Well or moderately differentiated (NE): 45	NR	NR	NR	NR	Plotted in Fig. 2, panel A.
	Vascular invasion (portal)	NR	Presence (E): 39 Absence (NE): 32	NR	NR	NR	NR	Plotted in Fig. 2, panel B.
	Vascular invasion (hepatic)	NR	Presence (E): 12 Absence (NE): 59	NR	NR	NR	NR	Plotted in Fig. 2, panel C.
	Biliary invasion	NR	Presence (E): 30 Absence (NE): 41	NR	NR	NR	NR	Plotted in Fig. 2, panel E.
	Pseudocapsule	A noncapsule was defined as the virtual absence of a fibrous band around the metastasis in which tumour cells faced the hepatic parenchyma directly. A thin fibrous tissue layer was defined as intermediate between the capsule and the noncapsule.	Absence (E): 55 Presence (NE): 14	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel F. Although the study reported the number of events, our primary analysis was HR.
Mańin Hernández et al., 2009	Degree of tumour differentiation	NR	Poorly differentiated (E): 4 Well or moderately differentiated (NE): 203	NR	E: 58 NE: 109.5	NR	NR	Did not report HR to be plotted in Fig. 2, panel A. Although the study reported the number of events, our primary analysis was HR.
	Vascular invasion	NR	Presence (E): 29 Absence (NE): 178	NR	E: 40 NE: 73	NR	NR	Did not report HR to be plotted in Fig. 2, panels B and C. Although the study reported the number of events, our primary analysis was HR.
	Satellite nodules	NR	Presence (E): 32 Absence (NE): 175	NR	E: 35.3 NE: 73.8	NR	NR	Plotted in Fig. 3, panel C.

Table 2. (continued).

Minagawa et al., 2007; Kubo et al., 2002; Yamamoto et al., 1995; Yamamoto et al., 1999; Okano et al., 1999, 2000	Degree of tumour differentiation	The histologic type of the tumours was determined according to the WHO classification.	Poorly differentiated (E): 1 Well or moderately differentiated (NE): 142	NR	E: NR NE: 88.3*	NR	NR	Did not report any data related to either OS or DFS.
	Vascular invasion (portal)	The histologic type of the tumours was determined according to the WHO classification.	Presence (E): 25 Absence (NE): 71	NR	NR	NR	NR	Plotted in Fig. 2, panel B.
	Vascular invasion (hepatic)	The histologic type of the tumours was determined according to the WHO classification.	Presence (E): 9 Absence (NE): 87	NR	NR	NR	NR	Plotted in Fig. 2, panel C.
	Perineural invasion	The histologic type of the tumours was determined according to the WHO classification.	Presence (E): 18 Absence (NE): 131	NR	E: 33.4 NE: 64.2	NR	NR	Plotted in Fig. 2, panel D.
	Biliary invasion	The histologic type of the tumours was determined according to the WHO classification.	Presence (E): 19 Absence (NE): 350	NR	E: 4.2£ NE: 3.1£	NR	NR	Plotted in Fig. 2, panel E.
	Pseudocapsule	The histologic type of the tumours was determined according to the WHO classification.	Absence (E): 59 Presence (NE): 93	NR	NR	NR	NR	Plotted in Fig. 2, panel F.
	Satellite nodules	The histologic type of the tumours was determined according to the WHO classification.	Presence (E): 1 Absence (NE): 39	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
Morino et al., 1991	Pseudocapsule		Absence (E): 21 Presence (NE): 8	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel F. Although the study reported the number of events, our primary analysis was HR.
	Tumour border	Tumour growth patterns were classified into three types: 1) the sinusoidal type: the cancer cells invade the sinusoids and destroy the normal hepatocytes; 2) the expansive type: the cancer cells are seen compressing the hepatocytes along the liver cell cord; there is no destruction of peripheral hepatocytes; and 3) the mixed type: some lesions are recognized as sinusoidal, and some are the expansive type.	Infiltrative (E): 22 Expansive (NE): 6	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
Nagashima et al., 1999	Pseudocapsule	Marginal fibrosis was defined as when the margin of the hepatic tumour was dominantly replaced by fibrosis.	Absence (E): 13 Presence (NE): 46	NR	E: 10.6 NE: 33.2	NR	NR	Did not report any data related to either OS or DFS.
	Tumour border	Tumours were considered “infiltrative growth of the hepatic tumour” when the hepatic tumour invaded in a diffuse manner with the widespread penetration of normal liver tissue, and tumours were considered “expansive growth of the hepatic tumour” when the hepatic tumour was pushing out of the normal liver tissue and reasonably well circumscribed.	Infiltrative (E): 54 Expansive (NE): 5	NR	E: 12.2 NE: 39.6	NR	NR	Did not report any data related to either OS or DFS.
	Peritumoural inflammatory	Lymphocytic infiltration was considered when there was conspicuous infiltration of lymphocytes and other inflammatory cells around the hepatic tumour.	Presence (E): 25 Absence (NE): 34	NR	E: 34.8 NE: 32.4	NR	NR	Did not report any data related to either OS or DFS.
Okano et al., 2003	Degree of tumour differentiation	The histologic type of the tumours was determined according to the WHO classification.	Poorly differentiated (E): NR Well or moderately differentiated (NE): 37	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel A. Although the study reported the number of events, our primary analysis was HR.
	Vascular invasion (portal and hepatic)	The histologic type of the tumours was determined according to the WHO classification.	Presence (E): 10 Absence (NE): 31	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panels B and C. Although the study reported the number of events, our primary analysis was HR.
	Biliary invasion	The histologic type of the tumours was determined according to the WHO classification.	Presence (E): 6 Absence (NE): 35	NR	NR	NR	NR	Plotted in Fig. 2, panel E.
	Peritumoural inflammatory	Lymphocytic infiltration between the tumour and hepatic parenchyma was graded according to the classification of Ropponen et al., 1997**.	Presence (E): 18 Absence (NE): 23	NR	NR	NR	NR	Plotted in Fig. 3, panel D.

Table 2. (continued).

Park et al., 2014	Degree of tumour differentiation	Dedifferentiation was defined as microscopic clusters of tumour cells with a large solid sheet, cribriform pattern, spindle cell morphology, trabecular or palisading pattern or extensive single cells (more than 50% of tumour).	Poorly differentiated (E): 13 Well or moderately differentiated (NE): 104	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
	Vascular invasion	Presence of cancer cells within endothelial-lined channels.	Presence (E): 40 Absence (NE): 77	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
	Tumour budding	An isolated cell or a small cluster of <5 carcinoma cells in the invasive front was defined as a budding focus, and ≥10 budding foci when viewed at 200-fold magnification were considered positive for tumour budding.	Presence (E): 95 Absence (NE): 22	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
Rajaganeshan et al., 2007	Tumour border	The invasive margin of the primary cancer was classified as either pushing or infiltrative based on the predominant morphology, as defined by JassΔ. A modified classification based on Yasui56 was used for liver metastases, with metastases being classified as capsulated if 450% of the margin exhibited a fibrous capsule separating the tumour from the stroma.	Infiltrative (E): 29 Expansive (NE): 26	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
Reijonen et al., 2018	Vascular invasion	Tumour cell growth in the vascular space and nerve invasion or tumour cell growth in the nerve sheath or perineural space.	Presence (E): 26 Absence (NE): 82	NR	NR	NR	NR	Plotted in Fig. 2, panels B and C.
	Perineural invasion	Tumour cell growth in the nerve sheath or perineural space.	Presence (E): 15 Absence (NE): 94	NR	NR	NR	NR	Plotted in Fig. 2, panel D.
	Biliary invasion	Tumour cells growing along the ductal wall replacing the normal biliary epithelium.	Presence (E): 31 Absence (NE): 78	NR	NR	NR	NR	Plotted in Fig. 2, panel E.
Sasaki et al., 2002	Degree of tumour differentiation	NR	Poorly differentiated (E): 28 Well or moderately differentiated (NE): 39	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel A. Although the study reported the number of events, our primary analysis was HR.
	Lymphatic invasion	Present when cancer cells were seen in the luminal structure in the portal area, which was lined by endothelial cells. Perineural invasion in the liver was included in the intrahepatic lymphatic invasion classification.	Presence (E): 10 Absence (NE): 55	NR	NR	NR	NR	Plotted in Fig. 3, panel A.
	Vascular invasion (portal)	Portal vein invasion and hepatic vein invasion were considered present when cancer cells were growing in the lumen of a vessel or bile duct branches within the liver.	Presence (E): 15 Absence (NE): 50	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel B. Although the study reported the number of events, our primary analysis was HR.
	Vascular invasion (hepatic)		Presence (E): 3 Absence (NE): 62	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel C. Single study reporting the number of events.
	Biliary invasion	Present when cancer cells were growing in the lumen of a vessel or bile duct branches within the liver.	Presence (E): 10 Absence (NE): 55	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel E. Although the study reported the number of events, our primary analysis was HR.
Serrablo et al., 2016; Borrego-Estella et al., 2012	Degree of tumour differentiation	Tumour differentiation grade was established based on the percentage of gland formation: >90%, 50-90%, and <50% for well, moderately, and poorly differentiated, respectively.	Poorly differentiated (E): 16 Well or moderately differentiated (NE): 130	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel A. Although the study reported the number of events, our primary analysis was HR.
	Pseudocapsule	Defined according to the Lunevicius criterion56 as the presence of a perilesional fibrous reaction ≥0.5 mm around the entire contour of the lesion.	Absence (E): 122 Presence (NE): 25	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel F. Although the study reported the number of events, our primary analysis was HR.
	Satellite nodules	Presence of neoplastic foci near the lesion borders (<5 mm) without evidence of continuity between the lesion and microsatellites.	Presence (E): 22 Absence (NE): 125	NR	NR	NR	NR	Plotted in Fig. 3, panel C.
	Tumour border68	The factor “tumour growth type” (infiltrative or expansive) was previously described by Borrego-Estella et al., 2012b****, and hypoxic or nonhypoxic was evaluated as two different “growth patterns”.	Infiltrative (E): 68 Expansive (NE): 77	NR	NR	NR	NR	Plotted in Appendix Figure 2.

Table 2. (continued).

Shirabe et al., 1997	Degree of tumour differentiation	NR	Poorly differentiated (E): NR Well or moderately differentiated (NE): 31	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel A. Although the study reported the number of events, our primary analysis was HR.
	Vascular invasion (portal)	NR	Presence (E): 10 Absence (NE): 21	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel B. Although the study reported the number of events, our primary analysis was HR.
	Vascular invasion (hepatic)	NR	Presence (E): 6 Absence (NE): 25	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel C. Single study reporting the number of events.
	Biliary invasion	NR	Presence (E): 9 Absence (NE): 22	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel E. Although the study reported the number of events, our primary analysis was HR.
	Satellite nodules	NR	Presence (E): 8 Absence (NE): 23	NR	NR	NR	NR	Plotted in Fig. 3, panel C.
Siriwardana et al., 2016	Degree of tumour differentiation	NR	Poorly differentiated (E): 0 Well or moderately differentiated (NE): 22	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
	Pseudocapsule	NR	Absence (E): NR$^{\Psi}$ Presence (NE): 13$^{\Theta}$	NR	NR	NR	NR	Did not report HR to be plotted in Fig. 2, panel F. Although the study reported the number of events, our primary analysis was HR.
	Tumour border	If 2 types of interfaces were present in separate areas of the tumour margin, the metastasis was classified as 1 or the other type if 75% or more of the interface fit the above description. However, if both types were present and if any 1 type was more than 25% of the interface, it was classified as a mixed type.	Infiltrative (E): 16 Expansive (NE): 13	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
Stift et al., 2018	Perineural invasion	Described by Rubbia-Brandt et al., 2007$^{\zeta}$.	Presence (E): 25 Absence (NE): 116	Time from surgery until the day of death or censored at the last follow-up.	E: --$^{\theta}$ NE: --$^{\theta}$	NR	NR	Plotted in Fig. 3, panel D.
	Biliary invasion		Presence (E): 18 Absence (NE): 123		E: 32.8$^{\pounds}$ NE: --$^{\theta}$	NR	NR	Plotted in Fig. 3, panel E.
Tanaka et al., 2005	Degree of tumour differentiation	NR	Poorly differentiated (E): 0 Well or moderately differentiated (NE): 17 and 20, respectively	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
	Vascular invasion (portal and hepatic)	NR	Presence (E): 22 Absence (NE): 15	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
Wiggans et al., 2013	Degree of tumour differentiation	NR	Poorly differentiated (E): 3 Well or moderate differentiated (NE): 62	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
	Vascular invasion	NR	Presence (E): 9 Absence (NE): 56	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
	Pseudocapsule	The pseudocapsule was identified as a paucicellular collagenous band present between the tumour cells and the adjacent hepatocytes measuring at least 0.1 mm in thickness. In cases of heterogeneity between tumours, the amount of pseudocapsule in up to the three largest tumours was measured, and the average value calculated according to a simple formula (>50% =2, <50% =1, no pseudocapsule =0) was used in the analyses.	Absence (E): 36 Presence (NE): 27	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
	Satellite nodules	NR	Presence (E): 0 Absence (NE): 65	NR	NR	NR	NR	Did not report any data related to either OS or DFS.

in OS related to hepatic invasion (HR, 0.64 [95% CI, 0.21 to 1.98], p=0.44; I^2=77%, p=0.04; RD 192/1,000) (two groups of studies (Yamamoto et al., 1995, 1999; Okano et al., 1999, 2000; Koike et al., 2000; Lunevicius et al., 2001; Kubo et al., 2002; Minagawa et al., 2007) (438 participants) (Fig 2, panel C). The certainty of evidence was downgraded to moderate certainty due to risk of bias (Table 3).

Perineural invasion. The presence of perineural invasion was associated with a statistically significant decrease in OS (HR, 0.55 [95% CI, 0.36 to 0.83], p=0.005; I^2=0%, p=0.37; RD 340/1,000) according to three group of studies (Yamamoto et al., 1995, 1999; Okano et al., 1999, 2000; Kubo et al., 2002; Minagawa et al., 2007; Reijonen et al., 2018; Stift et al., 2018) (399 participants) (Fig 2, panel D). The certainty of evidence was downgraded to moderate certainty due to the risk of bias (Table 3).

Biliary invasion. The presence of biliary invasion was not statistically associated with a decrease in OS (HR, 0.59 [95% CI, 0.29 to 1.20], p=0.14; I^2=63%, p=0.05, RD 166/1,000) according to four groups of studies (Yamamoto et al., 1995, 1999; Okano et al., 1999, 2000; Koike et al., 2000; Lunevicius et al., 2001; Kubo et al., 2002; Minagawa et al., 2007; Reijonen et al., 2018; Stift et al., 2018) (690 participants) (Fig 2,

Table 2. (continued).

Yamaguchi et al., 2002; Nanashima et al., 2009	Degree of tumour differentiation	NR	Poorly differentiated (E): 17 Well or moderately differentiated (NE): 11	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
	Vascular invasion	NR	Presence (E): 9 Absence (NE): 19	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
	Biliary invasion	NR	Presence (E): 0 Absence (NE): 28	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
	Pseudocapsule	NR	Absence (E): 16 Presence (NE): 12	NR	NR	NR	NR	Did not report any data related to either OS or DFS.
Yonemura et al., 2019	PDCs	Clusters of ≥5 cancer cells infiltrating the stroma and lacking a glandular formation. PDC was graded as G1 (<5 clusters), G2 (5 to 9 clusters), and G3 (≥10 clusters) based on the highest number of PDC observed under ×20 magnification.	Presence, G1 or G2 (E): NR Absence or G3 (NE): NR		E (G1 only): 55 NE (G2/G3): 105x			Single study reporting number of events, and also combined different categories from our pre defined methods (ie, G2 and G3).
Zakaria et al., 2007	Degree of tumour differentiation	The Broder's system***** was used to histologically grade metastases.	Poorly differentiated (E): 249[§] Well or moderately differentiated (NE): 366[§]	Time interval between the date of hepatic resection and the date of death or the most recent date of follow-up if the patient was alive.	NR	Time from hepatic resection to death from the primary cancer.	NR	Did not report HR to be plotted in Fig. 2, panel A. Although the study reported the number of events, our primary analysis was HR.

DFS, disease-free survival; E, exposure; Fig, figure; HR, hazard ratio; mo., months; NE, nonexposure; NR, not reported; No., number; OR, odds ratio; OS, overall survival; PDCs, poorly differentiated clusters; RR, risk relative; UK, United Kingdom; WHO, World Health Organization. [£]: Median. [¢]: We considered both scarse and intense reported by the included study as a good prognosis (i.e., nonexposure group). [€]: We considered both thin and thick reported by the included study as a good prognosis (i.e., nonexposure group). [₢]: Absence and mild were considered good prognostic factors (i.e., nonexposure group), while moderate and severe were considered poor prognostic factors (i.e., exposure group). [Δ]: Lancet 1987;1:1303–1306. [§]: For the degree of tumour differentiation, we considered G1 and/or G2 as good prognostic factors (i.e., nonexposure group), while G3 and/or G4 were considered poor prognostic factors (i.e., exposure group). [¥]: Am. J. Surg. Pathol. 2012;36:193-201. [þ]: Noncapsulated metastasis. [¶]: Encapsulated metastasis. [✒]: Thin. [⌘]: Thick. *: The mean OS calculated was based on the mean OS from the included study. **J. Pathol. 1997;182:318-329. ****J Gastroenterol Hepatol Res 2012b;1:294-301. *****American Joint Committee on Cancer. AJCC Cancer Staging Manual, 5th ed. Philadelphia: Lippincott-Raven; 1997:66–69. [Ψ]: Noncapsulated and infiltrative. [Θ]: Encapsulated and expansive. [ζ]: Ann. Oncol. 2007;18:299e304. [θ]: By contacting the main author of the study, it was concluded that the median was not reached. [ϟ]: For PDCs, we considered G1 and G2 as poor prognostic factors (i.e., exposure group), while G3 was considered a good prognostic factor (i.e., nonexposure group). [x]Authors only reported G2 with G3.

panel E). The certainty of evidence was downgraded to low certainty due to risk of bias, inconsistency, and imprecision (Table 3).

Tumour budding. One group of studies (Murad et al., 2007; Lupinacci et al., 2014a,b; Pinheiro et al., 2014; Fonseca et al., 2018b) (229 participants) showed a statistically significant difference in TB for OS (HR, 0.64 [95% CI, 0.43 to 0.96]; I^2=not applicable; RD not applicable) (S3 table). The certainty of evidence was downgraded to very low certainty due to risk of bias, inconsistency, and imprecision (Table 3).

Pseudocapsule. The absence of a pseudocapsule was associated with a decrease in OS (HR, 0,41 [95% CI, 0.29 to 0.57], p<0.00001; I^2=0%, p=0.77; RD 193/1,000) according to three groups of studies (Yamamoto et al., 1995, 1999; Okano et al., 1999, 2000; Kubo et al., 2002; Minagawa et al., 2007; Murad et al., 2007; Brunner et al., 2014; Lupinacci et al., 2014a,b; Pinheiro et al., 2014; Fonseca et al., 2018b) (582 participants) (Fig 2, panel F). The certainty of evidence was downgraded to moderate certainty due to risk of bias, inconsistency, and imprecision (Table 3).

Satellite nodules. Three groups of studies (Shirabe et al., 1997; Marín Hernández et al., 2009; Borrego-Estella et al., 2012; Serrablo et al., 2016) (385 participants) addressed the presence of satellite nodules, suggesting a statistically significant decrease in OS in patients with satellite nodules (OR, 0.45 [95% CI, 0.26 to 0.80], p=0.006; I^2=0%, p=0.75; RD 151/1,000) (Fig 3, panel C). The certainty of evidence was downgraded to moderate certainty due to risk of bias (Table 3).

Tumour borders. One group of studies (Murad et al., 2007; Lupinacci et al., 2014a,b; Pinheiro et al., 2014; Fonseca et al., 2018b) (229 participants) showed a statistically significant decrease in OS in patients presenting with tumours with infiltrative borders (HR, 0.33 [95% CI, 0.19 to 0.58]; I^2=not applicable; RD not applicable) (S3 table). Another study (Falcão et al., 2018) reported this variable but as pushing and desmoplastic (HR, 2.85 [95% CI, 1.33 to 6.12]; I^2=not applicable; RD not applicable) (S3 table). The certainty of evidence was downgraded to very low certainty due to risk of bias (Table 3).

Peritumoural inflammatory tissue. The absence of peritumoural inflammatory tissue decreased OS (OR, 0.20 [95% CI, 0.08 to 0.54], p=0.002; I^2=0%, p=0.35; RD 73/1,000) according to two groups of studies (Okano et al., 2003; Murad et al., 2007; Lupinacci et al., 2014a,b; Pinheiro et al., 2014; Fonseca et al., 2018b) with 270 participants (Fig 3, panel D). The certainty of evidence was downgraded to moderate certainty due to risk of bias (Table 3).

Poorly differentiated clusters (PDCs). One group of studies (Murad et al., 2007; Lupinacci et al., 2014a,b;

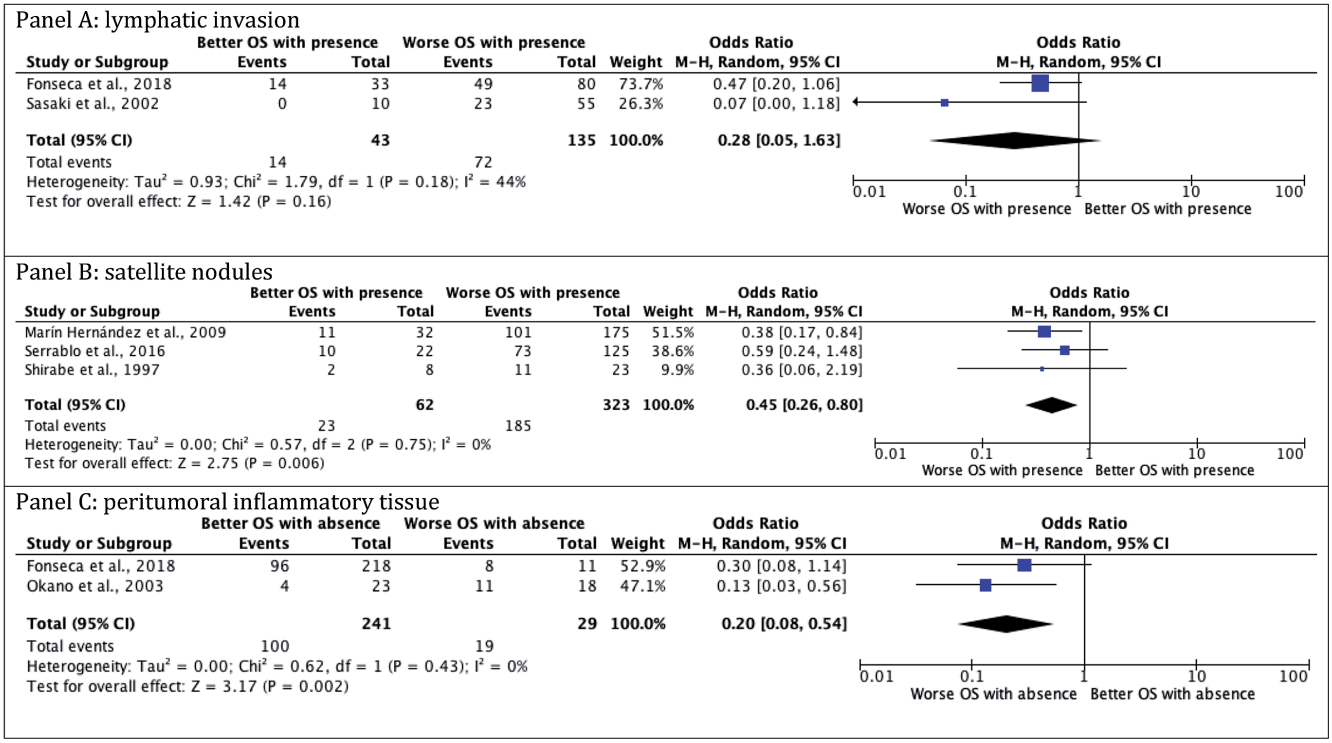

Fig. 3. Meta-analysis of odds ratios on histopathological prognostic factors and overall survival.

Table 3. GRADE evidence profile for the histopathological prognostic meta-analysis factors and overall survival.

Certainty assessment						Study event rates			Effect		
№ of participants and studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Nonexposure group	Exposure group	Baseline risk (bad risk factor)	Hazard or odds ratio (95% CI) (relative to the worst risk factor)	Absolute (95% CI) (worst risk factor)	Certainty
Degree of tumour differentiation											
221 (3)	serious[a]	not serious	not serious	serious[f]	NA[b]	pooled data using inverse variance[c]	pooled data using inverse variance[c]	486/1,000 (48.6%)[d]	HR 0.61 (0.37 to 1.01)	180 fewer per 1,000 (from 344 fewer to 3 more)	⊕⊕⊖⊖ low
Lymphatic invasion											
183 (2)	serious[a]	serious[e]	not serious	serious[f]	NA[b]	14/43	72/135	424/1,000 (42.4%)[d]	OR 0.28 (0.05 to 1.63)	305 fewer per 1,000 (from 403 fewer to 267 more)	⊕⊕⊖⊖ low
Vascular invasion (portal)[g]											
504 (3)	serious[a]	not serious	not serious	not serious	NA[b]	pooled data using inverse variance[c]	pooled data using inverse variance[c]	401/1,000 (40.1%)[d]	HR 0.50 (0.36 to 0.69)	240 fewer per 1,000 (from 322 fewer to 135 fewer)	⊕⊕⊕⊖ moderate
Vascular invasion (hepatic)[g]											
438 (2)	serious[a]	not serious	not serious	not serious	NA[b]	pooled data using inverse variance[c]	pooled data using inverse variance[c]	401/1,000 (40.1%)[d]	HR 0.64 (0.21 to 1.98)	161 fewer per 1,000 (from 388 fewer to 229 more)	⊕⊕⊖⊖ low
Perineural invasion											
399 (3)	serious[a]	not serious	not serious	not serious	NA[b]	pooled data using inverse variance[c]	pooled data using inverse variance[c]	520/1,000 (52.0%)[d]	HR 0.55 (0.36 to 0.83)	215 fewer per 1,000 (from 357 fewer to 65 fewer)	⊕⊕⊕⊖ moderate
Biliary invasion											
690 (4)	serious[a]	serious[e]	not serious	serious[f]	NA[b]	pooled data using inverse variance[c]	pooled data using inverse variance[c]	400/1,000 (40.0%)[d]	HR 0.59 (0.29 to 1.20)	188 fewer per 1,000 (from 358 fewer to 66 more)	⊕⊕⊖⊖ low
Tumour budding											
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	⊕○○○ very low
Pseudocapsule											
582 (3)	serious[a]	serious[e]	not serious	serious[f]	NA[b]	pooled data using inverse variance[c]	pooled data using inverse variance[c]	306/1,000 (30.6%)[d]	HR 0.41 (0.29 to 0.57)	250 fewer per 1,000 (from 289 fewer to 181 fewer)	⊕⊕⊕⊖ moderate
Satellite nodules											
385 (3)	serious[a]	not serious	not serious	not serious	NA[b]	23/62	185/323	344/1,000 (34.4%)[d]	OR 0.45 (0.26 to 0.80)	189 fewer per 1,000 (from 255 fewer to 69 fewer)	⊕⊕⊕⊖ moderate
Tumour borders											
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	⊕○○○ very low
Peritumoural inflammatory tissue											
270 (2)	serious[a]	not serious	not serious	not serious	NA[b]	100/244	19/29	440/1,000 (44.0%)[d]	OR 0.20 (0.08 to 0.54)	352 fewer per 1,000 (from 408 fewer to 202 fewer)	⊕⊕⊕⊖ moderate
Poorly differentiated clusters G3 versus G1											
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	⊕○○○ very low
Poorly differentiated clusters G2 versus G1											
NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	⊕○○○ very low

CI, confidence interval; HR, hazard ratio; NA, not applicable; NR, not reported; OR, odds ratio. [a]: We decreased the certainty of evidence by 1 due to risk of bias (e.g., failure to describe exposure assessment, adjusted statistical analysis, and outcome assessment). [b]: Less than the recommended number of included studies (i.e., 10) to assess the possibility of publication bias. [c]: We did not display study event rates because we pooled data using the inverse variance method based on reported hazard ratios. [d]: Baseline risk estimates were derived from the control group (worst variable) of the study that presented greater weight in the meta-analysis of the odds ratio for OS. [e]: We decreased the certainty of evidence by 1 due to inconsistency (i.e., I^2>50% and p<0.1). [f]: We decreased the certainty of evidence by 1 due to imprecision. 95% CI for absolute effects include clinically important benefits and limitations. [g]: Only for those studies that reported data separately for both portal and hepatic invasion.

Pinheiro et al., 2014; Fonseca et al., 2018b) (229 participants) showed a statistically significant decrease in OS related to the presence of PDC G3 versus G1 (HR, 0.34 [95% CI, 0.16 to 0.74]; I^2=not applicable; RD not applicable) (S3 table). The certainty of evidence was downgraded to very low certainty due to risk of bias (Table 3). However, the same group of studies showed a non statistically significant difference in OS related to the presence of PDCs concerning G2 versus G1 (HR, 0.90 [95% CI, 0.55 to 1.47]; I^2=not applicable; RD not applicable) (S3 table). The certainty of evidence was downgraded to very low certainty due to risk of bias and imprecision (Table 3).

Disease-free survival

Three groups of studies (Sasaki et al., 2002; Korita et al., 2007; Murad et al., 2007; Wakai et al., 2008; Lupinacci et al., 2014a,b; Pinheiro et al., 2014; Fonseca et al., 2018b) reported the impact of lymphatic invasion using different effect measurements. Except for the group of studies by Fonseca et al. (2018b), the other two groups found a significant decrease in DFS with the presence of lymphatic invasion (S3 table).

Only one group of studies (Murad et al., 2007; Lupinacci et al., 2014a,b; Pinheiro et al., 2014; Fonseca et al., 2018b) reported the impact of vascular invasion, perineural invasion, and tumour budding and found a significant decrease in DFS with its presence (S3 table). The group of studies also found a significant decrease in DFS with the absence of a pseudocapsule and peritumoural inflammatory infiltrate, and a significant difference regarding PDC G3 versus G1.

Related to degree of tumour differentiation, type of tumour border (S2 Fig), the authors did not find a statistically significant difference between DFS and the histopathological factors (S3 table). The certainty of evidence was downgraded to low certainty due to risk of bias and imprecision (S4 table).

None of the included studies reported DFS regarding the presence of biliary invasion or satellite nodules.

The studies evaluated did not report enough data for a subgroup analysis on the size of the largest metastatic lesion (<or≥4 cm), the use (or not) of systemic chemotherapy, and the presence or absence of cointerventions.

Discussion

The resection of CRLMs offers prolonged survival, mainly due to surgical and anaesthesiologic advances, improved radiological diagnostic methods and chemotherapy regimens, and evolving multidisciplinary approaches. Despite this evolution, there is still a gap in understanding the biological behaviour of metastatic tumours that can impact clinical decision-making.

In recent years, several studies have sought to understand tumour biology through pathology, evaluating different histopathological aspects, such as vascular, lymphatic, and perineural invasion, among others. However, most pathologists continue to draw their reports based only on the presence of malignancy, differentiation, colorectal origin, and margin status (Knijn et al., 2013). Therefore, our group recently proposed a systematic evaluation protocol for CRLMs based on histopathological prognostic factors (Fonseca et al., 2018a). However, the review was not based on a systematic review or a meta-analysis. Therefore, we performed a systematic review and meta-analysis in which eleven histopathological prognostic factors based on 33 eligible studies involving 4,641 patients were evaluated.

Main findings

The current study describes the association between histopathological prognostic factors and both OS and DFS in patients who underwent liver resection for CRLMs. OS was significantly higher in patients without vascular and perineural invasions and satellite nodules as well as in patients presenting peritumoural inflammatory infiltrate. However, regarding DFS, due to data scarcity, the prognostic evaluation was possible only on tumour border type, with no significant impact. After applying the GRADE approach, the overall certainty of evidence was very low for all prognostic variables on both OS and DFS.

Regarding the degree of tumour differentiation, three studies were included in the meta-analysis. Despite no statistically significant difference, a tendency for a worse prognosis for poorly differentiated tumours could be inferred. This result can be explained by the small number of patients included (221 patients), lacking adequate statistical power.

The impact of lymphatic invasion on OS did not show a significant difference in the meta-analysis that included two studies with 183 patients, despite a tendency for a worse prognosis. Again, these results might be explained by the small number of patients (imprecision). Some studies could not be included in the meta-analysis because they reported only HR results, making a comparison impossible.

The presence of portal vascular invasion was significantly related to shorter OS, thus reinforcing its importance in the histopathological evaluation of CRLMs. Due to the scarcity of studies (two studies) our meta-analysis on hepatic vein invasion did not show a significant difference. Our results are in line with previous systematic reviews (Knijn et al., 2013; Fonseca et al, 2018a) and found similar results in which the presence of portal invasion is associated with a decrease in 5-year overall survival.

The presence of perineural invasion was associated with a worse prognosis in our meta-analysis, which differs from previous reviews (Knijn et al., 2013; Fonseca et al., 2018a). However, two recent studies (Reijonen et al., 2018; Stift et al., 2018) included in our meta-analysis showed a statistically significant impact.

Blood vessel invasion, lymphatic vessel invasion and perineural invasion are dissemination pathways that play a role in the metastatic process (Compton, 2007; Beaton et al., 2013; Bosch et al., 2013; Schneider and Langner, 2014). Moreover, it has been hypothesized that they could be considered markers of poor biological behaviour.

There was no significant difference related to bile duct invasion for OS, in accordance with previous reviews (Knijn et al., 2013; Fonseca et al., 2018a). Therefore, this metastatic route does not appear to impact prognosis.

In our study, the presence of a pseudocapsule was associated with a better outcome, which may reflect a probable host immune response to the tumour, acting as a protective barrier and blocking local dissemination (Koike et al., 2000; Lunevicius et al., 2001). The presence of peritumoural inflammatory infiltrate was also associated with good prognosis. The presence of a pseudocapsule and/or peritumoural inflammatory infiltrate reflects the importance of a greater capacity of the immune response. Further studies are required to characterize the type and mechanism of the response in patients with CRLMs.

In the meta-analysis, we found that the presence of satellite nodules was significantly related to an unfavourable prognosis, reflecting the aggressive biological behaviour of CRLMs (Wakai et al., 2008; Knijn et al., 2013).

Only one study reached the inclusion criteria to evaluate the prognostic impact of the presence of tumour budding and poorly differentiated clusters (PDCs) (Fonseca et al., 2018a), precluding the meta-analysis. Since these factors are routinely studied on the primary tumour and easily detected by routine haematoxylin and eosin staining (Fonseca et al., 2018a), they have great potential to also be studied in liver metastases. Although using a different criterion to what we established, and for this reason it did not enter our analysis, recently Yonemura et al. (2019) showed the importance of the PDC as a promising criterion.

Regarding tumour borders, there are different classifications that make a comparison difficult. We chose the Jass et al. (1987) classification due to its easy and straightforward evaluation. A standardized classification for this histopathological criterion is lacking.

With these findings in mind the next step is to study the association between the histopathological factors and the molecular biology for a better understanding of the patients' prognosis after resection and to manage the therapy armamentarium (e.g., chemotherapy, radioembolization).

Strengths and limitations

The strengths of our review include a comprehensive search; the assessment of eligibility, risk of bias and data abstraction independently and in duplicate; and the use of the GRADE approach in rating the certainty of evidence for each outcome.

The primary limitation was the insufficient number of included studies to allow the analysis we had previously planned. We were not able to assess publication bias in our meta-analysis because there were less than 10 eligible studies addressing the same outcome. In addition, the certainty of the evidence reached a moderate classification in the following variables that presented statistically significant results: vascular invasion, perineural invasion, absence of pseudocapsule, presence of satellite nodules, and absence of peritumoral inflammatory infiltrate.

Another limitation was that our analysis revealed significant heterogeneity in the clinical outcomes of the studied groups. Explanations for this heterogeneity could involve both clinical and methodological diversity. The studies differed considerably in their period of patient selection (i.e., before and after 2000) and different chemotherapy regimens (i.e., neoadjuvant and adjuvant). It is also important to note that this systematic review gathered information from case series studies, making it vulnerable to different types of bias.

Implications

In conclusion, the following histopathological prognostic factors were associated with a significant decrease in OS according to the meta-analysis: portal vein and perineural invasion, the presence of satellite nodules and the absence of peritumoural inflammatory infiltrate and a pseudocapsule. There is very limited evidence regarding DFS.

Despite very low certainty, this is the best evidence available on the histopathological factors of CRLMs. More studies are needed to extend our knowledge in this promising research area. Once their biology is known (Cady, 1997), the comprehension of histopathology aspects could provide us with a better understanding of CRLM behaviour.

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review: CVCO and GMF. Entering data into RevMan software: CVCO and PH. Interpreting data: CVCO, JAPK, GMF, ESM, and PH. Making statistical inferences: CVCO, JAPK, GMF, and PH. Writing the review: CVCO, ESM and PH. Taking responsibility for reading and checking the review before submission: CVCO and PH

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