# The primary tumor location impacts survival outcome of colorectal liver metastases after hepatic resection: A systematic review and meta-analysis

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## ARTICLE INFO

## ABSTRACT

*Objective:* Location of the primary tumor side has become an increasingly prognostic factor for colorectal liver metastasis. The present study was to perform a meta-analysis to investigate if primary right-sided tumor impacted on long-term survival outcome of colorectal liver metastases following local treatment.
*Method:* Eligible trials were identified from the Embase, PubMed, Web of Science and the Cochrane database that were published before October in 2018. English language trials that compared long-term survival outcome of primary left-sided tumor with right-sided tumor colorectal liver metastases following local treatment were included. Hepatic resection for colorectal liver metastases was investigated. The main study outcomes included overall survival and disease free survival of primary right-sided colorectal liver metastases following local treatment. The risk factors of largest tumor size, primary node metastases, multiple tumor and *RAS* mutation were also analyzed. A systematic review and meta-analysis was done using a fixed-effects model. Hazard ratio with a 95% confidence interval was used to measure the pooled effect.
*Results:* A total of twelve studies with 6387 patients were included. For primary right-sided colorectal liver metastases patients following hepatic resection, the overall pooled HR for 5-year overall survival rate was 1.354 (95% CI: 1.238—1.482; $p = 0.000$; $I^2 = 33.7\%$, $p = 0.138$). The pooled HR for 5-year disease free survival rate of primary right-sided CRLM in the included studies calculated using the fix-effects model was 1.104 (95% CI: 0.987—1.235; $p = 0.084$; $I^2 = 0\%$, $p = 0.477$).
*Conclusion:* It demonstrated that primary right-sided for colorectal liver metastases location was a significantly worse prognostic factor in terms of overall survival.

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Colorectal cancer (CRC) is the third most common cancer for globally [1]. Colorectal liver metastases (CRLM) occur in 50% of patients in the disease progress and account for two-thirds of deaths from CRC [2]. Indications for curative-intended treatment of CRLM have expanded in recent years. Hepatic resection is regarded as the only way to cure and a well-accepted modality in the treatment of CRLM, which has been able to achieve a 5-year overall survival (OS) 50% [3]. Unfortunately, long-term survival outcome has also been associated with multiple oncological factors, despite the surgical advancement.

It was increasingly recognized that location of the primary tumor impacts prognosis factor in metastatic colorectal cancer. Large population-based studies have demonstrated that survival following surgery for colon cancer differs by tumor location [4]. Previous studies have reported conflicting results regarding the survival of primary right-sided CRLM (RSCRLM) compared with primary left-sided CRLM (LSCRLM) after hepatic resection. This distinction is mainly based on embryonic origins, because the right colon develops from the midgut and the left colon from the hindgut. Tumors within these unique regions are known to differ in regard to clinicopathologic factors, such as microsatellite instability

(MSI) and BRAF mutation rates [5].

Differences in study results may be attributable to sample size, heterogeneity in treatment methodologies and limited information on molecular and pathological features. With this bias, we conducted this meta-analysis of retrospective studies to quantify the prognostic difference between LSCRLM and RSCRLM following hepatic resection.

## Materials and methods

### Literature search strategy

Eligible studies were identified from Embase, PubMed, the Web of Science and the Cochrane database were searched for eligible studies (January 1990 to October 2018). The following MeSH terms were searched: 'colorectal cancer' or 'colorectal neoplasm' and 'liver metastases' and 'hepatic resection' or 'liver resection' and the terms 'prognosis' or 'survival', combined with terms 'left' and 'right'.

### Study selection

Two authors (Wei Liu and Hong-Wei Wang) independently screened the potential titles and abstracts. We included studies based on the following inclusion criteria: (1) comparative studies investigated the association between primary tumor location and survival outcomes; (2) included a hazard ratio (HR) and 95% confidence interval (CI) for suvival according to primary tumor location, which were either reported or could be calculated from the data presented; (3) all the patients underwent hepatic resection or RFA; (4) right-sided primary tumor was defined as a malignant neoplasm in the cecum, ascending colon or transverse colon, and left-sided primary as that located from the splenic flexure to the sigmoid colon, recto-sigmoid colon or rectum; (5) publication language was limited to be English; (6) Only cohort studies were included in the review, be they prospective or retrospective.

The exclusion criteria were as follows: (1) letters, reviews, case reports, conference abstracts, editorials, comments, systematic reviews or studies unrelated with our topics were excluded from final analysis; (2) articles in which no information on survival outcome was given or the HR for survival could not be calculated from the given information; and (3) articles in which the prognostic effect was determined as a function of recurrence. The quality of the studies was assessed independently by two investigators.

### Data extraction

Two authors (Wei Liu and Hong-Wei Wang) independently extracted data from studies by a standardized extraction form. Any disagreement was resolved by consensus and discussion. The following data were extracted: number of patients (both of primary left-sided and right-sided), the study design, year of publication, country where study was conducted, characteristic of patients included in largest tumor size, synchronous liver metastases, primary node positive, multiple lesions, CEA>200, *Ras* mutation and survival outcome according to primary tumor location. A modified Newcastle-Ottawa scale was used to assess the quality of non-randomized studies included in this meta-analysis [6]. The scale assessed each study based on three broad perspectives: patient selection, comparability of the survival outcome of left or right side, and characteristic of studies. Given the variability in quality among observational studies, a high-quality study was defined if it had six or more NOS criteria scores.

### Statistical analysis

HR and 95% CI were used to estimate the impact of primary tumor location on survival outcome. A combined HR > 1 implied a worse survival for the RSCRLM. For the time-to-event variables, the HRs of OS with 95%CI were directly extracted or calculated by a calculation sheet as previously described if the value were not reported directly [7]. Pooled estimates of HR were calculated using the fixed-effects model. To assess for publication bias, we evaluated funnel plot asymmetry using the regression test by Begg [8]. Heterogeneity among the studies was evaluated using I [2] statistics [9]. The extent of heterogeneity was defined as follows: I [2]<25%, absent heterogeneity; I [2] = 25–50%, moderate heterogeneity; I [2] = 50–75%, high heterogeneity; and I [2]>75%, extreme heterogeneity [10]. A p value less than 0.05 was judged as statistically significant. All statistical analyses were performed using STATA version 12.0 (Stata Corporation, College Station, TX, USA).

## Results

### Identification of eligible studies

A total of 742 CRLM-related citations based on the initial search. After independent review, 730 studies were excluded due to the irrelevance to the current analysis or their disagreement with the inclusion criteria (Fig. 1). Finally, 12 studies (n = 6387) were ultimately included in the meta-analysis of the prognostic value of primary tumor location [11–22]. A total of 6135 patients were performed hepatic resection, among of them, 2228 patients were primary right-sided CRLM.

### Characteristics of eligible studies

The baseline characteristics and oncological characteristic of the 12 retrospective cohort studies are presented in Table 1 and Table 2, respectively. Hepatic resection were performed in 10 studies. RFA or MA were performed in other two studies. The quality of the included studies according to NOS was determined to be higher for nine studies, and lower for three studies. There were nine studies from non-Asian countries, and three studies from Asian countries. Eight studies reported data from which the HR was retrieved directly; in the remaining four studies, the HR was calculated indirectly from Kaplan-Meier curves.

### Prognosis of primary tumor location

All 12 studies included in the meta-analysis reported the results of 5-year OS rate. The pooled HR for 5-year OS rate of primary right-sided CRLM following local treatment in the included studies performed using the fixed-effects model was 1.322 (95% CI: 1.215–1.439; $I^2$=66.3%, p = 0.000)(Fig. 2a). After excluded two study of ablation[15,22], the pooled HR for 5-year OS rate of primary right-sided CRLM after hepatic resection in the included studies performed using the fix-effects model was 1.354 (95% CI: 1.238–1.482; $I^2$ = 33.7%, p = 0.138) (Fig. 2b). A sensitivity analysis was performed to examine the potential source of heterogeneity. One study was excluded[17], the pooled HR for the OS in the included studies performed using the fix-effects model was 1.350 (95% CI: 1.234–1.477; p = 0.000; $I^2$ = 35.4%, p = 0.135). The Egger's test (p = 0.215) and Begg's test (p = 0.304) revealed no publication bias. Six studies reported the 5-year DFS rate of primary tumor side[11,12,17,19,20,21]. The pooled HR for 5-year DFS of primary right-sided CRLM in the included studies calculated using the fix-effects model was 1.234 (95% CI: 1.120–1.360; p = 0.000; $I^2$ = 72.8%, p = 0.003) (Fig. 3a). After excluding the study by
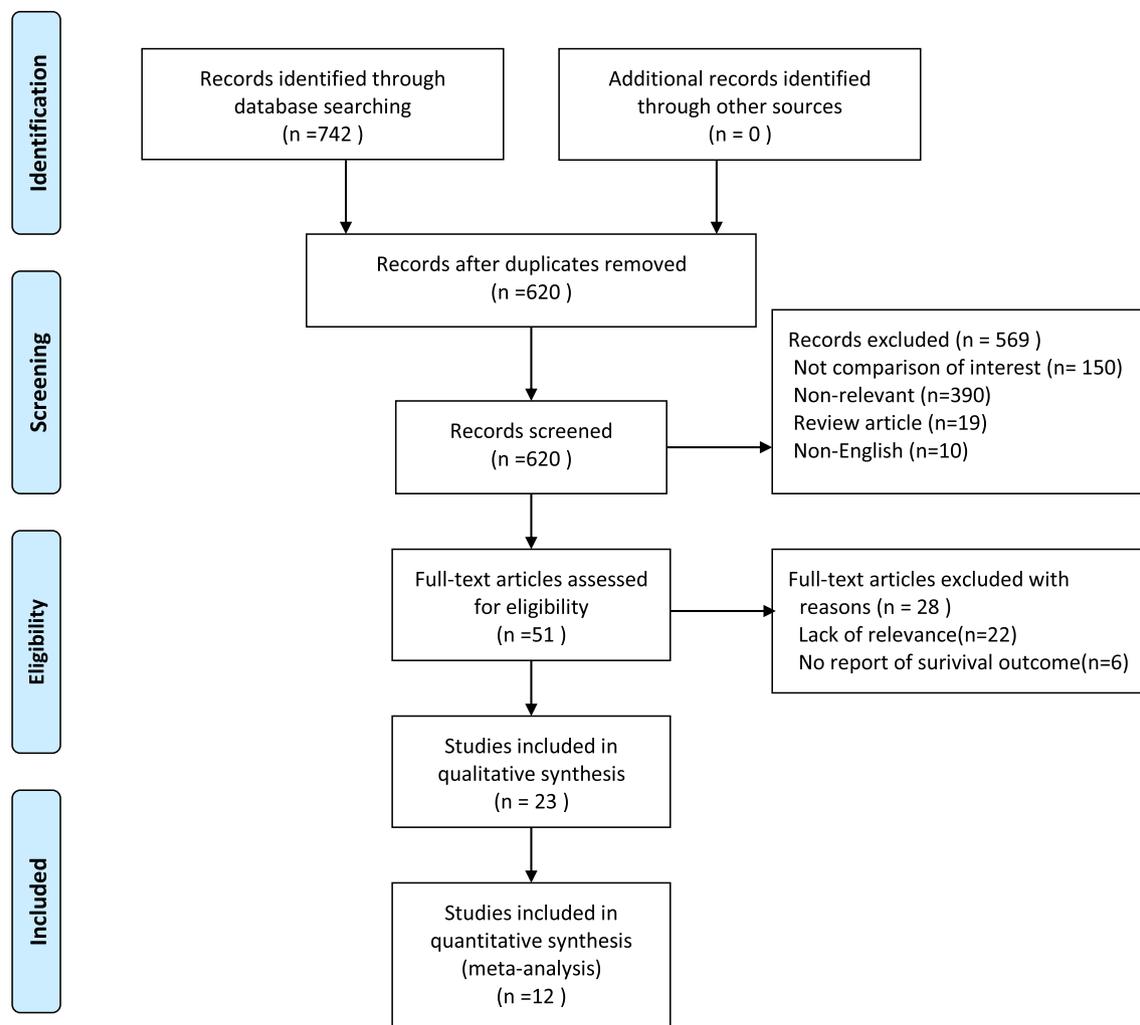
**Fig. 1.** Flow chart for the study selection method.

**Table 1**
Overview included studies.

| Study | Year | Design | Recruitment time | Left | Right | Treatment | Median FU(m) | Country | 5-year OS-L | 5-year OS-R | NOS | Outcome | Analysis of variance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Creasy[11] | 2018 | Retro | 1992–2004 | 578 | 392 | Resection | 136.8 | America | 50.4 | 38.5 | 9 | OS | Multi |
| Dupre[12] | 2018 | Retro | 2010–2015 | 290 | 74 | Resection | 41.8 | UK | 37.5 | 25.4 | 9 | OS | Multi |
| Engstrand[13] | 2018 | Retro | 2008–2008 | 57 | 11 | Resection | 63.6 | Sweden | 16.6 | 4.3 | 7 | OS | Multi |
| Goffredo[14] | 2018 | Retro | 2010–2015 | 1467 | 1188 | Resection | N/A | America | N/A | N/A | 8 | OS | Multi |
| Gu[15] | 2018 | Retro | 2007–2013 | 51 | 51 | RFA | N/A | China | 30 | 14 | 9 | OS | Multi |
| Makowiec[16] | 2018 | Retro | 2000–2016 | 158 | 63 | Resection | N/A | Germany | 41 | 46 | 9 | OS | Multi |
| Marques[17] | 2018 | Retro | 1998–2012 | 124 | 27 | Resection | 42 | Brazil | 8.9 | 1.4 | 8 | OS | Multi |
| Price[18] | 2015 | Retro | 2006–2015 | 307 | 107 | Resection | N/A | Australia | 65 | 24 | 9 | OS | Multi |
| Sasaki[19] | 2016 | Retro | 2000–2015 | 284 | 191 | Resection | 30.7 | America | 53.7 | 41.5 | 9 | OS | Multi |
| Wang[20] | 2018 | Retro | 2002–2015 | 334 | 86 | Resection | 26 | China | 38.3 | 46.5 | 9 | OS | Multi |
| Yamashita[21] | 2018 | Retro | 1990–2015 | 163 | 89 | Resection | 27 | America | N/A | N/A | 9 | OS | Multi |
| Zhou[22] | 2018 | Retro | 2006–2016 | 201 | 94 | MA | 24 | China | N/A | N/A | 9 | OS | Multi |

*OS* overall survival, *DFS* disease-free survival, *RFS* recurrence free survival, *NOS* Newcastle-Ottawa scale, *N* number, *FU* follow up, *N/A* not available, *MA* microwave ablation, *RFA* Radiofrequency ablation, *Multi* multiple variances, *Retro* retrospective.

Yamashita[21], the pooled HR for 5-year DFS of right side in the included studies calculated using the fix-effects model was 1.104 (95% CI: 0.987–1.235; p = 0.084; $I^2 = 0\%$, p = 0.477) (Fig. 3b).

*Risk factors of OS*

A subgroup analysis was performed to evaluate whether patients had a survival difference with respect to the oncology characteristics. The pooled HR for gender (female vs. male) was 1.068 (95% CI: 0.989–1.153; p = 0.093; $I^2 = 25.1\%$, p = 0.261) (Supplementary Fig. 1), for largest tumor size>5 cm was 1.678 (95% CI: 1.455–1.935; p = 0.000; $I^2 = 69.5\%$, p = 0.020) (Supplementary Fig. 2), for primary node positive was 1.519 (95% CI: 1.356–1.702; p = 0.000; $I^2 = 15.7\%$, p = 0.313) (Supplementary Fig. 3), for

**Table 2**
Oncological characteristics of the studies included in the meta-analysis.

| Study | Subgroup | Age | Tumor size(mm) | No. of tumors(n) | Primary N stage(+)(n) | Synchronous CRLM(n) | CEA>200 | Ras mutation | R1 |
|---|---|---|---|---|---|---|---|---|---|
| Creasy[11] | L = 578 | 62.6(23−89) | N/A | N/A | 231(40.0%) | 292(50.5%) | 48 | N/A | 51(8.8%) |
|  | R = 392 | 65.4(26−86) |  |  | 113(34.3%) | 202(61.4%) | 38 |  | 21(6.4%) |
| Dupre[12] | L = 290 | 65.1 ± 10.6 | 40.5 ± 27.3 | 2.8 ± 2.7 | 186(65.5%) | 148(51%) | N/A | 32(28.1%) | 141(51.6%) |
|  | R = 74 | 68.8 ± 10.9 | 38.8 ± 28.1 | 2.8 ± 3.2 | 30(40.5%) | 31(41.9%) |  | 13(54.2%) | 28(41.2%) |
| Engstrand[13] | L = 57 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
|  | R = 11 |  |  |  |  |  |  |  |  |
| Goffredo[14] | L = 1467 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
|  | R = 1188 |  |  |  |  |  |  | 647(58.4%) |  |
| Gu[15] | L = 51 | 63.0(31−74) | N/A | N/A | N/A | N/A | 17 | N/A | N/A |
|  | R = 51 | 61.5(27−73) |  |  |  |  | 16 |  |  |
| Makowiec[16] | L = 158 | 64(33−85) | 41 ± 27 | 2.4 ± 2.2 | 59(39%) | 83(52%) | N/A | N/A | 14(9%) |
|  | R = 63 | 65(39−82) | 44 ± 40 | 2.0 ± 1.6 | 23(39%) | 37(59%) |  |  | 9(14%) |
| Marques[17] | L = 124 | 57 (29−80) | 89 ± 48 | 2 (1−20) | 81(65.3%) | 84(67.7%) | N/A | 19(15.3%) | 11(8.9%) |
|  | R = 27 | 61 (23−73) | 37 ± 19 | 2 (1−9) | 15(55.5%) | 12(44.4%) |  | 9(33.3%) | 0(0%) |
| Price[18] | L = 307 | 70.6(17.4−103.3) | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
|  | R = 107 | 76(35.6−105.4) |  |  |  |  |  |  |  |
| Sasaki[19] | L = 284 | 58(48−66) | 26(16−42) | 2(1−3) | 86(30.3%) | 167(58.8%) | N/A | 68(28.8%) | 64(22.5%) |
|  | R = 191 | 63(53−72) | 25(17−40) | 2(1−3) | 106(55%) | 107(61.5%) |  | 78(48.8%) | 37(17.9%) |
| Wang [20] | L = 334 | 57(49.7−64) | 30(20−40) | 2(1−4) | 208(69.8%) | 169(50.8%) | N/A | 68(25.9%) | N/A |
|  | R = 86 | 58(49.7−65) | 30(20−40) | 2(1−3.5) | 47(63.5%) | 46(52.9%) |  | 29(43.3%) |  |
| Yamashita[21] | L = 487 | 58(50−66) | 22(15−35) | N/A | 335(69%) | 356(67%) | N/A | 170(35%) | 32 |
|  | R = 238 | 56(49−64) | 21(13−33) |  | 155(65%) | 181(76%) |  | 92(39%) | 20 |
| Zhou[22] | L = 201 | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
|  | R = 94 | 59 (39−83) | 30 (11−46) | 1 (1−3) | 31(33%) | 32(34%) | N/A | N/A | N/A |

**CRLM** colorectal cancer liver metastases, **N/A** not available, **Primary N stage** primary node stage.
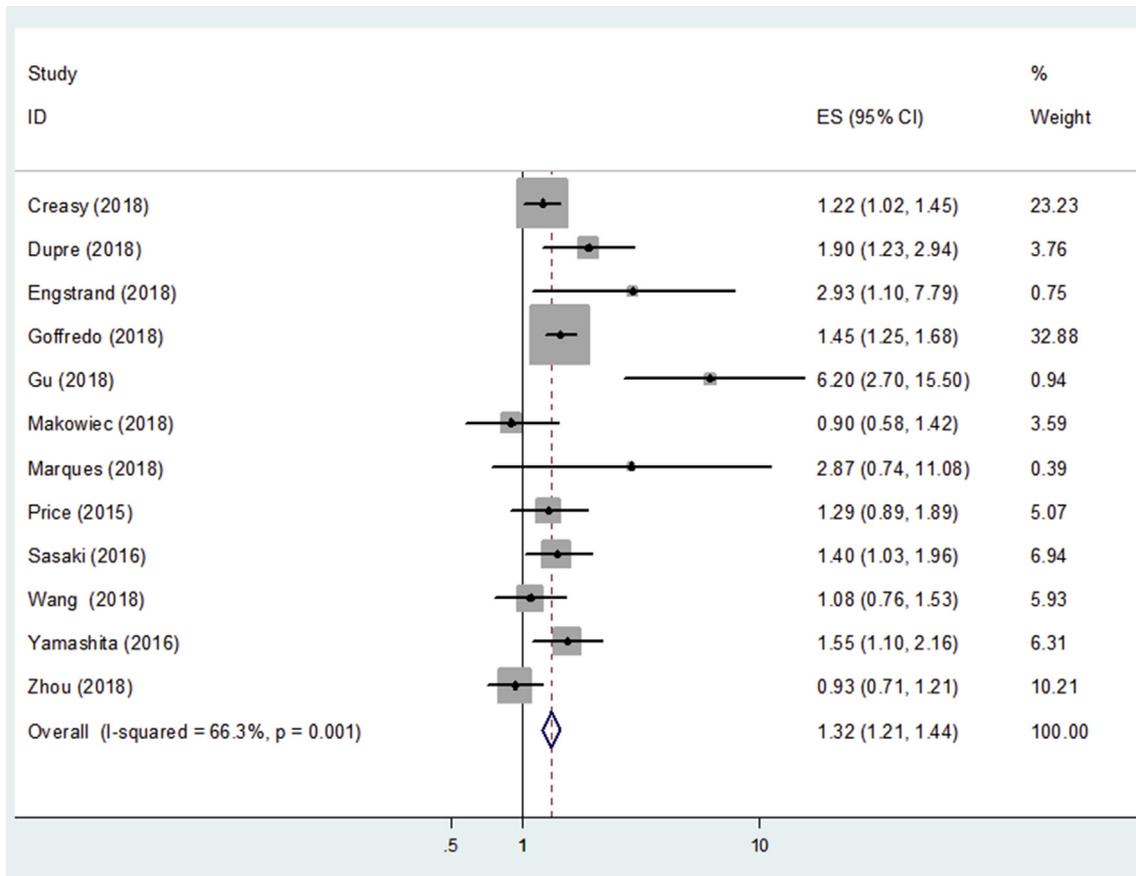


**Fig. 2a.** Forest plot of the hazard ratios for 5-year overall survival between primary right-sided and left-sided CRLM following hepatic resection or ablation. The pooled HR for 5-year OS rate of primary right-sided CRLM following local treatment in the included studies performed using the fixed-effects model was 1.322 (95% CI: 1.215–1.439; $I^2$ = 66.3%, p = 0.000). It demonstrated that primary right-sided for colorectal liver metastases location was a significantly worse prognosis than those with left-sided primary in terms of overall survival.
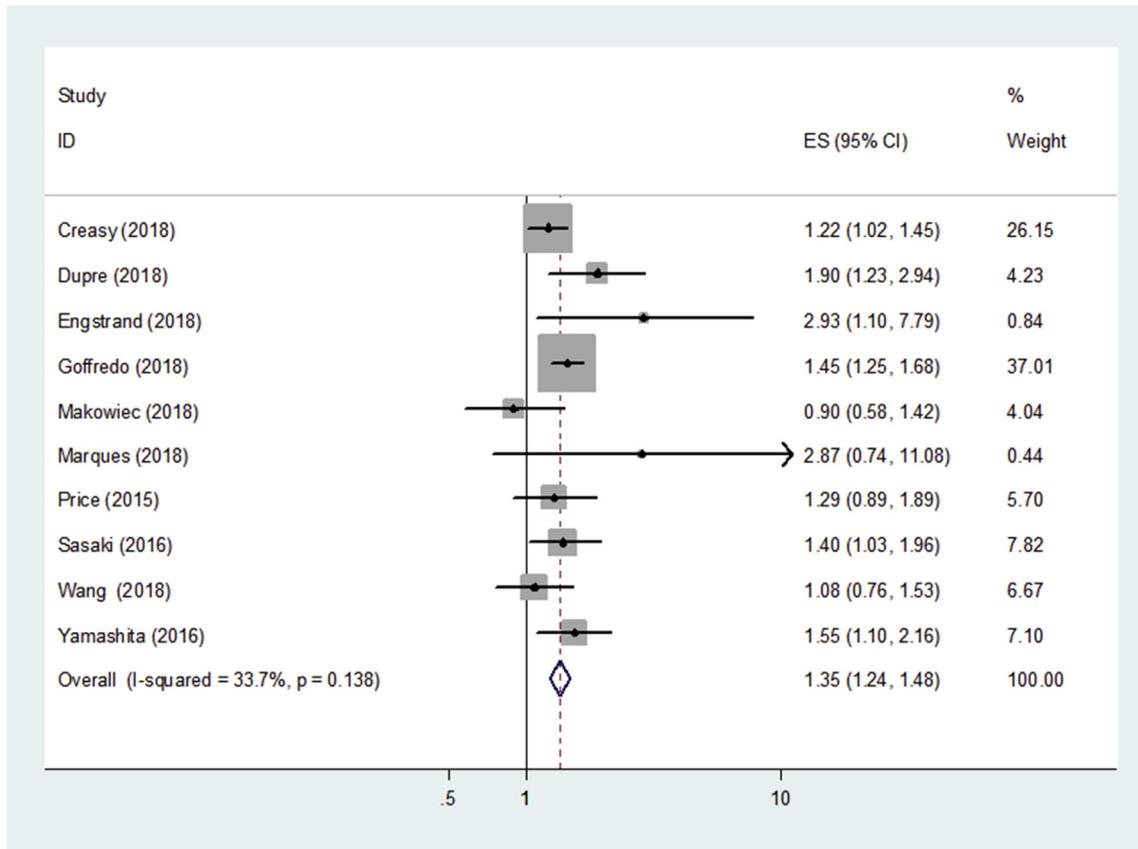
**Fig. 2b.** Forest plot of the hazard ratios for 5-year overall survival between primary right-sided and left-sided CRLM following hepatic resection. The pooled HR for 5-year OS rate of primary right-sided CRLM after hepatic resection in the included studies performed using the fix-effects model was 1.354 (95% CI: 1.238–1.482; $I^2 = 33.7\%$, p = 0.138). It demonstrated that primary right-sided for colorectal liver metastases following hepatic resection location was a significantly worse prognosis than those with left-sided primary in terms of overall survival.

multiple liver metastases was 1.278 (95% CI: 1.114–1.466; p = 0.000; $I^2 = 0\%$, p = 0.818) (Supplementary Fig. 4), for synchronous liver metastasis was 1.191 (95% CI: 1.059–1.340; p = 0.004; $I^2 = 3.4\%$, p = 0.387) (Supplementary Fig. 5), and for *Ras* mutation was 1.274 (95% CI: 1.141–1.422; p = 0.000; $I^2 = 22.5\%$, p = 0.271) (Supplementary Fig. 6).

## Discussion

In previous studies of stage I-III colon cancer, survival outcome of right-sided colon cancer was significantly worse than that of left-sided colon cancer among patients with poorly differentiated adenocarcinoma [23]. Many results correspond with what has been previously reported regarding the impact of primary location on OS in patients with metastatic colon cancer treated with palliative chemotherapy [24,25]. However, the survival outcome of primary right-sided CRLM after hepatic resection still remains debatable. To the best of our knowledge, the present study is the first meta-analysis to examine the implication of primary right-sided tumor in context of CRLM following hepatic resection. It was included in 12 studies and provided a solid evidence showing that primary right-sided tumor exhibited a significantly worse 5-year OS rates (HR = 1.354, 95% CI: 1.238–1.482; $I^2 = 33.7\%$, p = 0.138).

Primary left-sided tumor of CRC are present more often in early-stage disease, which is probably attributed to be diagnosed easily by apparent symptoms, such as rectal bleeding or a change in bowel habits. Consequently, this lead-time bias may partly related to the difference in prognosis. Patients with primary right-sided tumor were found to be older than those with left-sided tumor, and to have more comorbidities [26]. Tumors arising on the midgut and hindgut exhibit huge differences in their molecular and cellular features [26]. As a result, many studies have been conducted to search for theoretical genetic backgrounds of various lesions. Mutant KRAS and BRAF status was more frequent among patients with RCC. A significant interaction of KRAS status and primary tumor location was observed in terms of OS, indicating that LCC might be a predictor of cetuximab efficacy [27]. Furthermore, RCC were more commonly characterized by high Microsatellite instability (MIS), high CpG island methylation (CIMP), which could lead to poor response to chemotherapy for right-sided CRLM [28]. MSI has been proposed to be one of the most promising molecular markers investigated to date. Several studies have found that patients with microsatellite instability-positive (MSI-H) tumors have a better overall prognosis and that MSI status is a favorable independent predictor of survival [29].

Selecting patients who would benefit from hepatic resection has always been concerned. Previous studies developed scoring systems to stratify patients into different risk groups to predict survival outcome before surgery [30,31]. However, these studies did not examine the significance of right versus primary left-sided tumors following hepatic resection. Further studies regarding hepatic resection for CRLM should include primary tumor location as a clinicopathologic variable, and will better elucidate the overall impact it has on survival. Many studies on location of colon cancer as a prognostic factor for survival do not include rectal cancer. In the few studies that do, the results are consistent with right-sided
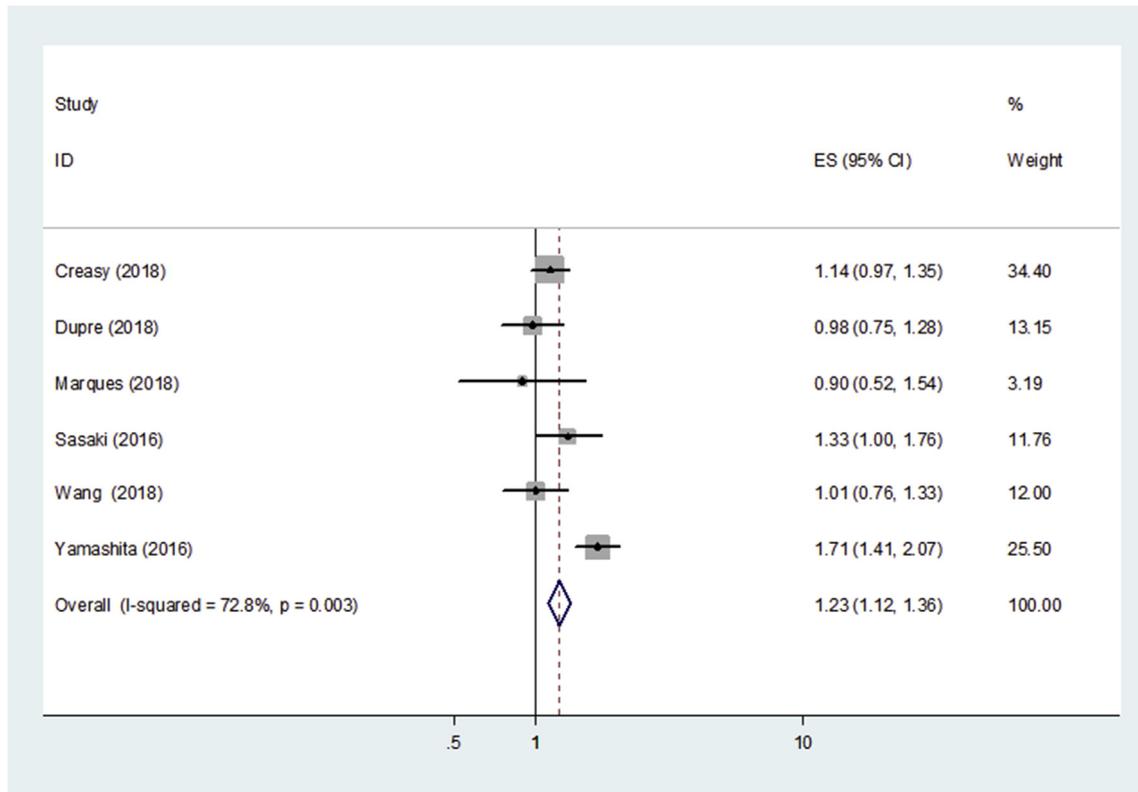
**Fig. 3a.** Forest plot of the hazard ratios for 5-year disease free survival between primary right-sided and left-sided CRLM following hepatic resection.
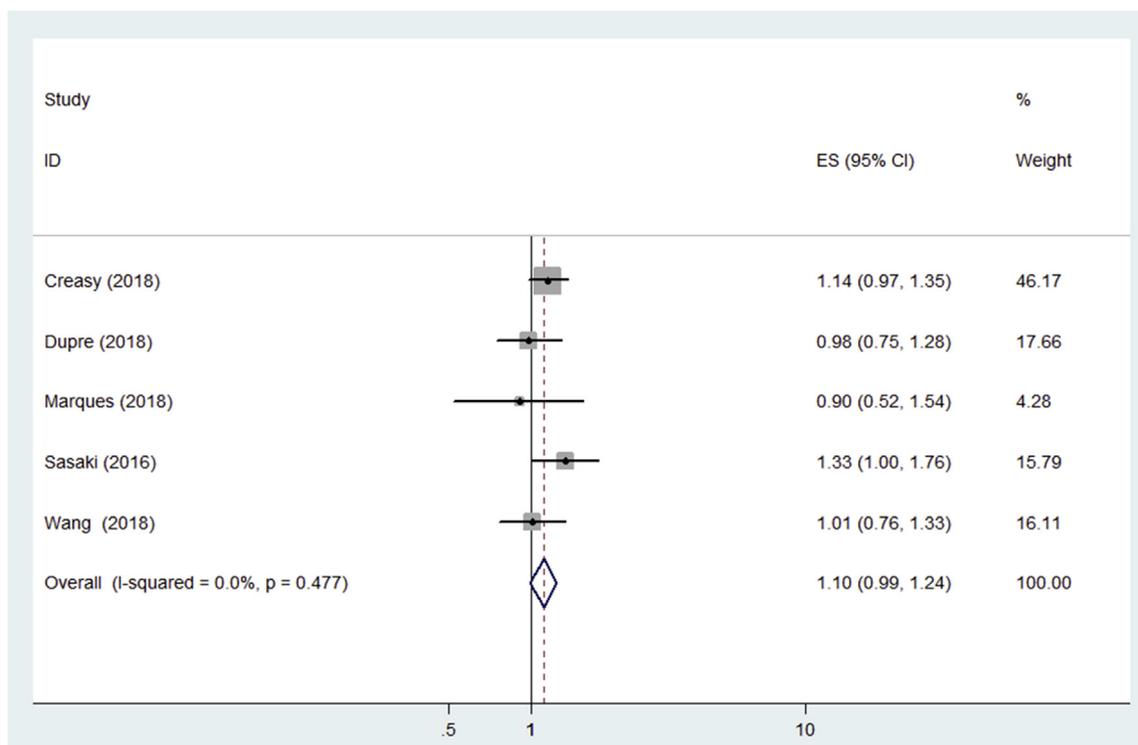


**Fig. 3b.** Forest plot of the hazard ratios for 5-year disease free survival between primary right-sided and left-sided CRLM after excluding study of Yamashita.

cancer having worse survival outcome compared with left-sided cancer [32,33].

When analysing early stage disease, there could be merit in not including rectal cancer in the analyses due to different treatment strategies, but in the setting of CRLM is not different between metastatic rectal and colon cancer. Although the primary right-sided tumor was associated with worse 5-year OS rate based on the present study, the OS was might be influenced by postoperative chemotherapy and the treatment of recurrent tumors. Primary tumor location, by itself, has limited utility to improve current methods of patient selection for surgery and should not yet alter surgical decision making. Recurrence after hepatic resection from right-sided may be less amenable to resection.

### Limitation

There were several limitations to our study. First, there was heterogeneity derived from definition of right and left sided primary, most studies on location of colon cancer as a prognostic factor for survival do not include rectal cancer. Second, limitation was related to the quality of enrolled studies. There were two studies due to small sample of patients. Finally, the characteristics of patients and perioperative chemotherapy regimens vary considerably between the included trials. These factors may increase the heterogeneity and affect the results.

### Conclusion

The primary right-sided CRLM patients were found to have a significantly worse prognosis than that of left-sided primary CRLM patients in terms of OS. An implication of this finding is that primary right-sided CRLM might be treated distinctively from left-sided CRLM, and the establishment of standardized management for CRLM by tumor location is needed.

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### Financial disclosure

There is no conflicts of interest. No drug or products were involved.

### Statement

The manuscript has not been a podium or poster meeting.

### Acknowledgement

### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.04.017.

### Abbreviations

DFS    Disease-free survival
OS    Overall survival
RFS    Recurrence free survival
NOS    Newcastle-Ottawa scale
N    Number
FU    Follow up
N/A    Not available
MA    Microwave ablation
RFA    Radiofrequency ablation
Multi    Multiple variances
Retro    Retrospective
CRLM    Colorectal liver metastases
RSCRLM    Primary right-sided colorectal cancer liver metastases
LSCRLM    Primary left-sided colorectal cancer liver metastases
HR    Hazard ratio

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