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GUIDELINE

Clinical practice guidelines for the management of liver metastases from extrahepatic primary cancers 2021

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Abstract

Background: Hepatectomy is standard treatment for colorectal liver metastases; however, it is unclear whether liver metastases from other primary cancers should be resected or not. The Japanese Society of Hepato-Biliary-Pancreatic Surgery therefore created clinical practice guidelines for the management of metastatic liver tumors.

Methods: Eight primary diseases were selected based on the number of hepatectomies performed for each malignancy per year. Clinical questions were structured in the population, intervention, comparison, and outcomes (PICO) format. Systematic reviews were performed, and the strength of recommendations and the level of quality of evidence for each clinical question were discussed and determined. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess evidence and make recommendations.

Results: The eight primary sites were grouped into five categories based on suggested indications for hepatectomy and consensus of the guidelines committee. Fourteen clinical questions were devised, covering five topics: (1) diagnosis, (2) operative treatment, (3) ablation therapy, (4) the eight primary diseases, and (5) systemic therapies. The grade of recommendation was strong for one clinical question and weak for the other 13 clinical questions. The quality of the evidence was moderate for two questions, low for 10, and very low for two.

A flowchart was made to summarize the outcomes of the guidelines for the indications of hepatectomy and systemic therapy.

Conclusions: These guidelines were developed to provide useful information based on evidence in the published literature for the clinical management of liver metastases, and they could be helpful for conducting future clinical trials to provide higher-quality evidence.

KEYWORDS

ablation therapy, disappearing liver metastases, hepatectomy, metastatic liver tumors, systemic therapy

1 | INTRODUCTION

The liver is one of the most frequent metastatic sites for various types of cancer, and the prognosis of patients with liver metastases is generally poor. Although systemic chemotherapy is usually used for cancer patients with liver metastases, liver resection is considered if resectable liver metastases from colorectal cancers and neuroendocrine tumors (NETs) are detected.[1,2] Many cases of hepatectomy for liver metastases from other cancers have also been reported on a national survey in Japan.[3] The major sites of primary extrahepatic malignancies for which hepatectomy was performed were gastric cancer, gastrointestinal stromal tumor (GIST), biliary tract cancer, ovarian cancer, pancreatic cancer, and breast cancer. The 5-year survival in patients with liver metastases who underwent hepatectomy varied from 17% to 72%, depending on the primary site. Hepatectomy can achieve a cure or long-term survival in some patients, but various factors influence the outcome, such as the primary site, histology, and the patient's condition. Therefore, the indications for hepatectomy of liver metastases from these extrahepatic sites remain controversial, and currently there are no internationally accepted standard guidelines for the management of liver metastases.

The Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) has developed a set of international guidelines for the diagnosis and management of liver metastases from eight primary extrahepatic malignancies: colorectal cancer, gastroenteropancreatic NET (GEP-NET), gastric cancer, GIST, biliary tract cancer, ovarian cancer, pancreatic cancer, and breast cancer. These guidelines represent the most accepted, evidence-based standard clinical practices for liver metastases at this time.

2 | MATERIALS AND METHODS

JSHBPS selected 43 specialists as committee members of the guideline development project. Members selected eight primary malignancies (colorectal cancer, gastric cancer, GIST, biliary tract cancer, ovarian cancer, breast cancer, pancreatic cancer, and GEP-NET) on the basis of the number of cases undergoing hepatectomy for liver metastases reported in the literature.[3] The committee addressed the following topics in the guidelines: (1) diagnosis, (2) operative treatment, (3) liver ablative therapy (ABT), (4) best practice for the eight primary extrahepatic malignancies, and (5) systemic therapy. Initially, a total of 39 clinical questions were formatted in the population, intervention, comparison or control, and outcomes (PICO) sections and systematic reviews were performed for each clinical question. Systematic literature searches of the Cochrane database and PubMed were performed for articles published from January 1 1996, to July 31 2018, for each clinical question. We synthesized studies to make a body of evidence after we assessed five factors: (1) Risk of bias, (2) Inconsistency, (3) Indirectness, (4) Imprecision, and (5) Publication bias.[4] The quality of evidence was defined as high (i.e., strongly confident of the estimate of effect), moderate (moderately confident), low (limited confidence), and very low (very little confidence).

The strength of recommendations was determined according to the concepts of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach,[4–6] and studies were classified as strong or weak by the voting of our guideline development group. We developed a recommendation grade based on the level of evidence, the balance between benefits and harms, patients' values and preferences, implications concerning cost and resources, and feasibility and acceptability of the intervention. A strong recommendation was made when votes for a strong recommendation accounted for over 70% of votes. A weak recommendation was made when votes for a weak recommendation accounted for over 70% of votes. A strong recommendation means that the desirable effects of adherence to a recommendation will clearly outweigh the undesirable effects. A weak or conditional recommendation reflects that the desirable effects of adherence to a recommendation probably will outweigh the undesirable effects.[4–6] All meta-analyses were performed using Review Manager (RevMan) Version 5.3 software (The Cochrane Collaboration, Oxford, United Kingdom). The fixed effects model and the random effects model were used. Heterogeneity was explored using the I^2 statistic, where a maximum value of 40% identified substantial heterogeneity. The risk ratio and odds ratio with corresponding 95% confidence intervals (CIs) were assessed for categorical variables.

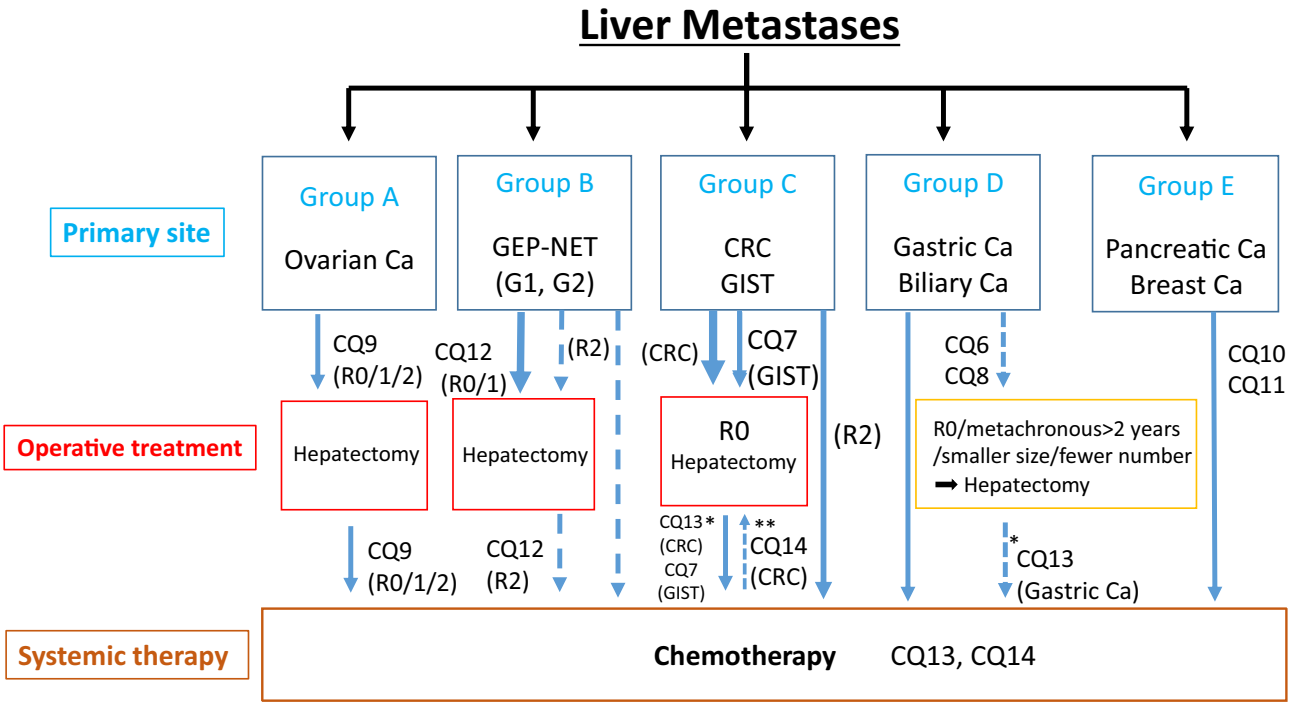
After consensus meetings with the committee members and international commentators, a public hearing was performed. The final version of this guideline includes 14 clinical questions and nine future research questions (Table S1).

The PICO information for each clinical question, the details of the systemic review, and the GRADE evidence-to-decisions framework are available on the JSHBPS home page (http://www.jshbps.jp/modules/en/index.php?content_id=57).

3 | RESULTS AND DISCUSSION

3.1 | Flowchart

A flowchart was made to summarize the outcomes of the guidelines for the indications of hepatectomy and systemic therapy for liver metastases from these eight primary sites (Figure 1).



Dotted line means recommendation based on case studies * Adjuvant therapy ** If chemotherapy is effective, conversion surgery should be considered
CQ: clinical question; GIST: gastrointestinal tumor; GEP-NET: gastroenteropancreatic neuroendocrine tumor; CRC: colorectal cancer; Ca: cancer

FIGURE 1 Flowchart for the management of liver metastases from extrahepatic primary cancers

Group A consists of ovarian cancer (clinical question 9). The basic strategy is debulking, which can be of one of three levels of resection: complete resection (R0 resection), optimal debulking (maximum size of the remnant tumor[s] <1 cm), or suboptimal debulking (maximum size of the remnant tumor[s] ≥1 cm) in order of the best postoperative prognosis. From the analysis of this clinical question, hepatectomy, even if only a substantial debulking procedure, combined with chemotherapy is recommended over chemotherapy alone for patients with liver metastases who have concomitant peritoneal dissemination with liver invasion, although the recommendation is weak.[7–9]

Group B consists of GEP-NETs (clinical question 12); hepatectomy with curative intent for liver metastases associated with a G1/G2 GEP-NET is strongly recommended compared with treatment not involving a hepatectomy, because a meta-analysis of this guideline showed that patients with hepatectomy who have an R0 resection had significantly better survival and better relief of symptoms. In some limited reports, a debulking procedure appeared to be beneficial not only for relief of symptoms but also for improved survival,[10–12] but the number of patients studied was insufficient to make any reasonable, evidence-based conclusion. Therefore, GEP-NETs are classified under Group B, and a strong recommendation can be made for R0 resection, but a recommendation for a debulking procedure cannot be made at this time because of insufficient evidence. In addition, NET G3 and neuroendocrine carcinoma are excluded from clinical question 12.

Group C includes colorectal cancer and GISTs (clinical question 7). For patients with colorectal or GIST cancers with synchronous liver metastases, many papers reported that patients able to undergo a simultaneous R0 resection of the primary tumor and hepatectomy had better survival generally when adjuvant chemotherapy was also used.[13,14]

Group D consists of gastric cancer (clinical question 6) and biliary tract cancer (clinical question 8). Hepatectomy for liver metastases from these primaries cannot be recommended even if an R0 resection is achievable. There may be a few exceptions, such as three or fewer metachronous tumors smaller than 3-5 cm developing >2 years after the resection of the primary site.[15–18]

Group E comprises breast cancer (clinical question 11) and pancreatic cancer (clinical question 10). Isolated hepatic metastases are extremely rare, and hepatectomy is recommended against except for very rare situations: e.g., situations in which liver metastases develop years after the resection of the primary cancer, an R0 resection is possible, there are no extrahepatic metastases, and concomitant systemic chemotherapy appears to be effective, or in highly controlled experimental trials.

Regarding adjuvant chemotherapy after hepatectomy (clinical question 13) for colorectal cancer, two randomized controlled trials (RCTs) and one pooled analysis have been

reported.[19–21] A meta-analysis of these three randomized, phase III trials was performed and was incorporated into this set of guidelines particularly in relation to the 5-year survival rate. The results showed that administering chemotherapy after hepatectomy for liver metastases from colorectal cancer increased the 5-year survival rate compared with hepatectomy alone. For liver metastases from gastric cancer, no reports of RCTs were found. A meta-analysis of the 5-year survival rate was performed using data from five of the reported retrospective cohort studies[22–26] and incorporated into this set of guidelines; our meta-analysis showed that giving chemotherapy after hepatectomy for liver metastases from gastric cancer increased the 5-year survival rate more than hepatectomy alone.

Overall 3-year and 5-year survival rates of conversion hepatectomy, i.e., hepatectomy in patients where the cancer was converted from an unresectable to resectable state by chemotherapy, would be better compared with those of chemotherapy alone for unresectable colorectal cancer (clinical question 14).[27–29]

The limitation of this set of guidelines is that our extensive literature review only supports hepatectomy strongly for liver metastases from colorectal cancer and GEP-NETs. In this set of guidelines, clinical questions were selected from the topics that still remain controversial, and a systematic literature search and analysis revealed that in the other clinical questions, robust, useful, evidenced-based recommendations cannot be provided because of insufficient reported literature. When additional research is published, the status of recommendations for these unsolved clinical questions will be updated in future revisions of these current guidelines.

3.2 | Clinical question 1

Is magnetic resonance imaging (MRI) recommended for the diagnosis and planning of appropriate treatment of liver metastases?

3.2.1 | Recommendation

When operative resection is planned for patients with liver metastases, the addition of preoperative MRI to computed tomography (CT) is recommended, but with only a weak level of confidence.

(Grade of recommendation: weak; quality of evidence: moderate).

Currently, CT and ultrasonography are commonly used for the diagnosis of liver metastases and for patient follow-up after treatment because of their wide availability and convenience. MRI (either gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced MRI [EOB-MRI] or diffusion-weighted MRI [DW-MRI]) is more sensitive than CT for the detection of liver metastases,[30,31] but it is still unclear whether MRI should be recommended for the diagnosis of liver metastases.

From our systematic review of the literature, one RCT, nine cohort or case-control studies, and two meta-analyses were accepted for this guideline. These studies reported the sensitivity and specificity of EOB-MRI for the diagnosis of liver metastases as 63%-100% and 42%-100%, respectively, whereas studies using CT gave sensitivities and specificities of 61%-91% and 42%-100%, respectively. Our meta-analysis of those reports (Figures 2 and 3) revealed that the diagnostic value of EOB-MRI is superior to that of CT.[30–48] One RCT also reported that EOB-MRI is superior to CT as a modality for operative planning because 47.1% of the planned operative procedures based on the preoperative CT evaluation of liver metastases were modified during the operation, whereas only 27.7% of the planned procedures were modified when EOB-MRI was used as the preoperative evaluation.[49] It should be noted that MRI cannot screen for metastases throughout the rest of the body and that MRI is available only in limited facilities. There are no reports in which MRI is suggested to be a useful modality for patient follow-up.

Regarding DW-MRI, an RCT demonstrated that DW-MRI is superior to CT in terms of diagnosis of liver metastases.[50] Therefore, when contrast material cannot be used for some reason, such as allergy, DW-MRI can be a useful substitution for EOB-MRI for the diagnosis of liver metastases when operative resection is planned.

In terms of the cost-effectiveness, EOB-MRI has a cost benefit for the evaluation of the resectability of liver metastases due to a lesser need for additional images and an overall similar cost compared to contrast-enhanced CT (CE-CT) or other CE-MRI techniques in some European and Asian countries.[51,52]

3.3 | Clinical question 2

Is MRI recommended for diagnosis of liver metastases that disappear after neoadjuvant therapy?

3.3.1 | Recommendation

MRI is recommended for diagnosis of liver metastases that disappear after neoadjuvant therapy, but with only a weak level of confidence.

(Grade of recommendation: weak; quality of evidence: low).

Even if liver metastases seem to “disappear” on imaging after neoadjuvant therapy (so-called “disappearing liver metastases”), this does not mean that a complete pathologic

MRI

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Arita 2015 [32]	232	3	48	10	0.83 [0.78, 0.87]	0.77 [0.46, 0.95]
berger-kulemann 2012 [30]	66	2	2	19	0.97 [0.90, 1.00]	0.90 [0.70, 0.99]
Cho 2015 [33]	10	1	6	104	0.63 [0.35, 0.85]	0.99 [0.95, 1.00]
chung 2011 [34]	78	6	0	22	1.00 [0.95, 1.00]	0.79 [0.59, 0.92]
colagrande 2016 [35]	113	2	3	17	0.97 [0.93, 0.99]	0.89 [0.67, 0.99]
donati 2010 [36]	50	0	5	30	0.91 [0.80, 0.97]	1.00 [0.88, 1.00]
koh 2012 [31]	301	4	9	103	0.97 [0.95, 0.99]	0.96 [0.91, 0.99]
marcera 2013 [37]	106	1	38	21	0.74 [0.66, 0.81]	0.95 [0.77, 1.00]
rojas 2014 [38]	83	7	9	5	0.90 [0.82, 0.95]	0.42 [0.15, 0.72]
rojas 2014 [38]	44	0	3	5	0.94 [0.82, 0.99]	1.00 [0.48, 1.00]
schulz 2015 [39]	126	27	14	175	0.90 [0.84, 0.94]	0.87 [0.81, 0.91]
sofue 2011 [40]	83	7	5	49	0.94 [0.87, 0.98]	0.88 [0.76, 0.95]

CT

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Arita 2015 [32]	227	3	53	10	0.81 [0.76, 0.85]	0.77 [0.46, 0.95]
berger-kulemann 2012 [30]	49	4	19	17	0.72 [0.60, 0.82]	0.81 [0.58, 0.95]
cantisani 2010 [41]	384	4	46	26	0.89 [0.86, 0.92]	0.87 [0.69, 0.96]
fioole 2008 [42]	84	15	53	46	0.61 [0.53, 0.70]	0.75 [0.63, 0.86]
garcia 2013 [43]	105	0	10	5	0.91 [0.85, 0.96]	1.00 [0.48, 1.00]
lubezky 2007 [44]	64	6	35	18	0.65 [0.54, 0.74]	0.75 [0.53, 0.90]
nanashima 2008 [45]	92	18	3	15	0.97 [0.91, 0.99]	0.45 [0.28, 0.64]
ramos 2011 [46]	161	28	33	3	0.83 [0.77, 0.88]	0.10 [0.02, 0.26]
rojas 2014 [38]	53	1	5	7	0.91 [0.81, 0.97]	0.88 [0.47, 1.00]
rojas 2014 [38]	74	7	22	5	0.77 [0.67, 0.85]	0.42 [0.15, 0.72]
schulz 2015 [39]	95	12	45	190	0.68 [0.59, 0.75]	0.94 [0.90, 0.97]

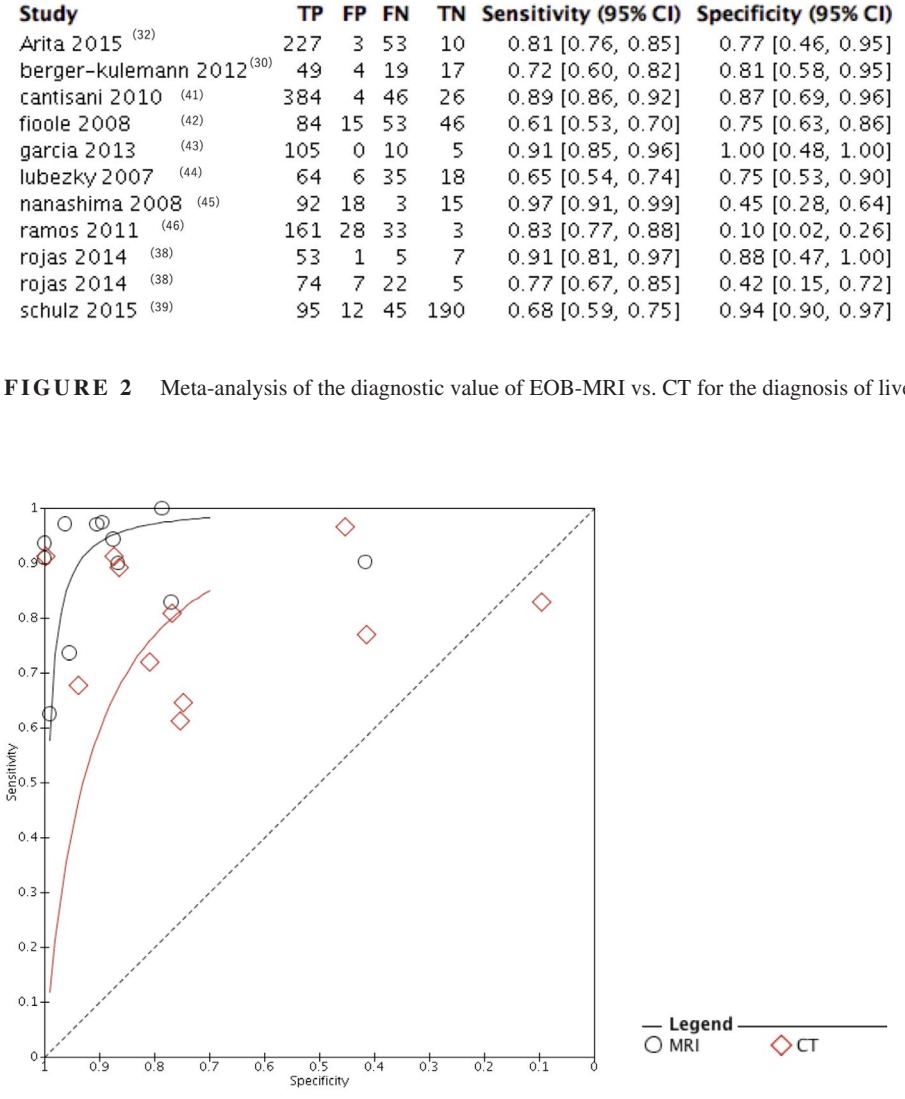


FIGURE 2 Meta-analysis of the diagnostic value of EOB-MRI vs. CT for the diagnosis of liver metastases

FIGURE 3 Summary receiver operating characteristics curve from the meta-analysis of the diagnostic value of EOB-MRI vs. CT

response of the liver metastases has been attained. The different MRI techniques (EOB-MRI and DW-MRI) are more sensitive than CT for the detection of liver metastases,[30,31] but it is still unclear whether EOB-MRI is clinically useful or cost-effective and should be recommended for the diagnosis of liver metastases that disappear after neoadjuvant therapy.

From our systematic review of the literature, eight cohort/case-control studies and two meta-analyses were accepted for this guideline. Chemotherapy can cause fatty changes in the liver or sinusoid injury, and it decreases the sensitivity of both CT and MRI for detecting liver metastases; however, MRI has been reported to be superior to CT in diagnostic

accuracy.[48] According to the literature, the positive predictive values of EOB-MRI and CT in the diagnosis of liver metastases that disappear after neoadjuvant therapy are 78%-85% and 35%-41%, respectively.[53,54] The recurrence rate of liver metastases that disappear after chemotherapy as defined by EOB-MRI was reported to be 6%-11%,[53–55] whereas the recurrence rate for those defined by CT was 31%-33%.[53,54]

Given these findings, EOB-MRI appears to be superior to CT in the diagnosis of "true" disappearance (i.e., complete pathologic resolution) of liver metastases; however, reports showing the usefulness of MRI for the diagnosis of liver metastases that disappear after neoadjuvant therapy are currently only based on the small cohort studies.

In terms of the cost-effectiveness, two studies have reported that EOB-MRI was superior to CT because no additional imaging examinations were needed, and changes in the operative procedure due to new lesions found during the operation were less frequent than with CT.[51,52]

In CQ1 and 2, the majority of studies investigated colorectal liver metastases. Therefore, it is still unclear whether this recommendation can be applicable to the diagnosis of liver metastases from not only colorectal cancer but other malignancies. However, in the hepatobiliary phase of EOB-MRI, it has been reported that up to half of the administered dose progressively accumulates in hepatocytes, and therefore, metastatic tumors which do not include hepatocyte are well recognized. Thus, theoretically, this recommendation could be applicable to liver metastases from all types of malignancies, but further investigation will be needed in the future.

3.4 | Clinical question 3

Is a parenchymal-sparing hepatectomy more effective than a major hepatectomy for patients with liver metastases?

3.4.1 | Recommendation

Parenchymal-sparing hepatectomy is recommended over major hepatectomy for patients with colorectal liver metastases, but with only a weak level of confidence.

(Grade of recommendation: weak; quality of evidence: low).

Hepatectomy is an effective treatment for the multidisciplinary treatment of colorectal liver metastases (CRLMs). In recent years, parenchymal-sparing hepatectomy (PSH) has often been performed to maximize the residual liver capacity and thereby avoid the risk of postoperative liver failure.[56–62] PSH is more useful than major hepatectomy (MH) from the viewpoint of preserving residual liver capacity, but the resection distance from the tumor is usually less, so many investigators worry that local recurrences will increase and the prognosis will worsen. Therefore, for this clinical question, we performed a systematic review of PSH and MH and performed a meta-analysis concerning prognosis and complications.

Our literature search identified no RCTs comparing PSH and MH. Since 2000, seven cohort studies have been published comparing PSH with MH.[56–62] All of these cohort studies focused on CRLMs. Although each of the accepted papers included almost more than 100 patients, the evidence level for evaluating the superiority of PSH to MH was low (C). A meta-analysis showed no differences in 5-year overall survival (OS) rate and 3-year recurrence-free survival (RFS) rate; in contrast, the complication rate (Clavien-Dindo ≥ 3) was significantly less for PSH than for MH (Figure 4). There was no study comparing PSH and MH for liver metastases other than CRLMs.

Both PSH and MH are commonly performed types of hepatectomy and can be readily clinically adapted for CRLMs. The decreased rate of postoperative complications associated with PSH is a great benefit for the patient. In contrast, the potential disadvantage of PSH might be in postoperative local recurrence caused by a positivity of the surgical margin. Neither surgical margin positivity nor RFS rate differed statistically between PSH and MH in most reports. Nevertheless, because the current level of evidence remains poor, which procedure should be adopted depends on the values of the patient or the surgeon's experience.

3.5 | Clinical question 4

Is laparoscopic liver resection more effective than open liver resection for patients with liver metastases?

3.5.1 | Recommendation

Laparoscopic liver resection is recommended over open liver resection for patients with colorectal liver metastases, but with only a weak level of confidence.

(Grade of recommendation: weak; quality of evidence: moderate).

Two RCTs compared laparoscopic liver resection (LLR) with open liver resection (OLR) for CRLMs.[63,64] Note that most of the operative procedures in these RCTs were minor hepatectomies (Table 1); therefore, reliable evidence for MH is lacking. In short-term outcomes, postoperative morbidity and postoperative hospital stay were statistically significantly less after LLR than after OLR, whereas operative time, intraoperative blood loss, rate of blood transfusion, and mortality were equal between the two groups. Furthermore, the health-related quality of life assessed by the Short Form 36 questionnaire was better in the LLR group for up to 4 months postoperatively;[65] importantly, there were no differences regarding OS and disease-free survival (DFS).[64]

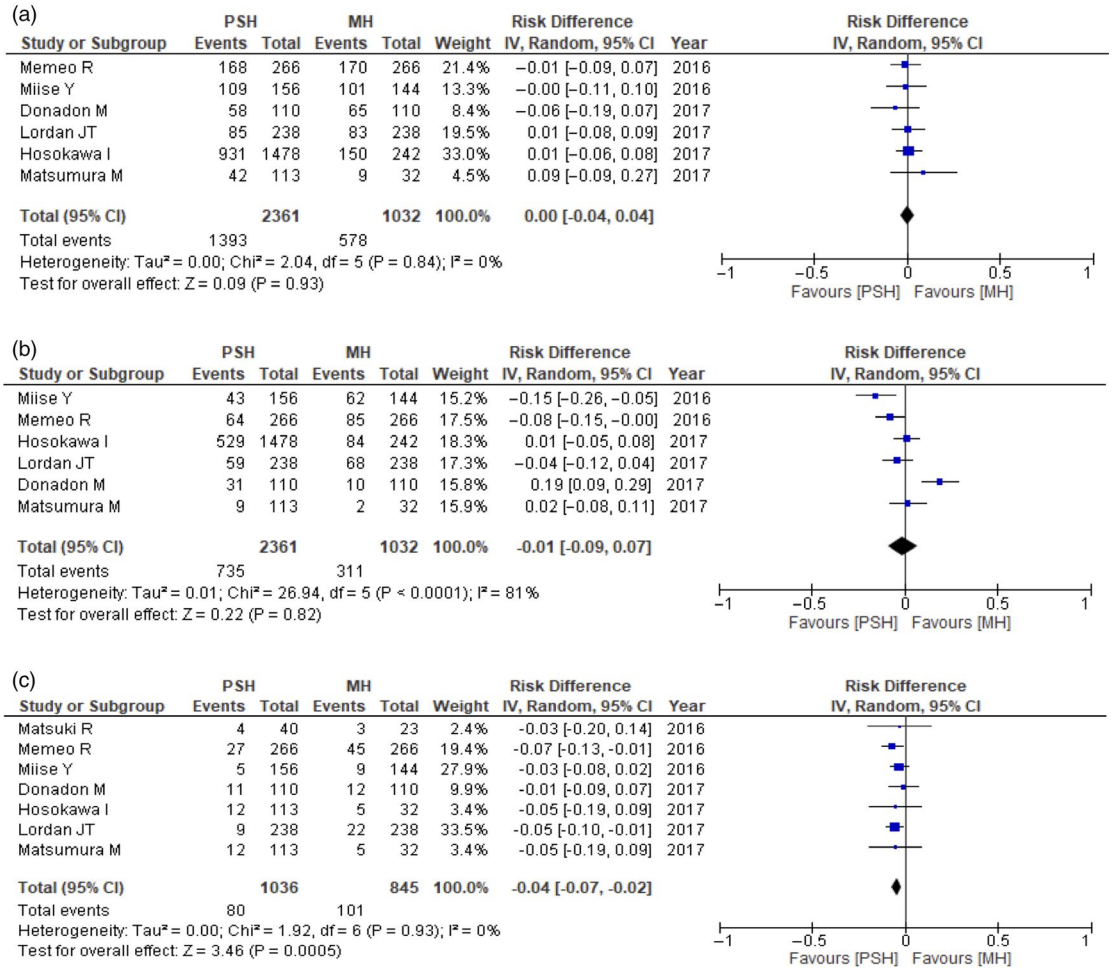


FIGURE 4 Meta-analyses of survival and complication rates for parenchymal-sparing versus major hepatectomy. (A) Five-year overall survival rate. (B) Three-year recurrence-free survival rate. (C) Complication rate (Clavien-Dindo ≥ 3)

In addition to the RCTs, numerous non-RCT studies have been performed. However, many contained potential biases in terms of selection for tumor size, number of metastases, and location of the CRLMs. Therefore, we conducted a meta-analysis limited to 11 studies using some form of propensity score matching (PSM)[66–76] with well-balanced patient characteristics regarding operative time, intraoperative blood loss, rates of blood transfusion, morbidity (Clavien-Dindo classification ≥ 3), mortality, postoperative hospital stay, R0 resection rate, 5-year OS, and 5-year DFS. Operative time was statistically significantly greater with LLR than with OLR, whereas intraoperative blood loss, morbidity rate, and postoperative hospital stay were significantly less with LLR (Figure 5). The mortality rate tended to be better after LLR, and the R0 resection rate tended to be greater after OLR. In contrast, the blood transfusion rate was identical in the two groups. With regard to long-term results, there were no significant differences in the 3- or 5-year OS and DFS between the groups. Of note, patients undergoing LLR in these PSM studies were well-selected patients. Therefore, clinicians should only recommend LLR for patients matching the selection criteria. Also, the location of the tumor should be considered when determining whether LLR is indicated because of the characteristics of the liver anatomy and technical difficulty during LLR of tumors in certain locations. The indications for LLR are well described in the inclusion and exclusion criteria of the two RCTs (Table 1). Recently, a unique patient-level meta-analysis of RCTs and PSM studies was published and demonstrated a long-term survival benefit of LLR over OLR.[77]

There was one study of LLR for liver metastases from gastric cancer,[78] but no studies for other kinds of extrahepatic cancers. The basic considerations for LLR for the other liver metastases should be similar to those for CRLMs, but further investigation is necessary to clarify the efficacy of LLR for other cancers.

3.6 | Clinical question 5

Is local ablation therapy recommended over hepatic resection for patients with liver metastases?

TABLE 1 Inclusion and exclusion criteria of two RCTs comparing laparoscopic liver resection with open liver resection (modified from references 63 and 64)

	Inclusion criteria	Exclusion criteria
Fretland AA. *Ann Surg* 2018	PSH (<3 segments) Scheduled for concomitant ablation Vascular or biliary reconstruction Repeat hepatectomy Synchronous resection of a primary tumor	MH (3 or more segments)
Robles Campos *Surg Endosc* 2019	PSH Segmentectomy (1-8) Right posterior sectionectomy Left lateral sectionectomy Left hepatectomy Tumor size <10 cm	Right hepatectomy Extended left/right hepatectomy Two-stage liver resection Repeat hepatectomy Synchronous resection of a primary tumor Disseminated disease (adrenal metastasis, peritoneal implants metastases close to major vessels, non-resectable extrahepatic disease)

Abbreviations: MH, major hepatectomy; PSH, parenchymal-sparing hepatectomy.

3.6.1 | Recommendation

Local ablation therapy is not more highly recommended than hepatic resection for patients with colorectal liver metastases, but with only a weak level of confidence.

(Grade of recommendation: weak; quality of evidence: low).

ABT has become a safe and minimally invasive therapy for local control of primary liver malignancies. Although ABT is performed frequently worldwide in patients with liver metastases from extrahepatic neoplasms, it is unclear whether ABT is as effective as hepatic resection (HR) for patients with liver metastases. To create guidelines, meta-analyses comparing HR and ABT were performed for three categories: (1) multiple metastases; (2) single isolated metastases, and (3) single metastases with ≤3 cm diameter; and a meta-analysis comparing HR and HR in combination with ABT (HRABT) was performed. No prospective studies comparing HR with ABT were identified. Outcomes of the studies in the meta-analysis included OS, DFS, local recurrence rate, hepatic recurrence rate, and rate of all complications. These meta-analyses were performed and limited to patients with CRLM treated with HR and/or ABT.

For multiple CRLMs, the 5-year OS, 3-year DFS, and local recurrence rate were statistically significantly better after HR than after ABT (Figure 6A–C).[79–91] Overall complication rates were comparable in the two groups. For a single CRLM, 5-year OS and local recurrence rates after HR were statistically significantly better than after ABT, whereas 3-year DFS and overall complication rates were comparable in the two groups. Similarly, for all single metastases and those with ≤3 cm diameter, there were no differences in 5-year OS and 3-year DFS between HR and ABT; however, the local recurrence rate was statistically significantly greater after ABT than after HR. Two studies that reviewed single CRLMs of ≤2 cm diameter showed that local recurrence rates after ABT were not different than after HR.[86,91] Comparing HR and HRABT for multiple liver metastases, the 3-year OS was statistically significantly greater after HR than after HRABT,[80,83,87,90,92–98] but there were no differences in the 3-year DFS and overall complication rate.

For patients with unresectable CRLM, a prospective randomized study comparing chemotherapy alone with chemotherapy plus ABT demonstrated better progression-free survival[99] and OS[100] in the chemotherapy-plus-ABT group than in the chemotherapy-alone group.

For non-CRLMs, there was a comparative cohort study of patients with liver metastases from gastric cancer and a meta-analysis of retrospective cohort studies of patients with liver metastases from breast cancer.[101,102] In the gastric cancer study, OS and DFS after HR were statistically significantly better than after ABT.[101] In the breast cancer study, HR was better than ABT for the 3-year DFS and OS.[102] Currently, there are no comparison studies that show ABT is better than HR for patients with non-CRLM.

HR is the treatment of choice for single CRLMs of ≤3 cm diameter. To clarify the evidence and the usefulness of ABT for patients with liver metastases, it will be necessary to carry out an RCT,[103] or at least to do a study with evidence-based PSM with detailed consideration of multiple factors such as size, number, and location of liver metastases; liver function; patient condition (age, comorbidities, and activities of daily living); timing of treatment; and chemotherapeutic effect. Additionally, it is necessary to consider the new microwave ablation system[104] for metastatic liver tumors.

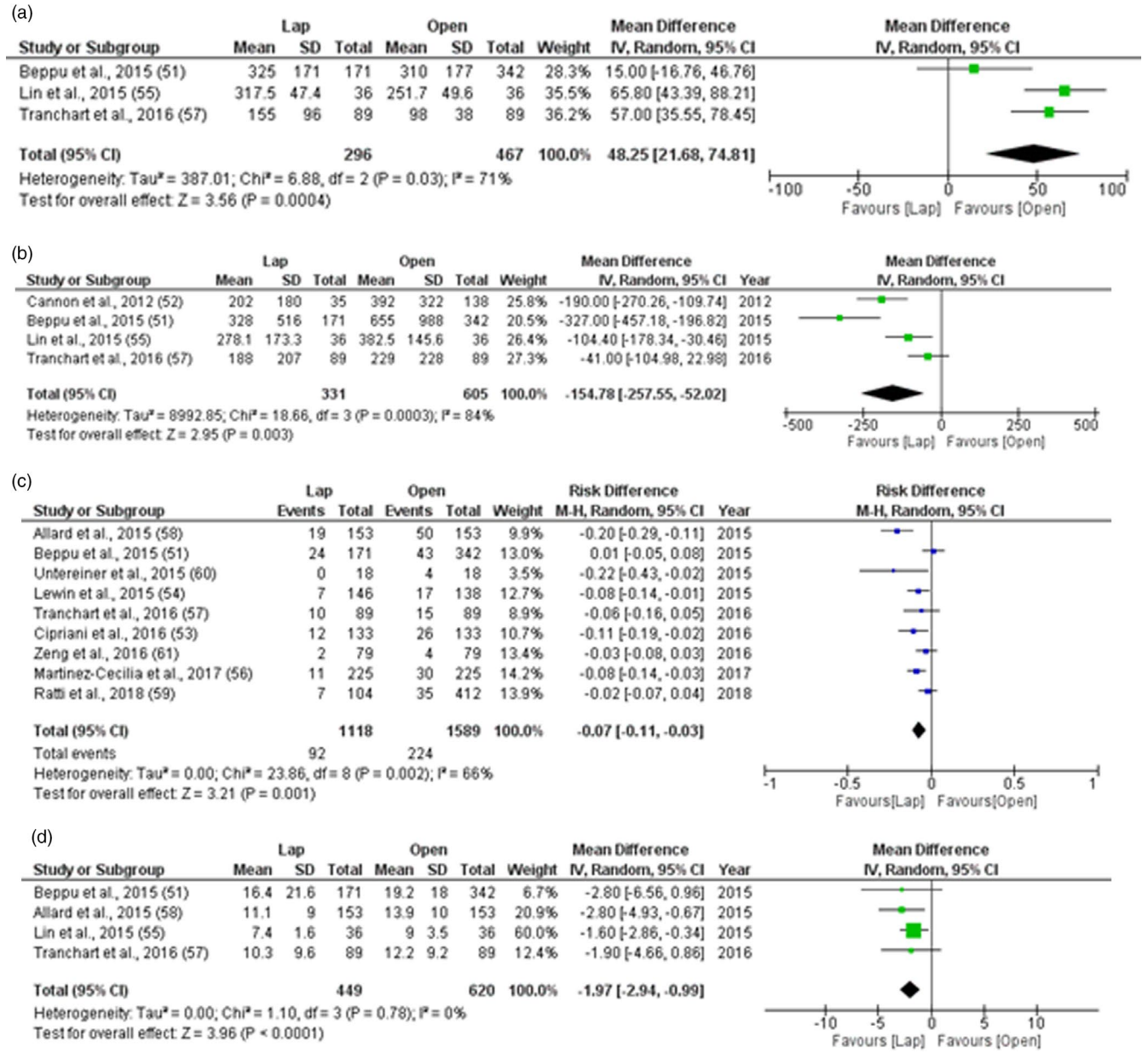


FIGURE 5 Meta-analysis of 11 studies using propensity score matching for liver resections in patients with CRLM. (A) Operative time. (B) Intraoperative blood loss. (C) Morbidity (Clavien-Dindo classification ≥ 3). (D) Postoperative hospital stay

3.7 | Clinical question 6

Is hepatectomy recommended for patients with liver metastases from gastric cancer?

3.7.1 | Recommendation

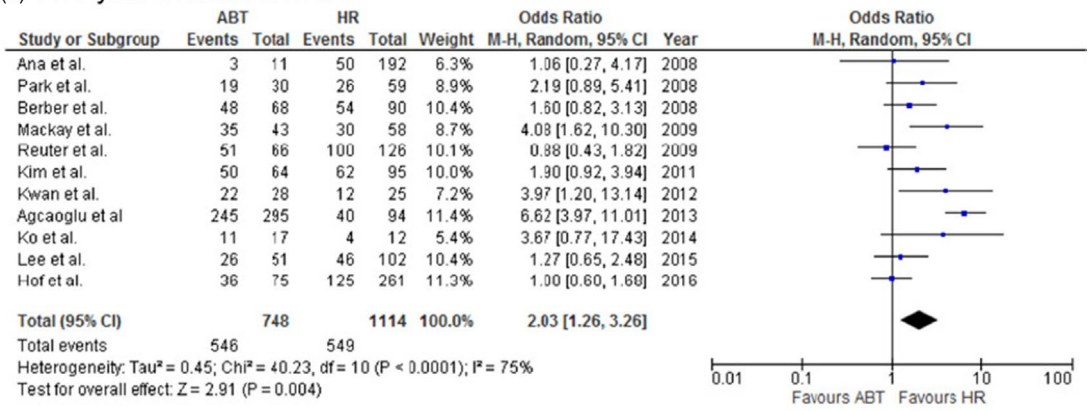
Hepatectomy is not recommended for patients with liver metastases from gastric cancer, but with only a weak level of confidence.

(Grade of recommendation: weak; quality of evidence: low).

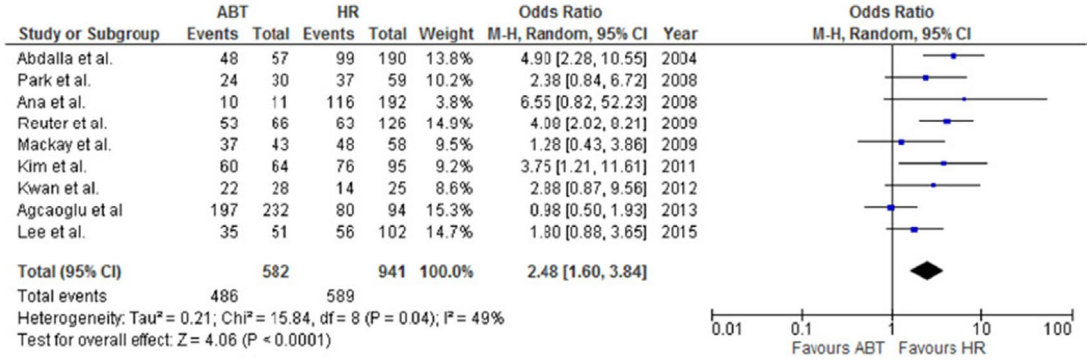
The prognosis of patients with gastric cancer–related liver metastases (GCLM) is quite poor due to the coexistence of non-curable clinical factors, such as peritoneal dissemination or distant lymph node metastases. Although chemotherapy is generally considered the treatment of choice, hepatectomy for selected patients with GCLMs of a small number (<3) or size (<5 cm) has been reported to lead to long-term survival in some patients.[15,16] The aim of this clinical question was to investigate whether hepatectomy with adjuvant chemotherapy or chemotherapy alone should be recommended for GCLM.

Although there was no study using PSM to compare hepatectomy with adjuvant chemotherapy to chemotherapy alone for patients with GCLM, several studies reported

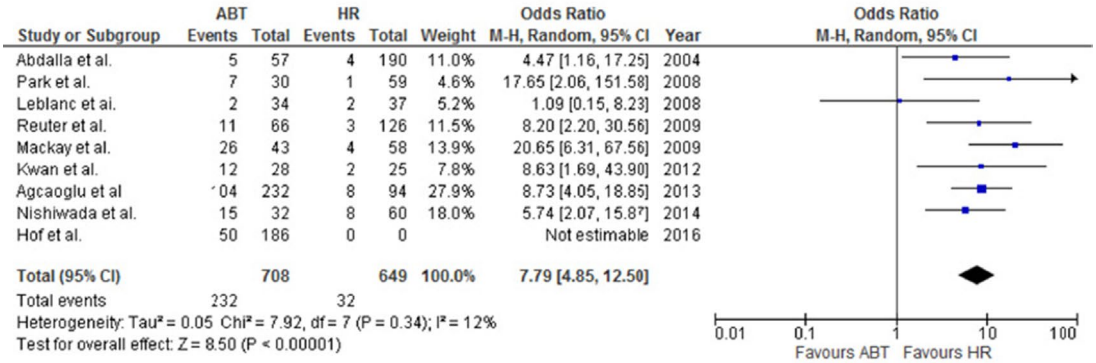
(a) Five-year overall survival



(b) Three-year disease-free survival



(c) Local recurrence rate



(d) Three-year overall survival (HR vs HRABT)

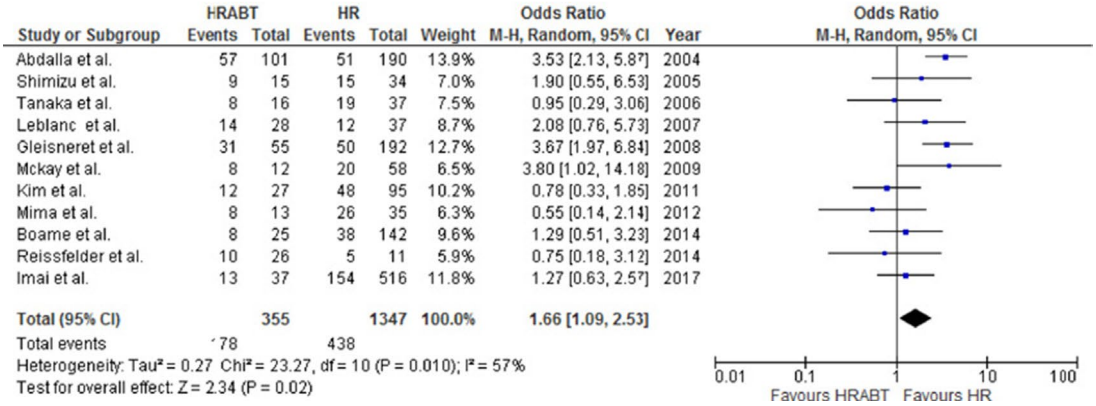


FIGURE 6 Outcomes for the treatment of multiple CRLMs comparing hepatic resection (HR) with ablative therapy (ABT) and HR versus HR in combination with ablation therapy (HRABT). (A) Five-year overall survival. (B) Three-year disease-free survival. (C) Local recurrence rate. (D) Three-year overall survival (HR vs HRABT)

the efficacy of adjuvant chemotherapy after hepatectomy with regimens such as docetaxel/cisplatin/5-fluorouracil or epirubicin/cisplatin/5-fluorouracil.[105,106] Case series have also reported that adjuvant chemotherapy may provide benefit for GCLM.[107–109] In contrast, systematic reviews of 17 studies[110] and 19 studies[111] showed that hepatectomy appears to provide a survival benefit for patients with a solitary metastasis, unilobar metastases, and metachronous presentation. Shirasu et al[108] showed that unilobar liver metastases treated with hepatectomy were the only independent favorable prognostic factor. Tiberio et al[112] also reported that aggressive, multimodal management combining radical operation with adjuvant chemotherapy offers the best results and the possibility of long-term survival in selected patients undergoing synchronous resection of liver metastases along with resection of the primary gastric cancer.

Several prognostic factors associated with better survival were identified, such as a solitary metastasis, unilobar metastases, size of the GCLMs ≤3 or ≤5 cm, metachronous metastases, and a more favorable pathology of cellular differentiation of the primary cancer.[15,16,24,25,105,109,110,112–125] Although selection bias in each study should be considered when interpreting outcomes, 5-year OS after hepatectomy for GCLM was 9%-43%.[15,16,24,25,105,106,113,115–125] Postoperative complications, such as intra-abdominal abscess and bile leakage, were almost the same as those in other studies of hepatectomy.[105]

Although the above review contained only retrospective studies with small sample sizes, radical resection of GCLM might lead to greater survival in selected patients. The inherent selection bias of each article should be strongly considered. When interpreting the prognosis of patients with GCLM, survival will be poor if there are coexisting non-curable clinical factors, such as peritoneal dissemination or lymph node metastases. Therefore, hepatectomy with adjuvant chemotherapy for patients with GCLM cannot be recommended compared with chemotherapy alone other than for a limited number of appropriately selected patients.

3.8 | Clinical question 7

Is hepatectomy recommended for patients with liver metastases from gastrointestinal stromal tumors (GIST)?

3.8.1 | Recommendation

Hepatectomy with adjuvant imatinib therapy is recommended for patients with liver metastases from GIST, but with only a weak level of confidence.

(Grade of recommendation: weak; quality of evidence: low).

Operative resection combined with tyrosine kinase inhibitors (TKIs) including imatinib is standard therapy for GIST. Liver metastases mainly occur either as metastatic disease at the time of diagnosis or as recurrent disease after prior resection of the primary site. Before imatinib therapy was available, the hepatic recurrence rate after resection of liver metastases was as great as 80%-90%. Currently, however, imatinib therapy is available and may be administered in conjunction with HR.

No large RCT has yet been conducted to compare the therapeutic results of hepatectomy with those of treatment with TKIs alone. According to a small RCT, hepatectomy with preoperative (neoadjuvant) and postoperative (adjuvant) imatinib therapy was associated with significantly greater OS than imatinib therapy alone.[13] Additionally, a multicenter, retrospective study showed that hepatectomy with concomitant TKI therapy resulted in longer median OS (89 months) than TKI therapy alone (53 months).[14]

Most studies have shown that therapeutic results for patients with GIST liver metastases improved when hepatectomy is combined with a TKI. According to recent reports, the 5-year survival rate of these patients is 50%-91%,[126–129] with a median OS of 41.8 months.[130] The occurrence of postoperative complications was found to be 0%-50%,[13,126,128,129,131–134] and only a few mortalities were reported.[133,134]

Although hepatectomy was reported to be performed 6-12 months after imatinib therapy was given as neoadjuvant treatment,[13,134–136] little evidence is available to clarify the optimal timing of hepatectomy after imatinib therapy. In one study, imatinib resistance occurred in approximately 50% of patients after 18 months of neoadjuvant imatinib therapy.[137]

Regarding adjuvant imatinib therapy, it has been recommended that a 3-year postoperative course of adjuvant therapy with imatinib after complete resection for high-risk GISTs is appropriate.[138] The optimal duration for imatinib therapy after hepatectomy, however, has also not been determined.

Switching to sunitinib therapy has been recommended in patients with imatinib resistance. However, metastatic lesions could be completely resected after sunitinib therapy in only 50% of patients, and in addition, the morbidity rate was as great as 54%, including a re-operation rate of 16%, and the DFS was reported to be as short as 5.8 months.[139] Based on these results from a single report, resection of GIST-related liver metastases after sunitinib therapy administered following the development of imatinib resistance is not included in this recommendation.

Thus, hepatectomy with neoadjuvant and/or postoperative adjuvant imatinib therapy for resectable GIST liver metastases is recommended, but with only a weak level of confidence.

3.9 | Clinical question 8

Is hepatectomy recommended for patients with liver metastases from biliary tract cancer?

3.9.1 | Recommendation

Hepatectomy is not recommended for patients with liver metastases from biliary tract cancer, but with only a weak level of confidence.

(Grade of recommendation: weak; quality of evidence: low).

Small case series and observational studies regarding treatment strategies for liver metastases from biliary tract cancers have been published. Sano et al. reported a series of 139 cases of hepatectomy for liver metastases from biliary tract cancer with a 5-year survival of 17% after the hepatectomy.[3] In an observational study, 5-year survival rates were 45% for 13 cases of hepatectomy for metachronous liver metastases from biliary tract cancer and 0% for nine cases of unresectable liver metastases.[17] Motoyama et al also reported 5-year OS rates of 40% after hepatectomy in 15 patients and 7% in 16 patients who had chemotherapy alone and concluded that hepatectomy can improve the prognosis in selected patients.[18] All of these are retrospective, case-observation studies, and a strong selection bias is likely involved; nevertheless, hepatectomy might be effective treatment for highly selected patients with metachronous liver metastases from biliary tract cancer who fulfill certain strict criteria. Although it is difficult to provide definitive evidence about who is eligible for resection, Sano et al. reported that three or fewer metastases of <3 cm diameter each and a potentially R0/1 resection are independent prognostic factors for a better outcome.[3] Others have reported that patients with solitary liver metastases[18] and those in whom the metachronous liver recurrence occurred more than 2 years after resection of the biliary primary have a better prognosis.[140] There is still no evidence regarding the benefit of liver resection for synchronous liver metastases from biliary tract cancer. In the studies above, the indications for hepatectomy for liver metastases from biliary tract cancer should be strict, involving not only non-synchronous hepatic metastases which can be removed with an R0/1 resection but also those with certain other conditions, such as three or fewer metachronous tumors smaller than 3 cm developing >2 years after the resection of the primary site. Therefore, in the absence of definitive evidence, hepatectomy for liver metastases from biliary tract cancer is not recommended except when the patient fulfills the strict criteria outlined above, but this recommendation is given with only a weak level of confidence.

3.10 | Clinical question 9

Is hepatectomy recommended for patients with liver metastases from ovarian cancer?

3.10.1 | Recommendation

Hepatectomy is recommended for patients with liver metastases from ovarian cancer including peritoneal dissemination invading the liver, but with only a weak level of confidence.

(Grade of recommendation: weak; quality of evidence: low).

Complete resection is the best treatment to prolong survival for advanced ovarian cancer, and primary debulking followed by chemotherapy is currently regarded as the standard strategy. Several studies support a survival advantage in patients who undergo optimal debulking (<1 cm residual disease) compared to suboptimal debulking (≥1 cm residual disease).[141–144] Hepatectomy is needed for patients with liver metastases or peritoneal dissemination invading into the liver from ovarian cancer. Currently, however, there are no criteria concerning whether liver resection should be performed.

Although we could not identify any RCTs, four retrospective cohort studies and seven case series were identified. A meta-analysis of OS was not possible because the operative outcomes were analyzed differently in the studies. The reported 5-year survival rates were 39%-50%.[7,8,145,146] Roh et al[7] reported that debulking with hepatectomy improved OS in patients with ovarian cancer with liver metastases. Although optimal debulking improved OS in patients with liver metastases or peritoneal dissemination invading into the liver from ovarian cancer,[147] oncologic outcomes improved in patients in whom a complete resection of the liver lesions (R0) can be achieved.[9,148,149] Prognosis after hepatectomy for liver involvement via peritoneal dissemination was better than for hematogenous liver metastases.[150] The morbidity rates of debulking involving a hepatectomy were 0%-20%, but these data included complications of the concomitant resection of the primary site and peritoneal metastases performed at the time of the hepatectomy. Because mortality associated with hepatectomy was also reported,[151] it is necessary to evaluate preoperative liver function and residual liver volume after resection for estimating the safety of hepatectomy.

Based on these results, hepatectomy with chemotherapy for patients with liver metastases or peritoneal dissemination invading into the liver from ovarian cancer is recommended over chemotherapy alone, but with a weak level of confidence. Regarding hematogenous hepatic metastasis, hepatectomy should be done only selectively, after considering the invasiveness of hepatectomy and the need for complete resection.

3.11 | Clinical question 10

Is hepatectomy recommended for patients with liver metastases from pancreatic cancer?

3.11.1 | Recommendation

Hepatectomy is recommended against for patients with liver metastases from pancreatic cancer, but with only a weak level of confidence.

(Grade of recommendation: weak; quality of evidence: low).

In general, liver metastases in patients with pancreatic cancer represent an incurable disease, and mean survival is less than 1 year. There have been several anecdotal series and some retrospective case series that reported relatively favorable prognoses with OS of 20-26 months when hepatectomy was performed, but all the reports have involved highly selected patients, such as those with isolated metastases and no evidence of other sites of disease.[3,152] No prospective study has compared hepatectomy for liver metastases from pancreatic cancer with non-operative treatment. In previous retrospective studies of simultaneous resection of the primary pancreatic cancer and synchronous liver metastases, median survival was from 5.9 to 14.5 months; and the 5-year survival rates were from 0% and 7% (Table 2).[153–159] For patients with synchronous liver metastases from pancreatic cancer, Tachezy and colleagues conducted a multicenter, retrospective, comparative study evaluating operative resection of the primary pancreatic cancer and the liver metastases with a "matched" cohort who underwent biliary and duodenal bypass only, and showed better OS in the resection group (14.5 vs 7.5 months; $P < .001$).[158] This report, however, is subject to considerable bias in terms of patient selection related to the methodology of matching. OS after resection of metachronous metastases was reported as ranging from 7 to 26 months,[3,152,160–162] but the evidence to support operative resection for metachronous liver metastases is poor due to the heterogeneity of each report and the very real suspicion of patient selection. In contrast, in recent years, there have been some reports of so-called "conversion surgery," which is defined as operative resection for patients who achieved good therapeutic outcomes with effective neoadjuvant chemotherapy with or without radiation therapy for initially unresectable pancreatic cancer, even with liver metastases.[163,164] Although the results of conversion surgery are encouraging, its clinical value is as yet unproven as no formal studies comparing comparable groups are available; therefore, this topic requires additional investigation. In conclusion, there is no reliable evidence to support hepatectomy for liver metastases of pancreatic cancer.

3.12 | Clinical question 11

Is hepatectomy recommended for patients with liver metastases from breast cancer?

3.12.1 | Recommendation

We recommend against hepatectomy for patients with liver metastases from breast cancer, but with only a weak level of confidence.

(Grade of recommendation: weak; quality of evidence: low).

Treatment for breast cancer with distant metastasis is generally palliative, and usually systemic treatment is selected. Most liver metastases from breast cancer do not occur as isolated metastases; they are usually associated with systemic disease at other sites, such as lung or bone. Therefore, liver resection is rarely performed for liver metastases from breast cancer. Despite this, several reports have suggested a more favorable prognosis after hepatectomy.

Although we could not identify any RCTs, four observational cohort studies[165–168] and 12 case series were identified. OS could be analyzed in three of the cohort studies. Our meta-analysis of these three cohorts revealed that hepatectomy did not improve 5-year OS (Figure 7), even though

TABLE 2 Outcomes of simultaneous resection for pancreatic cancer with synchronous liver metastases

Author	Study period	N	MST (m)	5-y OS (m)	Morbidity (%)	Mortality (%)
Takada[153]	1981-1995	11	6	0	NA	9
Gleinsner[154]	1995-2005	22	5.9	0	46	9
Shrikhande[155]	2001-2005	11	11.4	NA	24	0
Seelig[156]	2004-2007	14	10.6	NA	45	0
Klein[157]	2004-2009	22	7	0	18	0
Tachezy[158]	1994-2014	69	14.5	5.8	68	1
Andreou[159]	1993-2015	76	<12	7	50	5

Abbreviations: MST, median survival time; NA, not available; OS, overall survival.

hepatectomy in these studies was performed in highly selected patients in which an R0 resection was achieved, there were no extrahepatic metastases, the liver metastases become obvious years after the resection of the primary breast cancer, and concomitant effective systemic antitumor therapies (chemotherapy, hormonal therapy, and targeted therapy) were used.

Four cohorts and six case series that reported complications of the hepatectomy were identified. The complication rates were reported to be 10%-23%.[165–174]

These results indicate that liver metastases from breast cancer are rarely isolated to the liver, and hepatectomy cannot be recommended when compared to chemotherapy alone, except possibly in highly selected patients with confirmed isolated liver metastases. The invasiveness of the hepatectomy and the possibility of curative resection should be considered when selecting hepatectomy. Hepatectomy, however, may be justified in strictly selected patients who have very favorable prognostic circumstances and in whom the risk of the procedure is low.

3.13 | Clinical question 12

Is hepatectomy recommended for patients with liver metastases from gastroenteropancreatic neuroendocrine tumors (GEP-NETs)?

3.13.1 | Recommendation

Hepatectomy with curative intent is strongly recommended for patients with liver metastases from G1/G2 GEP-NET compared with non-resectional treatment.

(Grade of recommendation: strong; quality of evidence: low).

The long-term prognosis of patients with G1/G2 GEP-NET liver metastases without extrahepatic metastases is consistently reported to be improved by hepatectomy with curative intent.[10–12,175–186] A systematic review and meta-analysis were performed to evaluate the effectiveness of hepatectomy for liver metastases from GEP-NET.

No RCTs were identified from the systematic reviews. In the previous reports of hepatectomy for liver metastases from GEP-NET, the 5- and 10-year OS rates reached 71% (31%-100%) and 42% (0%-100%), respectively.[10–12,175–186] In contrast to these encouraging results, the 3-, 5-, and 10-year rates of RFS were 32% (24%-69%), 29% (6%-66%), and 1% (0%-11%), respectively.[10–12,175–186] Although hepatectomy for liver metastases from GEP-NET has consistently been reported to be effective, the evidence level was low due to small patient numbers and probable bias in patient selection. We accepted 11 cohort studies for a meta-analysis comparing outcomes between those receiving hepatectomy and those treated without hepatectomy; we evaluated the rates of 5-year OS, relief of symptoms, and postoperative complications.[175–185] The inclusion criteria for hepatectomy in each study were not thoroughly reported, and some questions remain as to whether the stage of disease was similar in the hepatectomy and non-hepatectomy groups. Although this meta-analysis included patients who underwent what was an R2 resection involving debulking combined with ABT, most patients underwent hepatectomy with curative intent. The rate of 5-year OS was consistently better in the hepatectomy group (74.7% vs 34.3%, $P < .00001$) (Figure 8A). Relief of symptoms, including those related to hormone secretion as well as mechanical symptoms, such as pain or obstruction, was also better in the hepatectomy group (93.4% vs 75%, $P = .02$) (Figure 8B), and the rate of post-treatment complications did not differ between the two groups ($P = .45$) (Figure 8C). Although the evidence level is low, hepatectomy for G1/G2 GEP-NET liver metastases with curative intent is strongly recommended compared to non-resectional treatment, because the majority of the reports demonstrated its usefulness.

Debulking for unresectable liver metastases from GEP-NET reportedly improved not only the long-term prognoses in patients with non-functional liver metastases from GEP-NET but also provided substantial relief of symptoms refractory to non-operative treatment; similar outcomes were present in patients with functional GEP-NET.[10–12,186] The appropriate criteria for patient selection for debulking for GEP-NET liver metastases are not yet well described nor accepted universally.

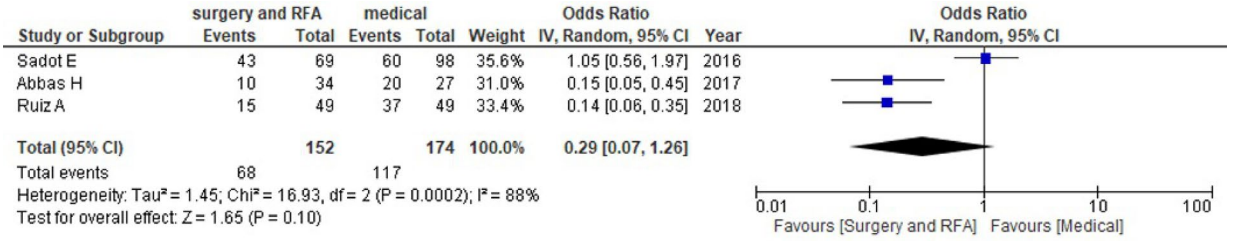


FIGURE 7 A meta-analysis of the 5-year survival rate from three randomized phase III trials of patients undergoing hepatic resection for liver metastases from breast cancer

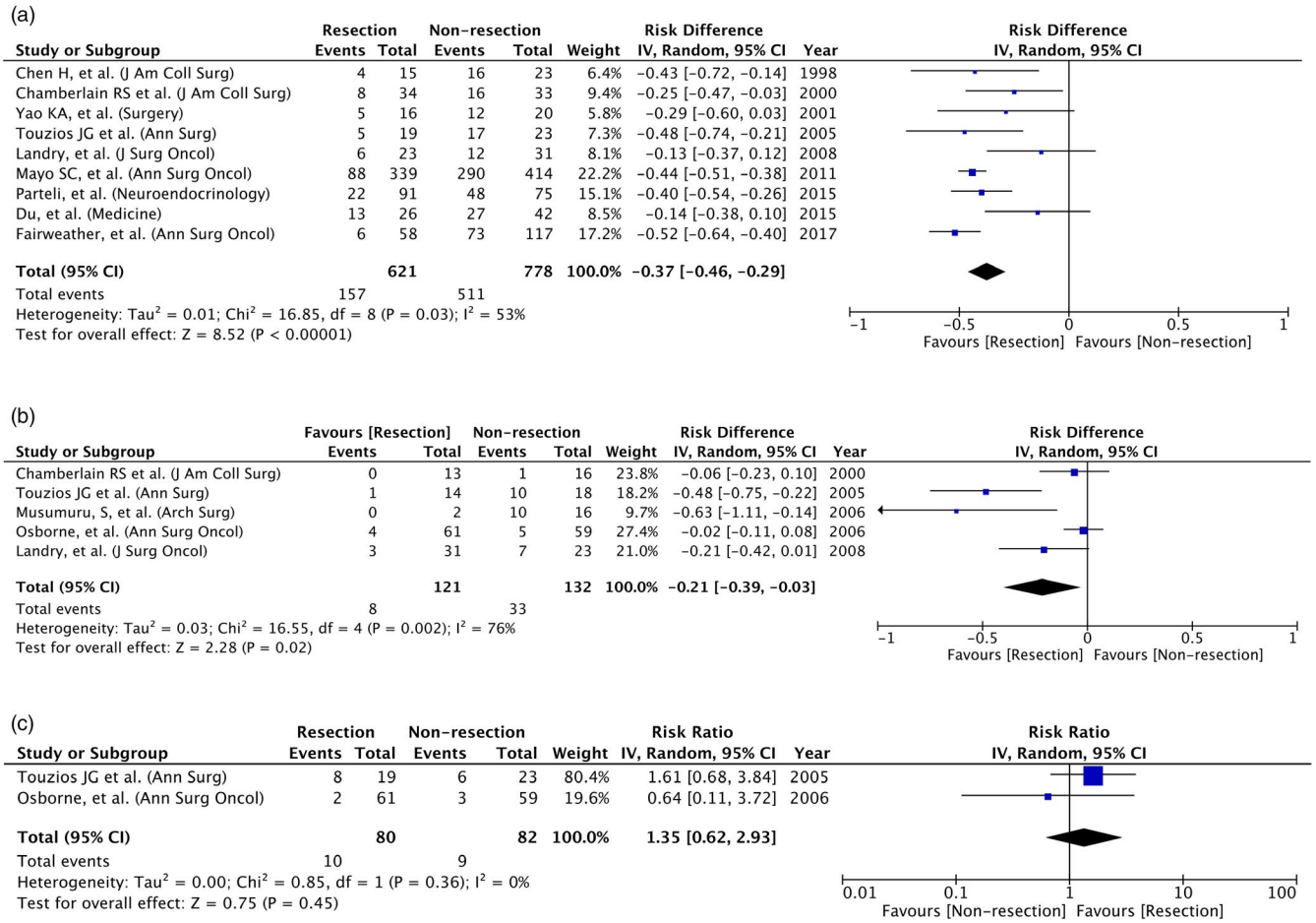


FIGURE 8 A meta-analysis of patients undergoing hepatic resection for liver metastases from GEP-NETs. (A) The 5-year overall survival rate is significantly better in the hepatectomy group. (B) The symptom relief rate is significantly better in hepatectomy group. (C) No significant difference was observed in the post-treatment complication rate

Therefore, a recommendation for debulking procedures cannot be made at this time because of insufficient evidence.

NET G3, which was newly defined in the 2019 revision of the WHO classification (Digestive System Tumours), was not included in this study, and neuroendocrine carcinoma was also excluded from this study because tumor characteristics differed significantly when compared to the more frequent G1/G2 GEP-NETs.

3.14 | Clinical question 13

Is systemic therapy after hepatectomy recommended for patients with liver metastases from any extrahepatic cancer?

3.14.1 | Recommendation

Systemic therapy after hepatectomy is recommended for patients with colorectal liver metastases, but with only a weak level of confidence.

(Grade of recommendation: weak; quality of evidence: high).

Systemic therapy after hepatectomy is recommended for patients with liver metastases from gastric cancer, but with only a weak level of confidence.

(Grade of recommendation: weak; quality of evidence: very low).

For patients with resectable liver metastases, the treatment method that is most expected to decrease mortality is operative resection. In general, however, the recurrence rate after resection is high. Therefore, whether chemotherapy after resection of liver metastases decreases the recurrence rate and mortality is an important clinical issue.

This clinical question studied colorectal cancer, gastric cancer, pancreatic cancer, biliary tract cancer, and GEP-NET. We excluded GIST, breast, and ovarian cancers and GEP-NET because the type of chemotherapy is different from that for other cancers. Because few reports in pancreatic and biliary tract cancer and GEP-NET were identified, recommendations were made only for colorectal cancer and gastric cancer in this clinical question.

For colorectal cancer, two RCTs, the FFCD09002 trial,[19] a trial of oral uracil-tegafur with leucovorin by Hasegawa et al,[20] and one pooled analysis of fluorouracil plus folinic[21] acid have been reported. We performed a meta-analysis of 5-year survival rate in the three above-mentioned, randomized, phase III trials[20,21] regarding the 5-year survival rate (Figure 9A). Consistent with a recent retrospective study adopting PSM[187], the results suggested that administering chemotherapy after hepatectomy increased the 5-year survival rate by 10% (95% CI: 9%-28%, $P = .32$) compared with hepatectomy alone. The relative risk of overall survival was 0.80 (95% CI: 0.56-1.16, $P = .24$). The progression-free, disease-free, and recurrence-free survival rates were also better in the postoperative chemotherapy group in each controlled study. Furthermore, chemotherapy using fluorouracil-based regimens is generally well tolerated. Based on these data, we weakly recommend including adjuvant chemotherapy after resection of liver metastases from colorectal cancer.

For gastric cancer, however, there has been no RCT of adjuvant chemotherapy after resection of liver metastases. Retrospective cohort studies involving patients from single institutions and several multi-institutional studies have reported univariate analyses of patients who did or did not

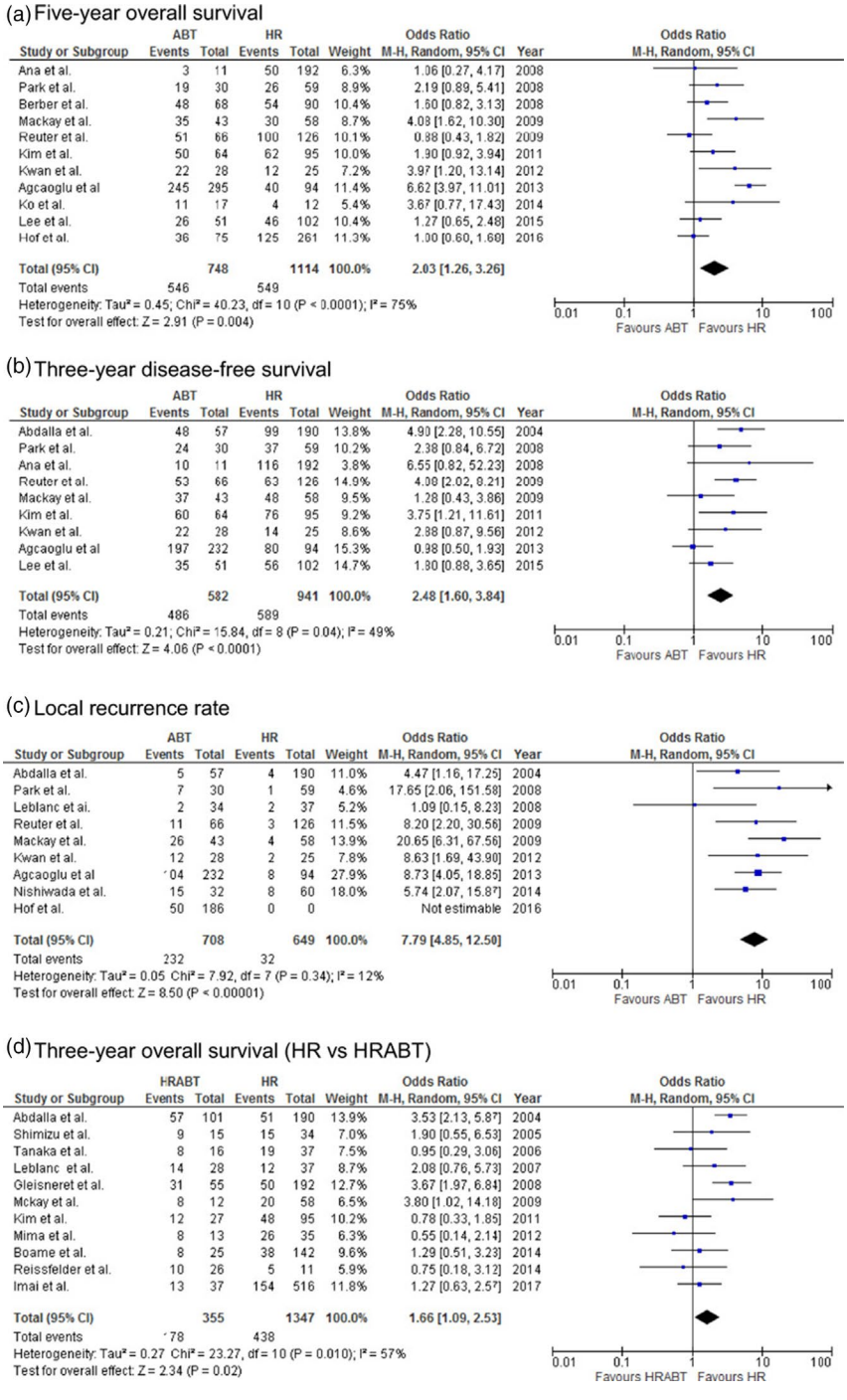


FIGURE 9 Meta-analyses of the 5-year survival rate for patients receiving chemotherapy after hepatectomy. (A) A meta-analysis of the 5-year survival rate for patients with colorectal cancer metastases to liver from three randomized phase III trials. (B) A meta-analysis of 5-year survival rate for patients with gastric cancer metastases to liver from five retrospective cohort studies

undergo postoperative chemotherapy after hepatectomy for gastric cancer liver metastases. Using data from five of the reports, we performed a meta-analysis of the 5-year survival rate (Figure 9B).[22–26] The results suggested that administering chemotherapy after hepatectomy did not significantly increase the 5-year survival rate compared with hepatectomy alone (improvement of 6%; 95% CI: 8%-19%, $P = .42$). The relative risk was 0.98 (95% CI: 0.84-1.14, $P = .82$).

Combining the above evidence, the consideration about the possibility of cure, and the global standard for advanced disease, we weakly recommend performing chemotherapy after hepatectomy for liver metastases from gastric cancer, but with only a weak level of confidence because there is no good evidence of effectiveness.

3.15 | Clinical question 14

Is conversion surgery recommended for patients with initially unresectable liver metastases from any extrahepatic cancer that become resectable after effective systemic therapy?

3.15.1 | Recommendation

Conversion surgery is recommended for patients with colorectal liver metastases, but with only a weak level of confidence.

(Grade of recommendation: weak; quality of evidence: very low).

Conversion surgery is defined as surgical resection of hepatic metastases that were evaluated initially as being unresectable but become resectable after chemotherapy. Its usefulness was examined in eight cancer types, including colorectal cancer, gastric cancer, GIST, biliary tract cancer, pancreatic cancer, breast cancer, ovarian cancer, and GEP-NET.

Although we could not identify any RCTs or retrospective cohort studies for colorectal cancer, case series were identified, including cases of extrahepatic metastasectomy, for patients with colorectal cancer. The reported 3-year and 5-year survival rates were 40%-80% and 30%-76%, respectively; these figures are promising when compared with the 5-year survival rate of 18.8% in patients with stage IV colorectal cancer.[25,28,29,188–199] Based on the large treatment effect, conversion surgery after systemic neoadjuvant chemotherapy in patients with liver metastases from colorectal cancer that were judged initially as unresectable can be weakly recommended, but with only low quality of evidence.

Although there have been several anecdotal reports of patients with a response to chemotherapy who underwent hepatectomy for liver metastases from other extrahepatic primary cancers and achieved greater survival compared with chemotherapy alone,[200,201] there are no RCTs, retrospective cohort studies, or case series to examine the benefit of conversion surgery. Therefore, at the present time, we cannot recommend conversion surgery for patients with gastric, biliary tract, pancreatic, breast, or ovarian cancer, nor for those with GIST or GEP-NET.

CONFLICTS OF INTEREST

Mizukami Takuro received research funding from Taiho Pharmaceutical Co. Ltd. and Eli Lilly Japan K.K. Makoto Ueno received research funding from MSD K.K., Bristol-Myers Squibb K.K., and Delta-Fly Pharma Inc. Yoichi Naito received research funding from Taiho Pharmaceutical Co. Ltd. and Daiichi Sankyo Co. Ltd. No other authors have any conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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CORRIGENDUM

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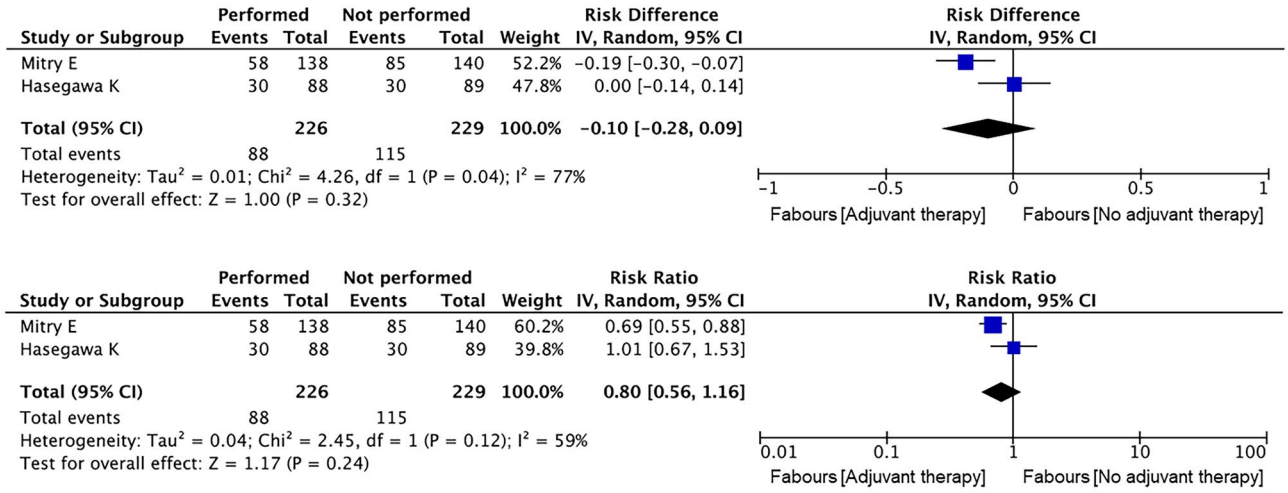
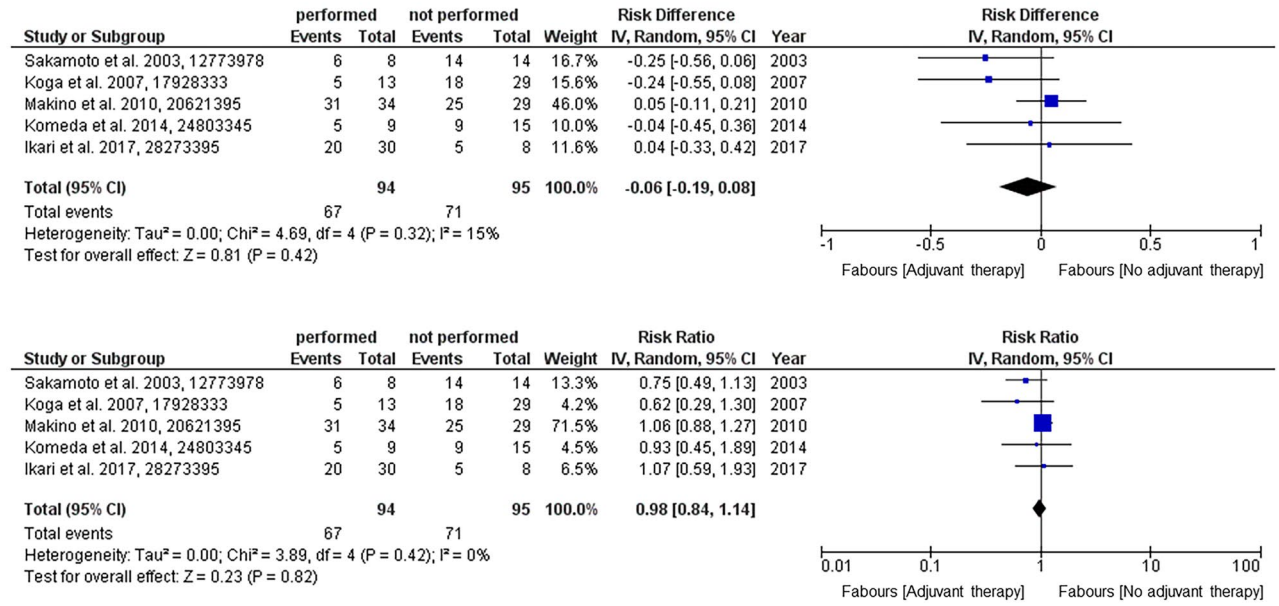
There was error in Figure 9 of the article. The correct Figure 9 is below:

(a)



(b)



The author apologizes for this error.