

Isolated hepatic perfusion for unresectable hepatic malignancies: A systematic review and meta-analysis

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Abstract

AIM

To investigate the efficacy and safety of isolated hepatic perfusion (IHP) in the management of unresectable liver malignancies.

METHODS

Studies were identified manually and on-line by using PubMed and EMBASE database. We formulate the eligibility criteria according to the PICOS elements, and accessed the quality of studies using the MINORS instrument. Data from all included studies were carefully investigated. We calculated the pooled response rate and incidences of mortality reported from all eligible studies by using the Meta-Analyst software, and we computed a pooled relative risk (RR) and 95%CI by using the Comprehensive Meta-Analysis software. Heterogeneity was quantified evaluated using I^2 statistic.

RESULTS

Eight studies, including 502 patients, were selected. Of these, six studies performed IHP, while the other two studies performed percutaneous IHP. The results showed that the pooled response rate was 60.8% (95%CI: 53.1%-68%), $I^2 = 37.1\%$. The median overall survival was 20 mo (range: 12.1 to 25 mo) following IHP or PIHP. The pooled mortality rate was 5.4% (95%CI: 2.5%-11.2%), $I^2 = 37.5\%$. Prognostic factors predict the response to IHP or survival, and were reported in six studies. Meta-analysis demonstrated that Gender was not associated with overall survival (RR = 0.877, 95%CI: 0.564-1.365); however, carcino-embryonic antigen ≤ 30 ng/mL was associated with a significant improvement in survival outcomes with colorectal cancer patients (RR = 2.082, 95%CI: 1.371-3.163), and there was no significant heterogeneity.

CONCLUSION

The present systemic review and meta-analysis suggest that IHP and PIHP are potentially efficient and safe techniques for unresectable liver primary and secondary

malignancies.

Key words: Isolated hepatic perfusion; Unresectable; Hepatic malignancy; Systematic review; Meta-analysis

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Core tip: The treatment of unresectable liver malignancies is an important and difficult clinical problem. Many studies suggested that isolated hepatic perfusion to be efficacious and safe in the management of unresectable liver malignancies. However, there has not yet been a systematic analysis to evaluate this method. Therefore we reviewed all the literature we could get and conducted a systemic review. In the present systemic review we demonstrated all details and results of this technique in every aspect and intensively investigated these data, so that it will help readers to understand this technique in a quick, comprehensive and objective way.

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INTRODUCTION

Liver metastases are frequent manifestations of a variety of malignancies and are often the cause of mortality. The optimal curative treatment of primary or secondary liver tumors is surgical resection. However, less than one third of cases with malignant liver tumors are candidates for surgical intervention, whereas the rest exhibit unresectable feature due to the degree of liver involvement, insufficient liver remnant, or medical comorbidity^[1,2]. For these patients, conventional chemotherapy may be applied systemically but with little benefit and substantial toxicity.

Isolated hepatic perfusion (IHP) was developed over the past several decades as a complex open surgical technique to isolate the liver and perfuse the entire organ with high dosage chemotherapy. The complete vascular isolation and mobilization of liver allow maximal anti-tumor effect as well as minimal systemic toxicity^[3,4]. As an alternative approach of IHP, percutaneous IHP (PIHP) obviate a large abdominal operation, and allows repeatable manipulation, which may enable the patients to get maximized therapeutic effects while having a faster recovery.

The management of patients with unresectable hepatic malignancies is a significant clinical problem. There are many uncertainties and controversies in treating these patients using either systemic or different regional therapies. Here we conduct this present study to systematically evaluate the existing literature of IHP

and PIHP with specific focus on the profiles of efficacy, safety, and survival benefit.

MATERIALS AND METHODS

Literature search strategy

Studies were identified from the Pubmed and EMBASE electronic databases through January 2016 for relevant studies, using a combined MeSH terms and keywords search strategy. The following search terms were used: "isolated hepatic perfusion", "tumor", "cancer", "neoplasm", "carcinoma", "metastases", "nonresectable". These themes were combined using the Boolean operator "AND", "OR" in several combinations without restrictions. Articles were assessed based on the inclusion and exclusion criteria. We also reviewed the reference lists of retrieved papers and recent reviews.

Selection criteria

We attempted to formulate the eligibility criteria according to the PICOS elements. We performed an initial screening of titles or abstracts, and a second screening was based on full-text review. Studies were considered eligible if they met the following criteria: (1) Patients with unresectable primary or secondary liver malignancies; (2) Studies using IHP or PIHP will be included. Variations in drug, dosage, timing, frequency and duration will be tolerated; (3) Studies reporting one or more of these outcomes are eligible: The therapeutic response, toxicity, survival and prognostic factors; (4) Clinical trials and prospective cohort studies, with patients who underwent IHP or PIHP ≥ 25 . If there were multiple articles based on the same sample, the one that reported the most detailed data will be included. If multiple publications from the same institution were identified, the most recent update with the largest number of patients will be included.

Quality assessments

We accessed the quality of studies using the MINORS instrument^[5]. Quality assessment was carried out independently by two reviewers. If both reviewers agreed, the study could be included to the systematic review. Discrepancies were in consultation with the senior author. The deviations between these included studies were taken into account during the quality assessment stage.

Data extraction

The data from all included studies were clearly tabulated. Information collected from these studies included study characteristics, patient and disease characteristics, parameters of IHP treatment, response rate, morbidity and mortality, survival information and prognostic factors.

Statistical analysis

We used a published analysis technique^[6] to calculate

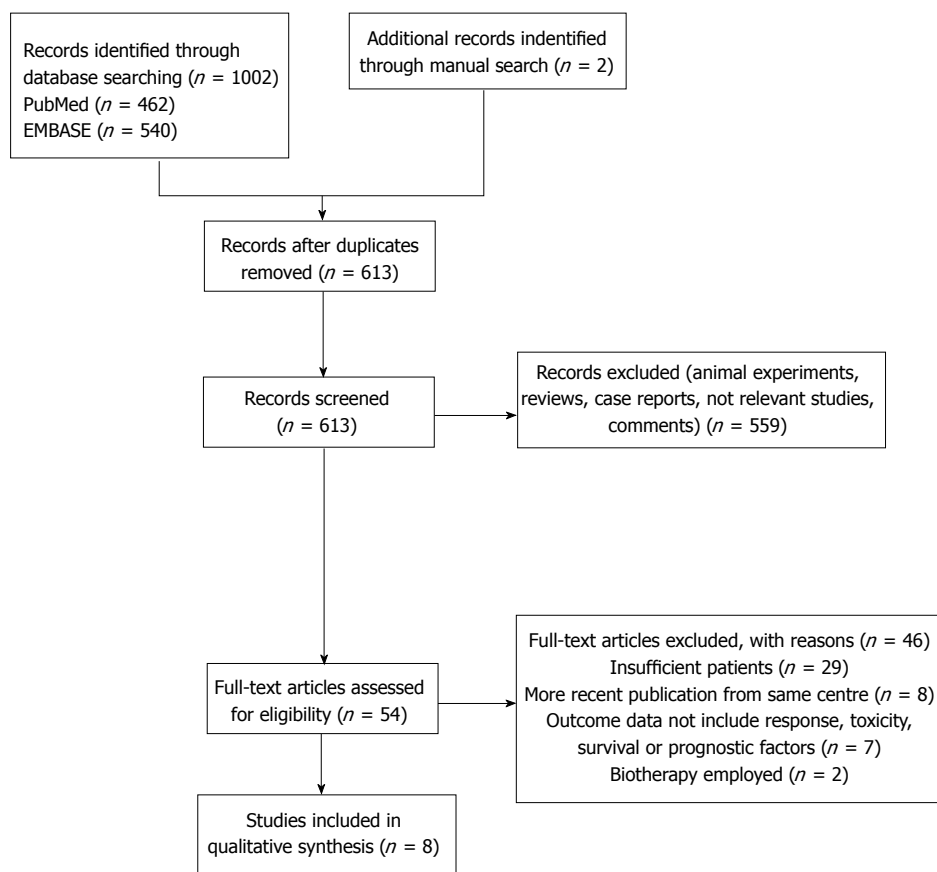


Figure 1 Literature search PRISMA flow diagram.

the pooled response rate and incidences of mortality reported from all eligible studies by using the Meta-Analyst software (version Beta 3.13, Tufts Medical Center). And we computed a pooled relative risk (RR) and 95%CI by using the Comprehensive Meta-Analysis software, version 2.2 (Biostat, Englewood, New Jersey). Heterogeneity was quantified evaluated using I^2 statistic. I^2 value of lower than 50% manifested with no or moderate heterogeneity, whereas I^2 value of greater than 50% was represented with large or extreme heterogeneity^[7]. The random effects model was used when heterogeneity existed.

RESULTS

Identification of eligible studies

The process of identifying eligible studies is summarized by the PRISMA chart^[8] in Figure 1. We initially retrieved 1002 articles from the PubMed and EMBASE database and two further articles were yielded through manual search of reference lists. After the removal of duplicates, 613 unique citations were identified. Of these, the majority was excluded after screening on titles or abstracts, mainly because they were animal experiments, reviews, case reports or not relevant to our analysis. Fifty-four full-text articles were intensively reviewed. Twenty-nine studies were considered to have

low volume patients (< 25)^[9-37]. Seven articles did not assess for response, toxicity, survival or prognostic factors^[38-44]. Two studies employed biotherapy^[45,46], and eight articles were excluded due to more publication from the same center or based on the same cohort^[47-54]. The remaining eight articles were included^[55-62]. The characteristics of included studies are summarized in Table 1.

Patient demographics and disease characteristics

The patient and disease characteristics are summarized in Table 2. Eight studies including a total of 502 patients were reviewed. Except one article that did not report the sex ratio, the rate of male vs female reported by other studies was 1.23:1. The majority of patients had unresectable colorectal origin liver metastasis (56%) or melanoma (27%). Other pathology causing liver malignancies include hepatocellular carcinoma (14%), cholangiocarcinoma (0.6%), neuroendocrine neoplasms (0.8%), breast cancer (0.4%), renal cell carcinoma (0.4%), pancreatic adenocarcinoma (0.2%), appendiceal cancer (0.2%), adrenal adenocarcinoma (0.2%), retroperitoneal sarcoma (0.2%), etc. All the included studies had reported the eligibility criteria for patients, including patients who had unresectable, biopsy-proven hepatic malignancies, Eastern Cooperative Oncology Group performance status of 0-1, and other criteria to

Table 1 Summary of data points presented in relevant clinical trials

Ref.	Year	Country	Research institution	Study period	MINORS score	IHP patients (n)	Tumor details	Eligibility and exclusion criteria	IHP details and response rate	Morbidity and mortality	Complications and toxicities	Long-term survival	Prognostic factors
Olofsson <i>et al</i> ^[55]	2014	Sweden	The Swedish National Board of Health and Welfare	April 2005 to March 2011	18	34	Y	Y	Y	Y	Y	Y	Y
Magge <i>et al</i> ^[56]	2014	United States	University of Pittsburgh Cancer Institute	November 2003 to February 2012	12	91	Y	NR	Y	Y	Y	Y	Y
Fukumoto <i>et al</i> ^[57]	2014	Japan	The Kobe University Hospital	January 1989 to December 2010	12	68	Y	Y	Y	NR	Y	Y	Y
Alexander <i>et al</i> ^[58]	2009	United States	NCI	June 1994 to July 2005	12	120	Y	Y	Y	Y	Y	Y	Y
van Iersel <i>et al</i> ^[59]	2008	Netherlands	Leiden University Medical Center	August 1994 to December 2004	12	105	Y	Y	Y	Y	Y	Y	Y
Rizell <i>et al</i> ^[60]	2008	Sweden	Sahlgrenska University Hospital	1985 to 2007	11	27	Y	Y	Y	Y	Y	Y	NR
Pingpank <i>et al</i> ^[61]	2005	United States	NCI	July 2001 to January 2004	12	28	Y	Y	Y	Y	Y	NR	NR
Alexander <i>et al</i> ^[62]	2003	United States	NCI	December 1997 to August 2002	12	29	Y	Y	Y	Y	Y	Y	Y

Y: Recorded data available; NR: Not reported; NCI: The National Cancer Institute; MINORS: Methodological index for non-randomized studies.

ensure that the patients would have good tolerance to the operation.

Isolated hepatic perfusion details and response

The isolated hepatic perfusion details and response rate are summarized in Table 3. Six of the eight studies performed IHP^[55,56,58-60,62], while the other two studies performed PIHP^[57,61]. Melphalan, TNF, or a combination of these two drugs was employed in most studies. The majority of studies reported to have a perfusion time of 60 min and the perfusate temperature was kept at 39.5 °C-40 °C. The pooled response rate was 60.8% (95%CI: 53.1%-68%), $I^2 = 37.1\%$ (Figure 2).

Morbidity and mortality

Toxicity, morbidity, and mortality are shown in Table 4. The pooled mortality rate was 5.4% (95%CI: 2.5%-11.2%), $I^2 = 37.5\%$ (Figure 3). The majority of studies reported a reversible hepatic toxicity, mainly manifested in transient elevations in transaminases and serum bilirubin, which return towards normal approximately by postoperative day 7. Besides hepatic toxicity, the most common hematologic toxicity was

anemia, thrombocytopenia, and neutropenia. Significant nonhematologic complications were rare.

Survival outcomes

Seven studies had assessed the survival outcomes we listed in Table 5. Following IHP or PIHP, the median overall survival was reported in a range of 12.1 to 25 mo, with the median value to be 20 mo. There is one study using PIHP protocol that reported the median overall survival to be 25 mo, while that for patients who underwent IHP was 19 mo.

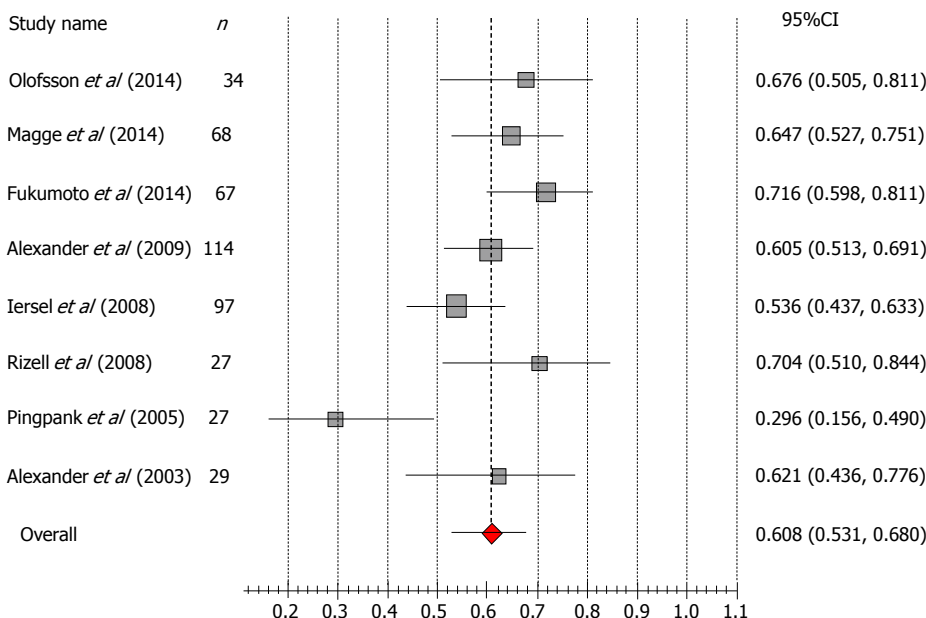
Prognostic factors

Prognostic factors predict the response to IHP or survival, and were reported in six studies (Table 6). Olofsson *et al*^[55] found the volume of liver occupied with metastases (RR = 1.04, $P = 0.02$) and, the diameter of the largest metastasis (RR = 1.23, $P = 0.01$) to be significant for survival on univariate analysis. Magge *et al*^[56] found that CRC patients who received FUDR within one year after IHP had better survival than those did not receive floxuridine (RR = 0.3, $P = 0.043$). Fukumoto *et al*^[57] reported that tumor response to PIHP

Table 2 Patient demographics and disease characteristics

Ref.	Patients (<i>n</i>)	Age (median)	Male: Female	Primary tumor	Primary tumor treatment <i>n</i> (%)			Liver involvement <i>n</i> (%) or mean percentage (range)			Number of liver metastases	Largest liver metastases diameter (cm), median (range)	Extra- hepatic metastases <i>n</i> (%)
					Excision	Chemo- therapy	No treatment	< 5%	25%-0%	> 0%			
Olofsson <i>et al</i> ^[55]	34	61 (17-77)	15:19	Ocular melanoma	15 (44%)	19 (56%)	None	31 (91%)	3 (9%)	None	1-100 31 (91%)	2.35 (1.0-6.4)	None
Magge <i>et al</i> ^[56]	91	54.3 (24-77)	50:41	CRC 54 (59.3%) Ocular melanoma 29 (32%) Others 8 (8.7%)	None	CRC 47 (87%)	44 (48%)	30% (5%-80%)			> 100 3(9%) 9 (2-105)	NR	NR
Fukumoto <i>et al</i> ^[57]	68	60 (52-67)	61:7	HCC	68 (100%)	NR	None	NR	NR	NR	≥ 4	8.3 (5.0-12.6)	None
Alexander <i>et al</i> ^[58]	120	52 (22-74)	41:79	CRC	NR	NR	NR	20% (5%-75%)			NR	8 (1-50)	NR
Iersel <i>et al</i> ^[59]	105	≤ 70	78:27	CRC	4 (3.8%)	51 (48.6%)	50 (47.6%)	NR	NR	NR	< 10 71 (68%) ≥ 10 34 (32%)	NR	34 (32.4%)
Rizell <i>et al</i> ^[60]	27	53 (36-77)	NR	Melanoma	NR	NR	NR	6 (22%)	11 (41%)	10 (37%)	NR	NR	NR
Pingpank <i>et al</i> ^[61]	28	49 (17-74)	14:14	Melanoma 13 CRC 2 Others 13	NR	NR	NR	NR	NR	NR	NR	NR	8 (29%)
Alexander <i>et al</i> ^[62]	29	49 (26-73)	15:14	Ocular melanoma	NR	NR	NR	20 (69%)	8 (28%)	1 (3%)	25 (4 ≥ 50)	5.6 (2-14)	NR

CRC: Colorectal cancer; HCC: Hepatocellular carcinoma; NR: Not reported.

**Figure 2 Forest plot of the studies for response rate.** Pooled estimate (%) = 60.8%, 95%CI: 53.1%-68.0%, $I^2 = 37.1\%$.

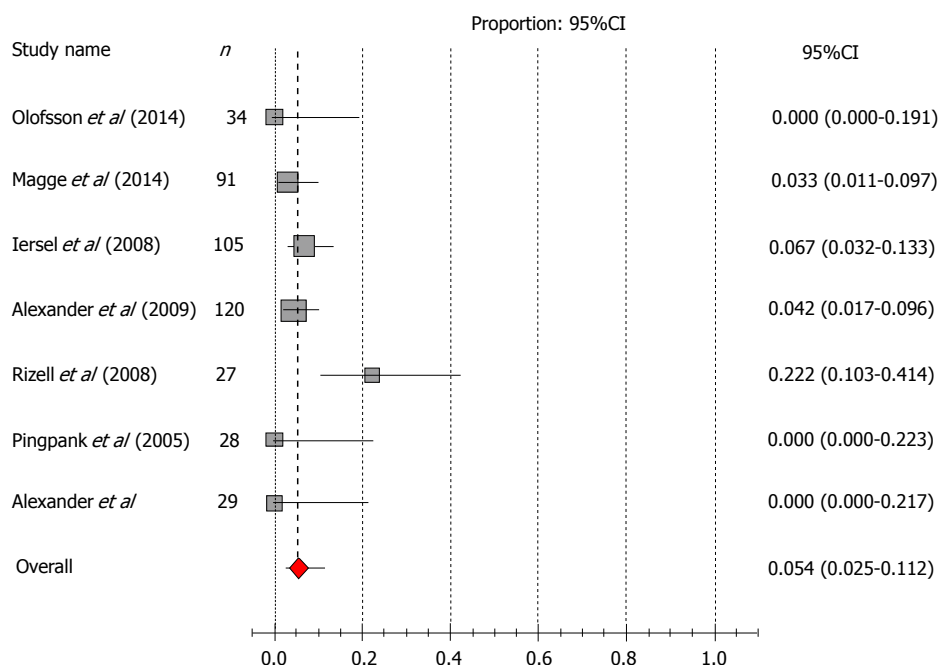
(RR = 0.108, $P < 0.001$) and normalization of serum des-γ-carboxy prothrombin (DCP) after PIHP (RR = 0.28, $P < 0.001$) were both independent prognostic factors in HCC patients for survival. In Alexander's study

published in 2009, they carried out further research on prognostic factors. They found that patients who received IHP with postoperative hepatic arterial infusion chemotherapy with Floxuridine (FUDR) markedly

Table 3 Isolated hepatic perfusion details and response rate

Ref.	Patients evaluable for response (n)	IHP/ PIHP	IHP chemotherapy protocol					Patient response				Overall response (CR + PR, %)
			Drug	Dose	Perfusion temperature	Perfusion time	Courses per patient (n)	Complete response (%)	Partial response (%)	Stable disease (%)	Progressive disease (%)	
Olofsson <i>et al</i> ^[55]	34	IHP	Melphalan	1 mg/kg	40 °C	60 min	1	4 (12%)	19 (56%)	6 (18%)	5 (15%)	68%
Magge <i>et al</i> ^[56]	68	IHP	Melphalan	1.5 mg/kg	40 °C	60 min	1	44 (64.7%)		24 (35.3%)		64.7%
			Oxaliplatin	40 mg/m ²								
			Oxaliplatin + 5FU	200 mg/m ²								
Fukumoto <i>et al</i> ^[57]	67	PIHP	Mitomycin C and/or Doxorubicin	20-40 mg/m ² 60-120 mg/m ²	NR	30-40 min	1.51 (range 1-3)	21 (31.3%)	27 (40.3%)	11 (16.4%)	8 (11.9%)	71.6%
Alexander <i>et al</i> ^[58]	114	IHP	Melphalan	1.5 mg/kg	39.5 °C-40 °C	60 min	1	2 (1.8%)	67 (58.8%)	NR	NR	60.5%
van Iersel <i>et al</i> ^[59]	97	IHP	Melphalan	200 mg	39.5 °C	60 min	1	3 (3.1%)	49 (50.5%)	23 (23.7%)	22 (22.7%)	53.6%
Rizell <i>et al</i> ^[60]	27	IHP	Melphalan	0.5, 1 and 2 mg/kg	≥ 40 °C	40-60 min	1	2 (7.4%)	17 (63.0%)	2 (7.4%)	6 (22.2%)	69.4%
			With or without TNF	30 µg								
Pingpank <i>et al</i> ^[61]	27	PIHP	Melphalan	2-3.5 mg/kg	NR	60 min	2.64	2 (7.4%)	6 (22.2%)	NR	NR	29.6%
Alexander <i>et al</i> ^[62]	29	IHP	Melphalan	1.5 mg/kg	NR	60 min	1	3 (10%)	15 (52%)	NR	NR	62%

NR: Not reported. IHP: Isolated hepatic perfusion; PIHP: Percutaneous isolated hepatic perfusion.

**Figure 3** Forest plot of the studies for mortality. Pooled estimate (%) = 5.4%, 95%CI: 2.5%-11.2%, $I^2 = 37.5\%$.

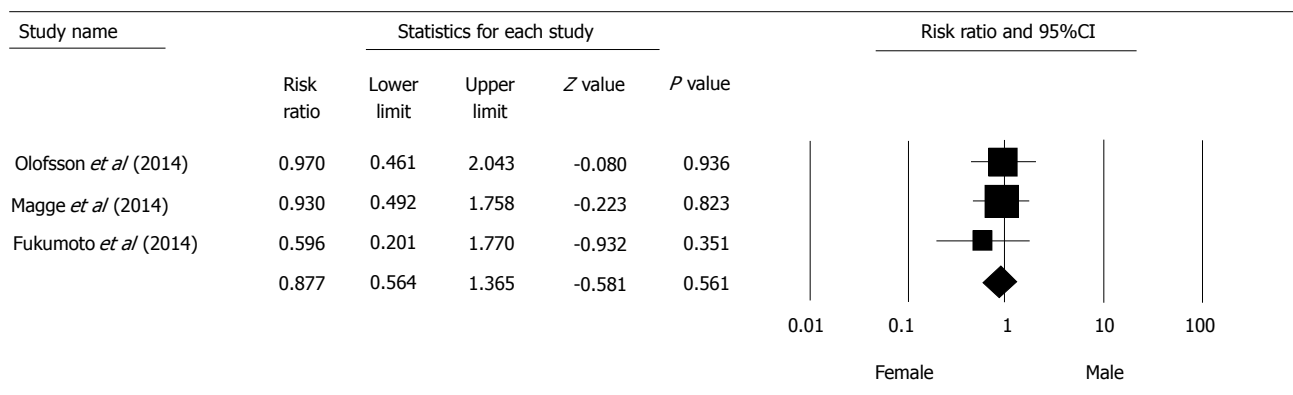
prolonged the duration of response from 5.8 to 13 mo ($P < 0.001$). Patients who received higher doses of Melphalan tended to have higher response rates ($P = 0.034$). In survival analysis, it was found that the use of hepatic artery infusion (HAI) following IHP (for OS: RR

= 1.78, $P = 0.0039$, for PFS: RR = 2.79, $P < 0.0001$) and preoperative carcino-embryonic antigen (CEA) ≤ 30 ng/mL (for OS: RR = 2.29, $P = 0.0012$, for PFS: RR = 2.35, $P = 0.0006$) were independently associated with hepatic PFS and OS. A study carried out by van

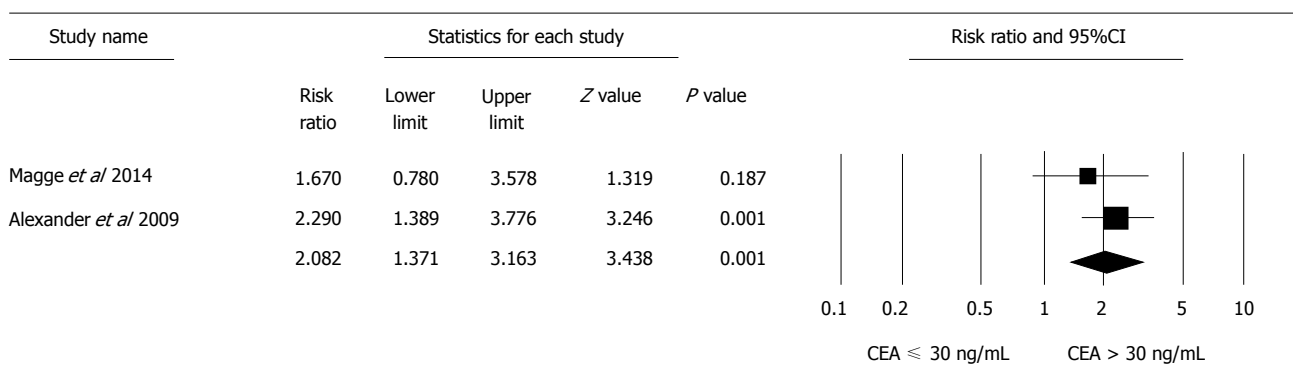
Table 4 Isolated hepatic perfusion morbidity and mortality

Ref.	Mortality	Toxicity grade 3/4 (%)						Complications grade 3/4 (%)				
		Bilirubin	Transaminases	Alkaline phosphatase	Neutropenia	Platelets	Anemia	Hepatic artery obstruction	Hepatic failure	Bleeding	Hypotension	Wound infection
Olofsson <i>et al</i> ^[55]	None	NR	NR	NR	NR	NR	NR	2.90%	NR	NR	NR	NR
Magge <i>et al</i> ^[56]	3.30%	20.50%	50.00%	3.40%	2.30%	18.20%	50.00%	NR	5.70%	NR	0%	3.40%
Fukumoto <i>et al</i> ^[57]	NR	NR	77.90%	NR	44.10%	NR	NR	NR	NR	1.50%	NR	8.80%
Alexander <i>et al</i> ^[58]	4%	46.70%	55.80%	4.20%	0.80%	10.00%	NR	NR	3.30%	0.80%	5.80%	2.50%
van Iersel <i>et al</i> ^[59]	6%	18.00%	20.00%	15.20%	2.90%	NR	NR	1.90%	NR	8.60%	NR	NR
Rizell <i>et al</i> ^[60]	22%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Pingpank <i>et al</i> ^[61]	None	18.9% (hepatic toxicity)			66.20%	35.10%	17.60%	NR	NR	NR	NR	NR
Alexander <i>et al</i> ^[62]	None	65.5% (hepatic toxicity)			NR	NR	NR	NR	NR	NR	NR	NR
Pooled P	5.4%				10.3	19.2	31.9%	2.2%	4.5%	4.50%	2.7%	5.7%
95%CI	(2.5%-11.2%)				(2%-39%)	(8.7%-37.2%)	(9.3%-68.1%)	(0.7%-6.6%)	(2.3%-8.4%)	(1.8-11.1%)	(0.3%-20.3%)	(3.1%-10.2%)

NR: Not reported.



Meta analysis

Figure 4 Forest plot of the relative risk of overall survival for different gender.

Meta analysis

Figure 5 Forest plot of the relative risk of overall survival for different preoperative carcino-embryonic antigen levels. CEA: Carcino embryonic antigen.

Iersel *et al*^[59] revealed that adjuvant chemotherapy was a positive prognostic factor for hepatic response to IHP (RR = 5.91, $P = 0.009$), while the female sex was borderline significant (RR = 2.65, $P = 0.05$). They confirmed adjuvant chemotherapy following IHP was a positive factor for PFS on multivariate analysis (RR = 0.05, $P = 0.039$), whereas on univariate analysis, no chemotherapy directed at liver metastases before IHP was a potential positive factor ($P = 0.09$). When

assessed for OS, they found ≥ 10 liver metastases (RR = 1.95, $P = 0.006$), absence of hepatic artery perfusion (RR = 4.15, $P = 0.003$), presence of postoperative complications (RR = 1.54, $P = 0.048$) were all negative factors. Alexander *et al*^[58] reported that patients with Ocular Melanoma who have a baseline lactate dehydrogenase (LDH) > 160 U/L were likely to have shorter survival courses (RR = 17.1, $P = 0.0062$).

According to the prognostic factors mentioned above,

Table 5 Long-term survival outcomes after isolated hepatic perfusion

Ref.	Median follow-up (mo)	Median time to local progression (mo)	Median time to systemic progression (mo)	Median hepatic progression-free survival (mo)	Overall survival					
					Median OS (mo from IHP)	1-yr survival (%)	2-yr survival (%)	3-yr survival (%)	4-yr survival (%)	5-yr survival (%)
Olofsson <i>et al</i> ^[55]	NR	7 (0-31)	13 (2-34)	NR	24	NR	NR	NR	NR	NR
Magge <i>et al</i> ^[56]	NR	NR	NR	For CRC group: 12 (10.53-13.47) For CR: 12 (10.1-13.9) For PR: 12.5 (10.53-13.47)	23 (15-28)	NR	NR	NR	NR	NR
Fukumoto <i>et al</i> ^[57]	20 (3-191)	NR	NR	NR	25	80.6%	NR	35.7%	NR	27.6%
Alexander <i>et al</i> ^[58]	78.1 (52.1-104.2)	7.3 (6.5-8.0)		NR	25 (19.4-30.6)	NR	53%	28%	14%	NR
van Iersel <i>et al</i> ^[59]	NR	NR	NR	7	17.4	NR	34%	NR	NR	NR
Rizell <i>et al</i> ^[60]	IHP I cohort: NR IHP II cohort: NR IHP III cohort: 7 (range 4-18)	NR	NR	NR	12.6 (2.5-57)	NR	NR	NR	NR	NR
Alexander <i>et al</i> ^[62]	11 (3-40)		8	12	12.1 (3-39+)	NR	NR	NR	NR	NR
Median value (range)					20 (12.1-25)					

OS: Overall survival; NR: Not reported; CRC: Colorectal cancer; CR: Complete response; PR: Partial response; SD: Stable disease.

Table 6 Summary of prognostic factors presented in relevant clinical trials

Ref.	Year	Prognostic factors for response	Prognostic factors for TTLP	Prognostic factors for PFS	Prognostic factors for OS
Olofsson <i>et al</i> ^[55]	2014	NR	Y	NR	Y
Magge <i>et al</i> ^[56]	2014	Y	NR	NR	Y
Fukumoto <i>et al</i> ^[57]	2014	NR	NR	NR	Y
Alexander <i>et al</i> ^[58]	2009	Y	NR	Y	Y
van Iersel <i>et al</i> ^[59]	2008	Y	NR	Y	Y
Rizell <i>et al</i> ^[60]	2008	NR	NR	NR	NR
Pingpank <i>et al</i> ^[61]	2005	NR	NR	NR	NR
Alexander <i>et al</i> ^[62]	2003	Y	NR	NR	Y

TTLP: Time to local progression; PFS: Progression free survival; OS: Overall survival; NR: Not reported.

gender and preoperative CEA level predictive of survival were the only comparable factors with sufficient data for meta-analysis. Gender was not associated with overall survival (Figure 4); however, CEA ≤ 30 ng/mL was associated with a significant improvement in survival outcomes with CRC patients (RR = 2.082, 95%CI: 1.371-3.163) (Figure 5). There was no significant heterogeneity.

DISCUSSION

The ideal curative intervention of primary or secondary liver malignancies is surgical resection. Nonetheless, the diseases are unresectable in the majority of patients when diagnosed^[2,63]. Systemic chemotherapy remains

the first-line of palliative therapy for metastatic disease and, little benefit is gained from long-term prospective, although it is associated with good initial response rates. Better tumor response has been shown to correlate with significant systemic toxicity in the setting of high dosage of chemotherapy, which limits the application of systemic chemotherapy^[64]. To circumvent such limitations, liver-directed regional therapies have emerged as novel therapeutic strategies. Regional therapies such as HAI, IHP, are based on the fact that higher doses of chemotherapy may improve the outcomes. HAI delivers chemotherapeutic regimens with a high rate of hepatic clearance directly to the hepatic artery, which provides the majority of blood supply to the tumor, thus avoiding systemic toxicity while achieving high concentrations of chemotherapeutic agents. The HAI method allows some regimens to achieve a 15-fold concentration in liver tumors compared to normal liver. IHP, which further blocks inferior vena cava (IVC), allows using more kinds of drugs and can reach up to 5 times higher tolerable drug doses than HAI without fear of systemic exposure^[65]. That is, IHP allows broader regimens and gets higher concentrations, which would be lethal if administered systemically.

IHP has been investigating and reporting worldwide since its first description five decades ago^[66]. Many studies evaluated the efficacy, safety, as well as the long-term survival of IHP, using generally accepted standards and yielded quantified results. Most studies acclaimed IHP to be efficacious and safe. Although promising, no current systemic evaluation of IHP is

available yet. Therefore we reviewed all the literature we could get and conducted a systemic review. As an alternate of IHP, here we discussed PIHP and IHP together.

Our systemic meta-analysis demonstrated a pooled response rate following IHP/PIHP treatment to be 60.8% (95%CI: 53.1%-68.0%), with each individual ranging from 29.6% to 71.6%. The median overall survival of IHP/PIHP was 20 mo (range: 12.1-25). This is particularly encouraging when considered with the low effects and high mortality with systemic chemotherapy. To our knowledge, there has been no randomized trial so far to compare the outcomes between IHP and systemic chemotherapy. A case-control study by van Iersel *et al.*^[53] for the first time revealed no statistical significance of overall survival (OS) between IHP and systemic chemotherapy in unresectable colorectal cancer liver metastases (median overall survival: 25.0 mo for IHP group and 21.7 mo for chemotherapy, $P = 0.29$). However, selection bias has to be considered given the disagreement of age and, the duration of follow-up between the two groups. Further investigations including randomized controlled trials are of great necessity to evaluate the efficacy of IHP/PIHP in comparison to conventional systemic chemotherapy and other regional therapies.

Most studies found the procedure of IHP and PIHP to be safe. Among the selected studies, mortality was varied between 0% and 6%, and we drew the pooled mortality rate to be 5.4%. Most investigators observed a transient liver toxicity, which manifested by increases of bilirubin and transaminases, and would approximately decrease to normal level by postoperative day 7. Grade 3-4 post-operative toxicity and major complications were listed in our review (Table 4). Albeit the major systemic toxicity was avoided and the mortality was acceptable, we still should take notice of selecting ideal patients to undergo these procedures.

Due to limited number and the heterogeneity of outcomes reported by different studies, the only definite prognostic factors with sufficient data for meta-analysis were gender and preoperative CEA levels predictive of survival (Figures 4 and 5). The result indicated that CRC patients with low preoperative CEA (≤ 30 ng/mL) tended to have a better outcome compared to those whose preoperative CEA level > 30 ng/mL. Of note, IHP followed by HAI has been reported as a positive factor of survival by several investigations^[49,51,56,58]. However, due to the inconsistency or the absence of detailed parameters, we cannot get the results combined into an integrated one.

As a repeatable, less invasive method of hepatic perfusion *via* percutaneous administration, PIHP has been under clinical evaluation since the early 1990s^[37,67]. Among all the studies, the majority was small-scale observational studies and case reports^[21,24,36,68-70], and only two studies met our inclusion criteria. Fukumoto

et al.^[57] performed 101 perfusions on 67 patients with hepatocellular carcinoma using Mitomycin C and/or Doxorubicin. They showed a hepatic response rate of 71.6% with overall survival of 25 mo, longer than the mean value of median OS of 19 mo reported by other six articles using IHP approach. Pingpank^[71] described a response rate of 29.6% in phase I study for patients with liver metastasis from various origins and of 34.1% in a phase III trial for patients with liver metastasis from melanoma. The phase III trial also reported the median hepatic PFS was longer in patients treated with PIHP than patients treated with standard of care (254 d vs 49 d). The distinction of response rates between these two sets of studies might be attributed to different cancer types and chemotherapy regimens. Additionally, in the phase I study, the response rate was not good perhaps due to the fact that the study was designed to evaluate toxicity and subsequently determine the MTD during dose escalation. In other words, the response rate was not their primary end point. Meanwhile, in the phase III study, the number of patients was relatively low, there were only a handful of patients who were refractory to systemic chemotherapy enrolled in the trial and associated with some withdrawers. All these factors might be selection bias for the study.

A number of limitations to this meta-analysis should not be ignored. All studies were non-randomized phase I/II clinical trials in design and may be liable to selection bias. Several aspects of heterogeneity may contribute to varied response and overall survival including pathological types of cancer, chemotherapy regimen, prior therapies, etc. In addition, the inconsistency of prognostic factors described in individual studies made it difficult to compare and evaluate in meta-analysis.

In general, IHP and PIHP have unique and obvious advantages compared to systemic chemotherapy. For decades, investigations of IHP and PIHP were continually conducted, different regimens, the combination of chemotherapy, hyperthermia and hypoxemia, variations for the inflow and the venovenous bypass have been tested to improve the efficacy and safety. The present systemic review and meta-analysis suggest that IHP and PIHP are potentially efficient and safe techniques for unresectable liver primary and secondary malignancies, exhibiting a relatively high response rate, low mortality rate, and potentially prolonged overall survival. Though the role of hepatic perfusion is still not fully understood, there are vacant areas need to be explored. Can IHP make benefits to patients who were chemorefractory? Will IHP followed by HAI play a more effective role than IHP does? Will it improve the outcomes when IHP is a component to therapy and is combined with systemic chemotherapy or other regional therapies? How effective is it when applied to other types of tumor, e.g., pancreatic carcinoma? What kinds of patients would benefit most from this procedure? What is the appropriate timing of using IHP? And for percutaneous

perfusion, which of the alternative techniques would be better, and how many times should they be repeated in different patients? These questions remain to be solved. Continued evaluation and great efforts are required to clarify its role and greater benefit each patient.

COMMENTS

Background

The optimal curative treatment of primary or secondary liver tumors is surgical resection. However, less than one third of cases with malignant liver tumors are candidates for surgical intervention. Conventional chemotherapy may be applied systemically but little benefit is gained from long-term prospective. Better tumor response has been shown to correlate with significant systemic toxicity in the setting of high dosage of chemotherapy, which limits the application of systemic chemotherapy. Isolated hepatic perfusion (IHP) as a liver-directed regional therapy, completely separating the liver's blood supply from the rest of the body through a surgical operation, and allows extremely high tolerable drug doses without fear of systemic exposure. As an alternative approach of IHP, percutaneous IHP (PIHP) is performed via a minimally invasive approach, using a double-balloon catheter to cut the liver's circulation. Here the authors conduct this study to investigate the efficacy, safety and survival benefit of these approaches.

Research frontiers

IHP has been investigating since its first description five decades ago. As a repeatable, less invasive method of hepatic perfusion, PIHP has been under clinical evaluation since the early 1990s. For decades, investigations of IHP and PIHP were continually conducted, different regimens, the combination of chemotherapy, hyperthermia and hypoxemia, variations for the inflow and the venovenous bypass have been tested to improve the efficacy and safety. Most studies acclaimed that IHP and PIHP have unique and obvious advantages compared to systemic chemotherapy. The role of hepatic perfusion in multidisciplinary treatment approaches for unresectable liver malignancies is still not fully understood. Continued evaluation and great efforts are required to clarify its role and greater benefit each patient.

Innovations and breakthroughs

IHP and PIHP have been successfully performed to treat primary or secondary unresectable liver cancers in various studies. In the present systemic review the authors reviewed the literature, carefully extracted and investigated the data, demonstrated all details and results of this technique in every aspect, so that it will help readers to understand this technique in a quick, comprehensive and objective way.

Applications

This review suggests that IHP and PIHP are potentially efficient and safe techniques for unresectable liver primary and secondary malignancies, exhibiting a relatively high response rate, low mortality rate, and potentially prolonged overall survival.

Terminology

IHP is a surgical technique that completely separating the liver's circulation from the rest of the body's circulatory system. The isolation of the liver's circulation allows an extremely high concentration of chemotherapy to the whole organ, while minimizing systemic toxicity. The procedure requires an open surgery which can be done only once. As an alternative approach of IHP, PIHP is performed via a minimally invasive approach, using a double-balloon catheter to cut the liver's circulation under fluoroscopic guidance. PIHP obviate a large abdominal operation, and allows repeatable manipulation, which may enable the patients to get maximized therapeutic effects while having a faster recovery.

Peer-review

This is an interesting review regarding the IHP for unresectable hepatic malignancies. The review of this topic may be useful for readers.

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