Original Article

Comparison of portal vein embolization, portal vein ligation, associating liver partition and portal vein ligation for staged hepatectomy in cases with a small future liver remnant: a network meta-analysis

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Background: The optimal surgery for liver cancer cases with small future liver remnant (FLR) remains controversial; associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), portal vein embolization (PVE), and portal vein ligation (PVL) are all used.

Methods: We conducted a systematic search in the EMBASE, Medline and Cochrane databases, without year or language restrictions, to identify studies that compared PVE, PVL, and ALPPS. We compared the feasibility, safety, and efficacy of PVE, PVL, and ALPPS using network meta-analyses. this study do not involve ethical issues.

Results: Ten studies and 451 patients were included. PVE had a significantly reduced FLR increase (42.2%; 95% CI, 26.52–57.87; P<0.001) and resection completion rate (89.2%; OR =0.108; 95% CI, 0.02–0.585; P=0.01) compared with ALPPS. PVE also had a non-significant reduction in morbidity and mortality, and a non-significant increase in waiting time from first intervention to removal of tumors than ALPPS. Similarly, PVL had a significantly reduced FLR increase (47.65%; 95% CI, 29.43–65.88%; P<0.001) and resection completion rate (91.6%; OR =0.084; 95% CI, 0.013–0.532; P=0.009) compared with ALPPS; as well as a non-significant reduction in morbidity and mortality, and increase in waiting time versus ALPPS. Rank analysis indicated that ALPPS was superior, with respective probabilities of 100%, 99.4%, and 44.9% for FLR increase, resection completion, and waiting time; PVE and PVL were not significantly different.

Conclusions: ALPPS was significantly more efficient than PVE and PVL regarding promotion of FLR hypertrophy, resection completion, and waiting time. The three techniques were similar regarding morbidity and mortality.

Keywords: Portal vein embolization (PVE); portal vein ligation (PVL); associating liver partition and portal vein ligation for staged hepatectomy (ALPPS); future liver remnant (FLR); staged hepatectomy

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Introduction

R0 resection of liver tumour is still the most effective treatment to improve long-term survival (1). However, many patients cannot reach R0 resection because of large tumor size and insufficient future liver remnant (FLR) after major hepatectomy. To completely remove the tumor and ensure sufficient liver remnant, portal vein occlusion, including portal vein embolization (PVE) and portal vein ligation (PVL) (2,3), was introduced. The mechanism of PVE or PVL is to blocking the ipsilateral liver segments' portal vein blood flow and stimulate contralateral liver growth (4). Using either PVE or PVL to promote residual liver growth is considered as the standard strategy in the cases with primarily unresectable liver malignancies and small FLR (5-7).

Findings regarding the comparative efficacy of PVL and PVE have varied between studies. Some studies demonstrated that PVL was less effective than PVE (8); however, other research indicated that PVL and PVE were equally effective in stimulating growth of the FLR (9). Although the use of PVL or PVE has improved the outcome for some advanced liver cancer patients, the complex blood flow in the liver itself makes it hard to maintain an adequate liver remnant, which would substantially improve survival.

A novel strategy of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) to resect liver tumors in cases with a small liver remnant was introduced in 2007 (10). This special type of hepatectomy is performed in two stages. During the first stage, surgeons conduct the PVL and liver parenchymal transection, which relatively reduces the blood flow of the liver segment containing the tumors and promotes rapid growth of residual liver. Although it has been widely reported that ALPPS induces more effective stimulation of residual liver growth (9,11), the use of ALPPS is highly controversial due to its relatively high morbidity and perioperative mortality (5). However, surgery for liver cancer becomes much safer with the increasing experience of surgeons and improved surgical techniques. Alvarez *et al.* showed that ALPPS can achieve a high resection completion rate and FLR hypertrophy rate, with a relatively low morbidity and mortality (12). For advanced liver cancer patients, it is difficult for doctors to decide whether PVE, PVL, or ALPPS is the best strategy.

This article aimed to compare the feasibility, safety, and efficacy of PVE, PVL, and ALPPS. The outcome measures included resection completion rate, FLR hypertrophy rate, morbidity, perioperative mortality, and waiting time from first intervention to removal of tumors.

Methods

Search strategy and selection criteria

We conducted a systematic search in the EMBASE, Medline and Cochrane databases for articles published from database inception until April 2016 using the following terms: ALPPS, portal vein ligation, portal vein embolization, staged hepatectomy, and liver resection. There were no language restrictions.

Studies comparing any two of the three techniques (ALPPS, PVL, and PVE) were included in this review. The following articles were excluded: studies including only one or all three of the abovementioned techniques, letters, editorials, opinion articles, conference abstracts, and case reports (*Figure 1*).

Relevant articles in reference lists were reviewed and duplicate articles were excluded. Two reviewers independently screening the titles and abstracts of each study. Disagreements were resolved by discussion.

Data extraction and quality assessment

Two reviewers independently extracted data. Extracted data included percentage increase in FLR, hepatic resection completion rate, overall morbidity and mortality, and waiting time from first intervention to removal of tumors. a third author was assigned to make sure the accuracy of the data. We conducted a quality assessment for each study using the Newcastle–Ottawa Scale.

Statistical methods

The outcomes we evaluated were waiting time from first intervention to removal of tumors, resection completion rate, rate of FLR increase, postoperative complications, and mortality rate.

Network meta-analysis (NMA) (13) was used to meta-analyze more than two treatments simultaneously. We drew a map of the network that shows which treatments were directly compared with other treatments, and how much information was provided for each treatment and its comparison. We conducted network ranking to evaluate the best operation in terms of waiting time from first intervention to removal of tumors, resection completion rate, FLR increase rate, postoperative complications, and

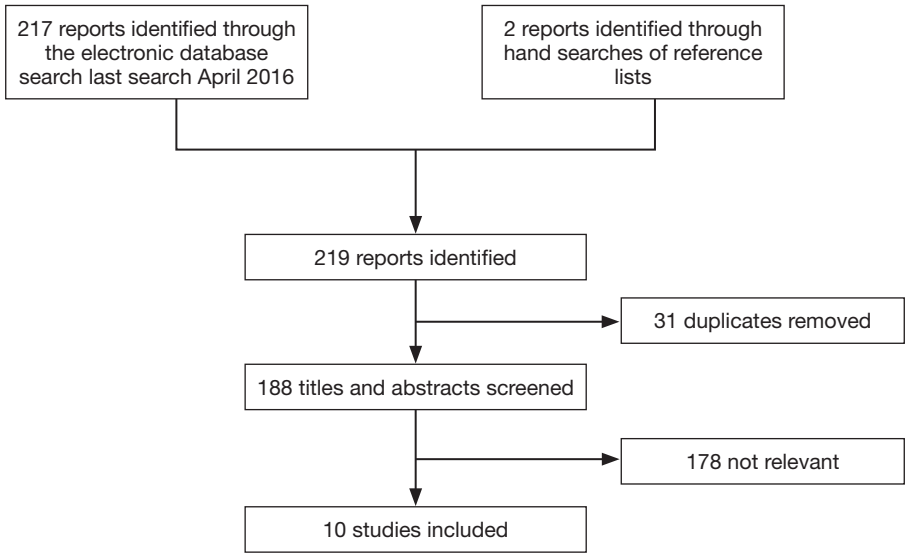

Figure 1 Flowchart of databases searched, study selection and exclusions performed.

mortality rate using Stata 12 software (StataCorp, College Station, TX, USA). We fitted the sidesplitting model to assess whether the direct overall results and indirect results were consistent. Differences were considered significant if the P value for Z was less than 0.05. We also summarized the direct and indirect results using a consistency or inconsistency model (14-16). Network forests were also provided the forest plot for pairwise meta-analyses. All data was provided as the odds ratio (OR) or mean difference (MD) with confidence interval (CI).

Results

Search results

Our initial electronic search yielded 217 references; of these, eight studies were included according to our inclusion and exclusion criteria. From the reference lists of these eight studies, we identified 2 relevant references for evaluation. A final total of 10 single studies (5,8,9,17-23) and total 451 patients were included in this NMA. The detailed search strategy and the process of study selection are summarized in *Figure 1*.

Study characteristics

All of the included studies were retrospective. Seven studies (9,17-21) compared PVE and PVL; totally including 218 patients. Three studies (5,22,23) compared PVE with ALPPS; these studies included 259 patients in all. This ten articles were evaluated by Newcastle–Ottawa Scale. Nine studies provided data on resection completion rates, six studies provided data on FLR increase, and seven studies provided waiting time, morbidity, and perioperative mortality data (*Table 1*).

Percentage increase in future liver remnant

Six studies were analyzed, The overall results indicated a 42.2% reduction in the percentage increase of FLR for PVE compared with ALPPS (95% CI, 26.52–57.87; P<0.001). There was also a 47.65% reduction in the percentage increase of FLR for PVL compared with ALPPS (95% CI, 29.43–65.88; P<0.001). as the forest plots showed in *Figure 2A*. The network rank analysis showed that the respective probabilities of ALPPS, PVE, and PVL being the best treatment strategy were 100%, 0%, and 0% (*Table 2*).

Resection completion rates

Nine studies were analyzed. The results indicated an 89.2% reduction in resection completion rate of hepatic resection for PVE compared with ALPPS (OR =0.108; 95% CI, 0.02–0.585; P=0.01). There was also a 91.6% reduction in resection completion rate for PVL compared with ALPPS (OR =0.084; 95% CI, 0.013–0.532; P=0.009), as the forest plots showed in *Figure 2B*. The respective probabilities of

Table 1 Characteristics of the included studies comparing PVE, PVL and ALPPS

Reference	Year of publication	Comparison type	Country	No. of patients	Tumor progression	Insufficient growth of FLR	Quality score (Newcastl–Ottawa)
Aussilhou *et al.*	2008	PVE *vs.* PVL	France	35	PVE: 4; PVL: 2	PVE: 2; PVL: 0	8
Broering *et al.*	2002	PVE *vs.* PVL	Germany	34	PVE: 5; PVL: 4	PVE: 2; PVL: 2	9
Capussotti *et al.*	2008	PVE *vs.* PVL	Italy, France	48	PVE: 7; PVL: 5	PVE: 0; PVL: 1	9
Iida *et al.*	2012	PVE *vs.* PVL	Japan	13	PVE: 0; PVL: NM	PVE: 0; PVL: NM	8
Robles *et al.*	2012	PVE *vs.* PVL	Spain	41	PVE: 0; PVL: 3	PVE: 0; PVL: 0	9
van Lienden *et al.*	2013	PVE *vs.* PVL	The Netherlands	21	PVE: 1; PVL: 0	PVE: 0; PVL: 7	8
Sturesson *et al.*	2010	PVE *vs.* PVL	Sweden	26	PVE: NM; PVL: NM	PVE: NM; PVL: NM	7
Knoefel *et al.*	2013	ALPPS *vs.* PVE	Germany	22	ALPPS: 0; PVE: 0	ALPPS: 0; PVE: 3	9
Shindoh *et al.*	2013	ALPPS *vs.* PVE	USA	169	ALPPS: 0; PVE: 27	ALPPS: 0; PVE: 5	9
Croome *et al.*	2015	ALPPS *vs.* PVE	USA, Canada	68	ALPPS: 0; PVE: 8	ALPPS: 0; PVE: 3	9

PVE, portal vein embolization; PVL, portal vein ligation; ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; FLR, future liver remnant.

ALPPS, PVE, and PVL being the best treatment strategy were 99.4%, 0.4% and 0.2% (*Table 2*).

Perioperative mortality

Seven studies were analyzed. There was a 44.7% reduction in mortality for PVE versus ALPPS; however, this difference was not statistically significant (OR =0.553; 95% CI, 0.158–1.938; P=0.371). A 42.9% non-significant reduction in mortality was also observed for PVL versus ALPPS (OR =0.571; 95% CI, 0.07–4.683; P=0.602), as the forest plots showed in *Figure 2C*. The respective probabilities of ALPPS, PVE, and PVL being the best treatment strategy were 12.6%, 43.6% and 43.8% (*Table 2*).

Perioperative morbidity

Seven studies were included in this analysis. Perioperative morbidity including all of the complications from the first step to the end. The pooled results showed a 27.7% reduction in the perioperative morbidity for PVE compared with ALPPS; however, this difference was not statistically significant (OR =0.723; 95% CI, 0.258–2.207; P=0.537), as the forest plots showed in *Figure 2D*. PVL also had a non-significantly lower morbidity rate, with a 35.6% reduction compared with ALPPS (OR =0.644; 95% CI, 0.166–2.499; P=0.524), as the forest plots showed in *Figure 2D*. ALPPS, PVE, and PVL had respective probabilities of 19%, 25.7% and 55.3% of being the best treatment strategy (*Table 2*).

Waiting time between the two stages

Seven studies were included in this analysis. There was an extra 3.42 days wait between the two stages for PVE versus ALPPS; however, this difference was not statistically significant (95% CI, −29.5–36.33; P=0.839). The waiting time for PVL was 7.95 days longer than for ALPPS; although this difference was not statistically significant (95% CI, −35.51–51.4; P=0.72), as the forest plots showed in *Figure 2E*. ALPPS had a 49.9% probability of being the best treatment strategy, followed by PVE and PVL with respective probabilities of 28% and 22.1% (*Table 2*).

Discussion

Radical resection is still the best treatment for primary or secondary liver malignancy. Safe hepatectomy mainly concerns the future liver remnant rather than the liver being resected. Patients with huge or multiple tumors undergoing a major hepatectomy may have a small FLR, which can lead to postoperative liver dysfunction or liver failure (24,25). Several strategies have been attempted to

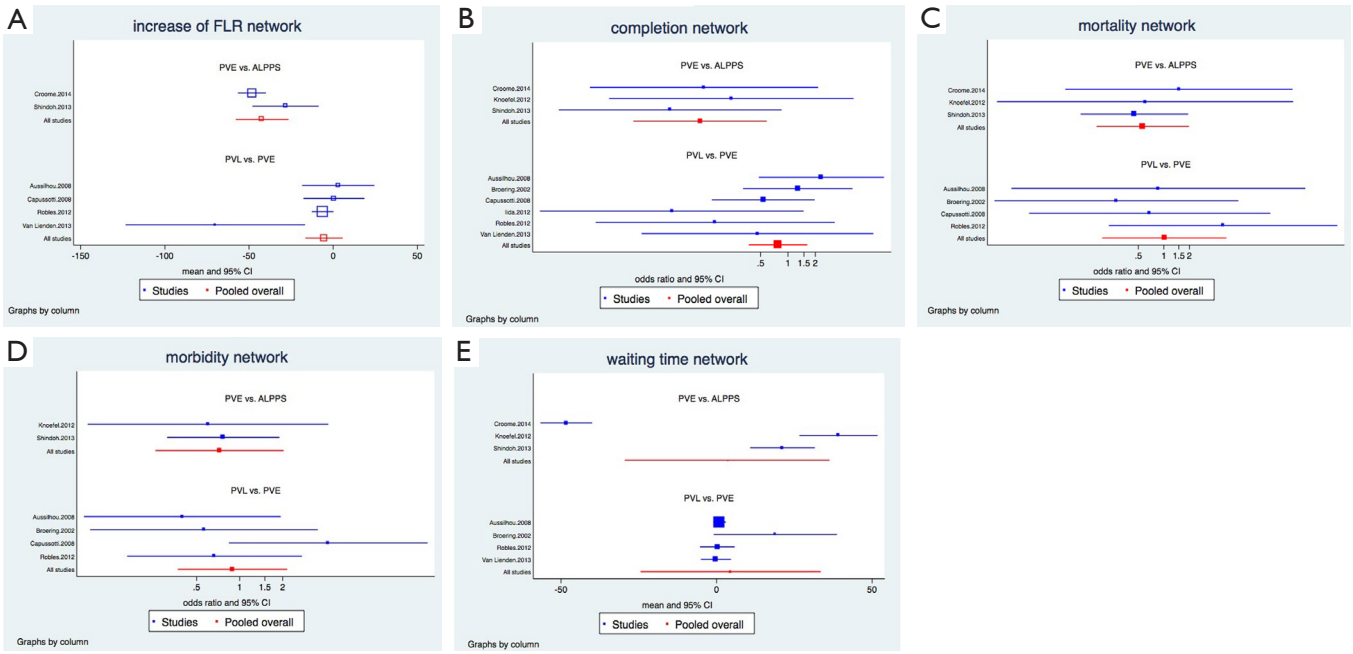

Figure 2 Forest plots demonstrate adjusted event rates and 95% CIs for each study and the relative weight of the study in the meta-analysis. (A) Meta-analysis of FLR increase in percentages; (B) metaanalysis of resection completion rate; (C) meta-analysis of mortality rate; (D) meta-analysis of morbidity; (E) meta-analysis of waiting time from first intervention to removal of tumors. CI confidence intervals.

Table 2 Rank treatment after network meta-analysis

Comparison	ALPPS (%)	PVE (%)	PVL (%)
FLR increase	100.0	0	0
Completion rate	99.4	0.4	0.2
Waiting time	49.9	28.0	22.1
Morbidity rate	19.0	25.7	55.3
Mortality rate	12.6	43.6	43.8

ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; PVE, portal vein embolization; PVL, portal vein ligation; FLR, future liver remnant.

improve the surgical resection rates for patients with a small FLR, including PVE, PVL, and ALPPS.

Liver volume partially reflects liver function; the volume calculated using abdominal computed tomography can be used to predict postoperative liver function. A small FLR is defined as FLR ≤ 20% total liver volume (TLV) in normal liver, and FLR ≤ 40% TLV in fibrotic or cirrhotic liver (26). However, remnant liver volume (RLV) to bodyweight ratio (RLV-BWR) is more specific than FLR-TLV as an indicator of the future remnant liver function after extended liver resection. If RLV ≤0.5% of bodyweight, patients are highly likely to experience hepatic dysfunction and postoperative mortality; the incidence of these complications would be even higher in cases involving cirrhotic liver (27).

PVE was introduced in the 1980s to stimulate growth of the remaining portion of the liver. Although PVE is a mature technique that is accepted worldwide, it still has some substantial disadvantages such as percutaneous puncture procedure-related complications, relatively long interval between PVE and the resection operation, and accelerated tumor progression during this interval (28,29); tumor growth is considered the main disadvantage of PVE (30,31).

PVL is widely used in patients with multiple liver metastases from colorectal tumors (32). PVL can be simultaneously performed with the resection of the primary tumor. There are few complications associated with PVL, but some patients undergoing PVE or PVL may fail to have the liver resection performed because of insufficient FLR hypertrophy or disease progression (33,34).

ALPPS was introduced as an alternative to conventional PVE or PVL recent years. Initial experiences indicated that the complication rate and perioperative mortality

following ALPPS were superior to those following PVE and PVL; with ALPPS, the FLR can be rapidly increased in a short time (35-38), and the short waiting time from first intervention to removal of tumors can significantly decrease the incidence of tumor progression. ALPPS approach can also be used as a salvage method for patients with inadequate FLR hypertrophy after PVE or PVL (33). PVE, PVL cannot be applied, particularly in cases where the PV is occluded by the tumor (39).

Staged liver resection has been mostly applied in patients with colorectal liver metastases (CLM) since the first time been proposed. Many of the patients accepted preoperative chemotherapy, which may have impacts on the two-stage hepatectomy. But there is study shows that staged liver resection with preoperative chemotherapy almost have the same morbidity and survival benefits as one-stage hepatectomy (40).

Our results showed that ALPPS was the most efficient strategy in promoting the hypertrophy of FLR in the shortest time, and also had the highest resection completion rate among the three surgical strategies; hence, the risk of tumor growth in the interval from first intervention to tumor resection was decreased. Although the mortality and morbidity rate of ALPPS tended to be higher than PVE and PVL, this difference was not statistically significant. Therefore, our study supported previous findings that ALPPS increased the advanced liver cancer resection rate, but did not induce superior morbidity and mortality rates in comparison with PVE and PVL. PVE and PVL had similar efficacy and safety as assessed by many variables. Furthermore, with the progression of surgical techniques, totally laparoscopic ALPPS procedure was performed on cases with bilateral CLM even cirrhotic hepatocellular carcinoma (41-43). This procedure aimed to avoiding adhesions in the first surgery and reducing the rate of complication. Although only a few cases be reported by now, it's a promising change.

This NMA had some limitations. There were a small number of included studies, and the included studies were retrospective. Furthermore, due to lack of long-term follow-up data, the impact of PVE, PVL, and ALPPS on recurrence and survival cannot be evaluated. All of the included studies cannot avoid bias caused by the lack of a uniform standardized indication for staged liver resection. More randomized clinical trials should be performed to verify the efficacy and safety of PVE, PVL, and ALPPS.

Conclusions

ALPPS was significantly more efficient than PVE and PVL regarding promotion of FLR hypertrophy, resection completion, and waiting time. The three techniques were similar regarding morbidity and mortality.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.08.21). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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