A systematic review and meta-analysis of portal vein ligation versus portal vein embolization for elective liver resection

Sanjay Pandanaboyana, FRCS, MPhil,[a] Richard Bell, MBCHB, MRCS,[a] Ernest Hidalgo, PhD, FRCS,[a] Giles Toogood, MD, FRCS,[a] K. Raj Prasad, MS, FRCS,[a] Adam Bartlett, PhD, FRACS,[b] *and* **J. Peter Lodge, MD, FRCS,[a]** *Leeds, West Yorkshire, United Kingdom, and Auckland, New Zealand*

Introduction. *This meta-analysis aimed to review the percentage increase in future liver remnant (FLR) and perioperative outcomes after portal vein ligation (PVL) and portal vein embolization (PVE) before liver resection.*

Methods. *An electronic search was performed of the MEDLINE, EMBASE, and PubMed databases using both subject headings (MeSH) and truncated word searches to identify all articles published that related to this topic. Pooled risk ratios were calculated for categorical outcomes and mean differences for secondary continuous outcomes using the fixed-effects and random-effects models for meta-analysis.*

Results. *Seven studies involving 218 patients met the inclusion criteria. There was no difference in the increase in FLR between the 2 groups 39% (PVE) versus 27% (PVL; mean difference [MD] 6.04; 95% CI, −0.23, 12.32; Z = 1.89; P = .06). Similarly, there was no difference in the morbidity (risk ratio [RR], 1.08; 95% CI, 0.55, 2.09; Z = 0.21; P = .83) and mortality (RR, 0.87; 95% CI, 0.19, 3.92; Z = 0.18; P = .85) in the 2 groups after liver resection. While awaiting liver resection after PVL and PVE, no difference was noted in the number of patients developing disease progression (RR, 0.93; 95% CI, 0.52, 1.66; Z = 0.24; P = .81). In a subset analysis comparing FLR with PVE and PVL as part of the procedure called an associating liver partition with PVL for staged hepatectomy (ALPPS), there was a significant increase in FLR in favor of ALPPS (MD, −17.09; 95% CI, −32.78, −1.40; Z = 2.14; P = .03).*

Conclusion. *PVL and PVE result in comparable percentage increase in FLR with similar morbidity and mortality rates. The ALPPS procedure results in an improved percentage increase in FLR compared with PVE alone. (Surgery 2015;157:690-8.)*

From the St James Hospital,[a] Leeds, West Yorkshire, United Kingdom; and the Department of Surgery,[b] Auckland City Hospital, Auckland, New Zealand

Over the past decade, advances in surgery, anesthesia, radiology, and oncology have resulted in an extension of the criteria for resectability of liver neoplasms,[1-3] but a small volume of the future liver remnant (FLR) has been the Achilles heel limiting major hepatectomy.[4,5] Several strategies have evolved over the last few years to achieve an adequate FLR. Portal vein embolization (PVE) is an effective strategy for inducing hypertrophy of the FLR and, therefore, increasing the safety of extended hepatectomy; however, a small fraction of patients do not achieve an adequate FLR after PVE.[6,7] In addition, there is some evidence to suggest that PVE leads to interval tumor progression.[8-11] Alternative methods to increase the FLR include portal vein ligation (PVL),[12] 2-stage hepatectomy,[13] and the associating liver partition with PVL for staged hepatectomy (ALPPS) procedure. Some studies have shown PVL to be less efficient than PVE[14] owing to intrahepatic portoportal collaterals, whereas others have shown a comparable increase in FLR.[15] In addition, PVL involves operative ligation of the portal vein, thereby incurring the risks of the operative procedure. The recently introduced ALPPS procedure has been used as an additional strategy to induce a rapid increase in FLR volume, but ALPPS seems to be associated with increased surgical morbidity.[16]

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Reprint requests: Sanjay Pandanaboyana, FRCS, MPhil, Consultant HPB and Transplant Surgeon, Surgical Offices, Level 7, Support Building, Auckland City Hospital, Grafton, Auckland, New Zealand, 1010. E-mail: sanjay.pandanaboyana@gmail.com.

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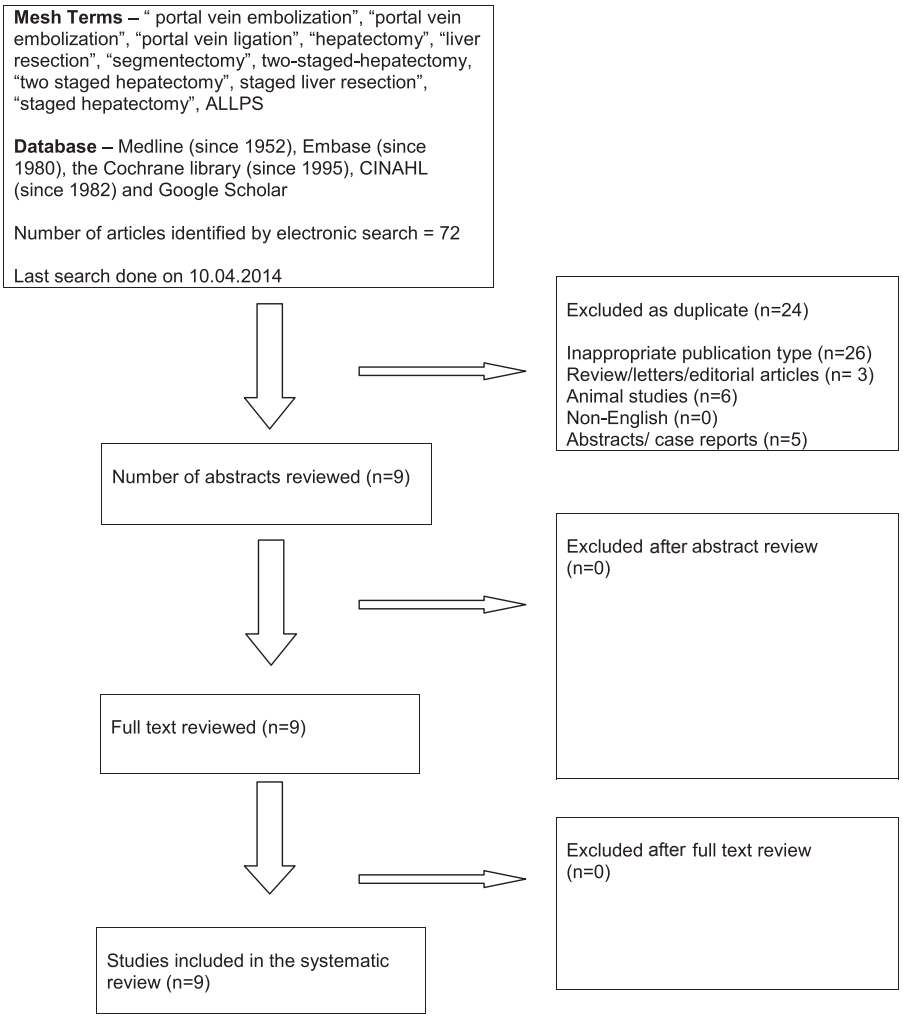

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. *ALPPS*, Associating liver partition with portal vein ligation for staged hepatectomy.

The purpose of this systematic review and meta-analysis was to compare PVL and PVE to assess the percentage increases in FLR, morbidity, mortality, and tumor progression with the 2 techniques. In addition, a subgroup analysis was performed to assess the percentage increase in FLR after PVE or ALPPS procedure.

METHODS

Randomized and case-controlled studies, irrespective of language, country of origin, hospital, blinding, sample size, or publication status, that compared the use of PVL and PVE for elective liver resection were included in this review. The Cochrane Colorectal Cancer Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials in the Cochrane Library, MEDLINE, Embase, and Science Citation Index Expanded were searched for articles published up to January 2014 using the medical subject headings (MeSH) terms portal vein ligation, PVE, staged hepatectomy, staged liver resection, liver resection, and ALPPS procedure. Equivalent free-text search terms, such as "portal vein ligation" and "portal vein embolization" were used in combination with "liver resection" and "hepatectomy." The references from the included studies were searched to identify additional studies comparing the 2 techniques (Fig 1).

All patients who underwent liver resection for both benign and malignant conditions in both normal and diseased (cirrhotic) livers were included. Inclusion criteria for searching were studies evaluating the use of use of PVE and PVL for elective liver resection.

Types of outcome measures. The primary outcome measure was percentage increase in FLR after PVE and PVL. Secondary outcome

measures were overall morbidity, mortality after liver resection, postoperative liver failure, duration of hospital stay, number of patients with disease progression after PVE/PVL, complications after PVE/PVL, and time from PVE/PVL to hepatectomy.

Data extraction and quality assessment. Studies were identified, and data were extracted by 2 authors (S.P., R.B.) independently. The accuracy of the extracted data was adjudicated further by a third author (E.H.).

Statistical analysis. Statistical analysis was performed using Review Manager Version 5.2 software (Cochrane Collaboration). The risk ratio (RR) with 95% CI was calculated for binary data, and the mean difference with 95% CI for continuous variables. When median and range were reported instead of mean and variance, their mean and variance were calculated based on the methods described by Hozo et al.[17] Random and fixed-effects models were used to calculate the combined outcomes of both binary and continuous data.[18,19] In cases of heterogeneity, only the results of the random-effects model were reported. Heterogeneity was explored using the Chi-square test, with significance set at $P < .05$. Low heterogeneity was defined as an I^2 value of ≤33%.[20] If the standard deviation was not available, it was calculated according to the guidelines of the Cochrane Collaboration.[21] This process involved assumptions that both groups had the same variance, which may not have been true, and variance was estimated either from the range or from the P value. Forest plots were used for graphic display of the results. Quality assessment of the included studies was bases on Newcastle–Ottawa scale.[22]

RESULTS

The strategies of the literature search and the selection of studies are summarized in Fig 1. Nine studies were included in the meta-analysis. Seven studies comparing PVE and PVL and 2 studies comparing PVE with ALPPS procedure met the inclusion criteria.[8,14,15,23-28] All studies were retrospective. The 7 studies involved 218 patients, of whom 89 were in the PVL group and 129 in the PVE group. The quality and characteristics of the included studies are summarized in the Table. Pooled data were analyzed by combining the results of the 7 studies. A subset analysis was also performed looking at 2 studies comparing PVE with ALPPS these compared 159 patients in the PVE group and 32 in the ALPPS group.[8,28]

Primary outcome measure. *Percentage increase in FLR.* Three studies were included in the analysis. There was no heterogeneity amongst the included studies (Chi-square = 2.26, df = 2; $P = .32$; $I^2 = 11\%$). The mean increase in FLR in the PVE group was 39% compared with 27% in the PVL group. In a fixed effects model, there was no difference in the percentage change in FLR between PVL and PVE (mean difference [MD], 6.04; 95% CI, −0.23, 12.32; $Z = 1.89$; $P = .06$; Fig 2).

Secondary outcome measure. *Time from PVE/PVL to hepatectomy.* Four studies were included in the analysis. There was heterogeneity amongst the included studies ($Tau^2 = 135.11$; df = 3; $P = .004$; $I^2 = 77\%$). The mean days to hepatectomy in the PVE group were 45 compared with 59 in the PVL group. In a random-effects model, the time from PVE and PVL to hepatectomy was similar, with a MD of −12.6 days (95% CI, −25.9, 0.68; $Z = 1.86$; $P = .06$).

Number of patients with disease progression after PVE and PVL. Four studies were included in the analysis. There was no heterogeneity amongst the included studies (Chi-square = 2.43, df = 3; $P = .49$; $I^2 = 0\%$). The disease progressed in 21% of patients in the PVE group compared with 22% in the PVL group. In a fixed-effects model, the number of patients with disease progression after PVE and PVL were similar (RR, 0.93; 95% CI, 0.52, 1.66; $Z = 0.24$; $P = .81$; Fig 3).

Operating time (resection). Two studies were included in the analysis. There was no heterogeneity amongst the included studies (Chi-square = 1.07; df = 1; $P = .30$; $I^2 = 6\%$). The mean operating time in the PVE group was 284 minutes compared with 309 minutes in the PVL group. The operating time for liver resection after PVL and PVE was similar with a mean difference of −28.76 (95% CI, −65.25, 7.72; $Z = 1.55$; $P = .12$).

Postoperative liver failure. Three studies were included in the analysis. There was no heterogeneity amongst the included studies (Chi-square = 0.65; df = 2; $P = .72$; $I^2 = 0\%$). Postoperative liver failure was seen in 15% of the PVE group and 13% in the PVL group. The postoperative liver failure rates were similar after PVL and PVE (RR, 1.12; 95% CI, 0.41, 3.06; $Z = 0.23$; $P = .82$; Fig 4).

Morbidity after resection. Five studies were included in the analysis. There was no heterogeneity amongst the included studies ($Tau^2 = 0.18$; Chi-square = 5.00; df = 3; $P = .17$; $I^2 = 40\%$). Morbidity was experienced in 29% of patients in the PVE group and 30% in the PVL group. In a random effects model, there was no difference

Table. Characteristics of the included studies comparing PVL and PVE

Reference	*Year*	*No. in each group*	*No. in each group proceeding to hepatectomy*	*With cirrhosis,* n *(%)*	*Segment 4 branches embolized?*	*Previous chemotherapy,* n *(%)*	*Decision for PVL made preoperatively*	*Simultaneous resection of tumor and PVL?*	*Quality Score (Newcastle - Ottawa)*
Aussilhou et al	2008	PVE: 18	18	0 (0)	No segment 4 branches embolized	18 (100)	PVE as metastases resectable in 1 stage	Enucleation of left sided metastases in 16 patients in PVL group	8
		PVL: 17	17	0 (0)		8 (47)	All decided preoperatively owing to disease extent ± resection of primary		
Broering et al	2002	PVE: 17	17	1 (6)	10 patients had partial or complete occlusion of segment 4 branches	4 (24)	9 decisions made intraoperatively; 7 had staging laparotomy; 1 failed percutaneous and minilaparotomy PVE	NS	9
		PVL: 17	17	1 (6)	5 patients had partial or complete occlusion of segment 4 branches	2 (12)			
Capussotti et al	2008	PVE: 31	24	0 (0)	NS	28 (90)	All decided preoperatively	1 patient underwent wedge resection of metastasis in segments 3 and 4 at the time of PVL	9
		PVL: 17	11	0 (0)		15 (88)			
Iida et al	2012	PVE: 9	9	2 (22)	NS	3 (33)	All preoperatively	2 patients underwent partial resection of the left hepatic lobe at the time of PVL	8
		PVL: 4	2	2 (50)		2 (50)			
Robles et al	2012	PVE: 18	18	0 (0)	3 cases had embolization of the segment 4 branches	15 (83)	All decided preoperatively	All the CRLM are removed from the left lobe followed by RFA	9
		PVL: 23	20	0 (0)	1 case underwent ligation of the segment 4 branches	17 (85)			
Van Lienden et al	2013	PVE: 14	13	5 (36)	NS	9 (64)	3 patients decided intraoperatively	2 patients underwent resection of metastases in the left hepatic lobe at the time of PVL	8
		PVL: 7	7	1 (14)	1 patient had segment 4 branches ligated	5 (71)			
Sturesson et al	2010	PVE: 22	22	NS	3 had segment 4 branches embolized	13 (59)	2 decided intraoperatively	No patients had left lobe resection	7
		PVL: 4	4	NS	NS	2 (50)			
Knoefel et al	2012	PVE: 15	15	NS	Yes	NS	1 intraoperatively	NS	9
		ALPPS: 7	7	NS	Yes	NS			
Shindoh et al	2013	PVE: 144	110	14 (10)	NS	94 (66)	NS	8 had concomitant partial left hepatectomy	9
		ALPPS: 25	25	3 (12)	NS	12 (48)			

ALPPS, Associating liver partition with portal vein ligation for staged hepatectomy; *CRLM*, Colorectal Liver Metastisis; *NS*, not significant; *PVE*, portal vein embolization; *PVL*, portal vein ligation; *RFA*, radiofrequency ablation.

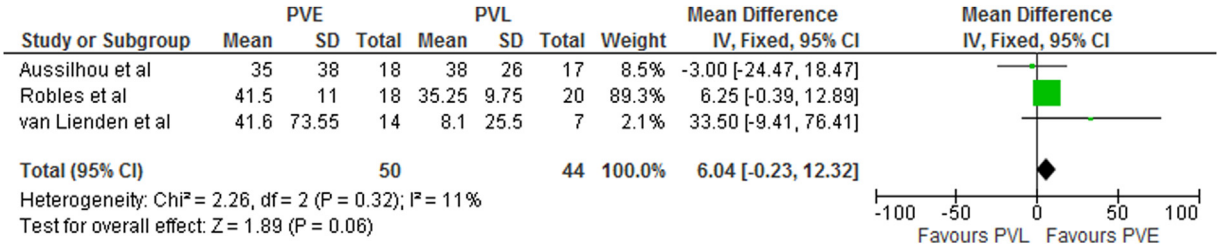

Fig 2. Forest plot comparing percentage increase in future liver remnant (FLR) with portal vein embolization (PVE) and portal vein ligation (PVL). A Mantel–Haenszel fixed effects model was used for meta-analysis. Mean differences are shown with 95% CIs. *SD*, Standard deviation.

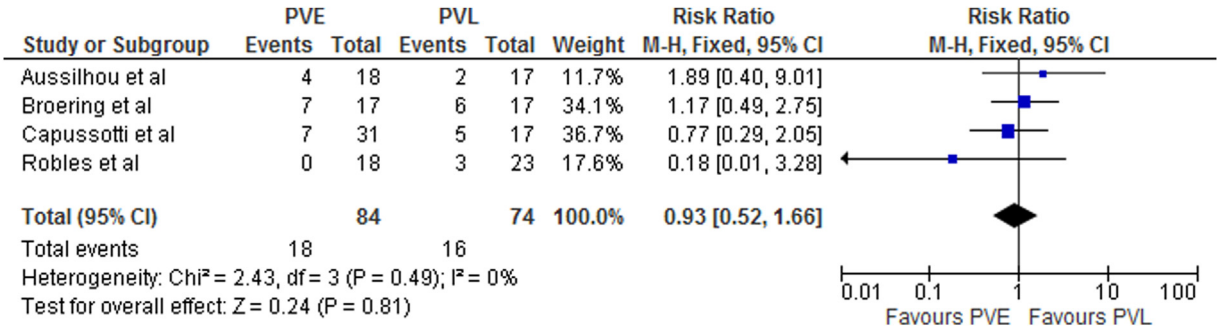

Fig 3. Forest plot showing number of patients with disease progression after portal vein embolization (PVE) or portal vein ligation (PVL) while awaiting resection. A Mantel–Haenszel fixed effects model was used for meta-analysis. Risk ratios are shown with 95% CIs.

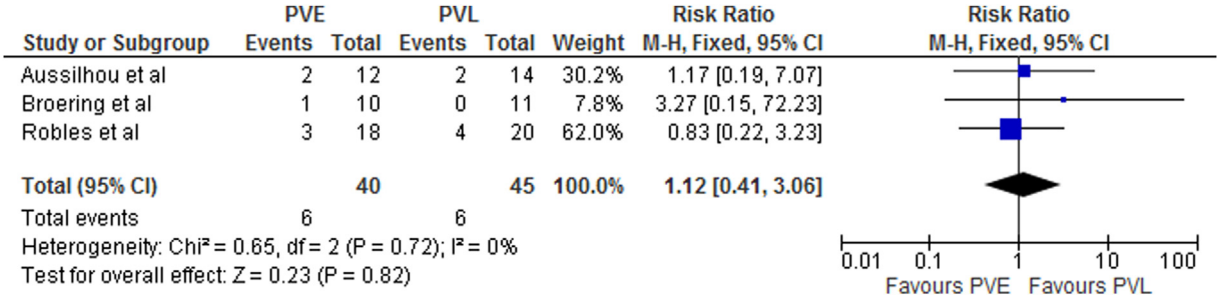

Fig 4. Forest plot showing the incidence of postoperative liver failure after hepatectomy. A Mantel–Haenszel fixed effects model was used for meta-analysis. Risk ratios are shown with 95% CIs.

between PVE and PVL (RR, 1.08; 95% CI, 0.55, 2.09; $Z = 0.21$; $P = .83$; Fig 5).

Mortality after resection. Four studies were included in the analysis. There was no heterogeneity amongst the included studies (Chi-square = 1.62; df = 2; $P = .44$; $I^2 = 0\%$). Mortality in the PVE group was a total of 3.0% compared with 3.6% in the PVL group. There was no difference between mortality rates after resection between the PVE or PVL group (RR, 0.87; 95% CI, 0.19, 3.92; $Z = 0.18$; $P = .85$).

Percentage increase in FLR comparing PVE with ALPPS. Two studies were included in the analysis. There was no heterogeneity amongst the included studies (Chi-square = 0.71, df = 1; $P = .40$; $I^2 = 0\%$). The mean percentage increase in FLR in the ALPPS group was 69% compared with 50% in the PVE group. ALPPS produced a greater percentage increase in FLR compared with PVE in a fixed effects model (MD, −17.09; 95% CI, −32.78, −1.40; $Z = 2.14$; $P = .03$; Fig 6).

DISCUSSION

Despite advances in the multimodality treatment of liver neoplasms and improvements in chemotherapeutic regimens, management of

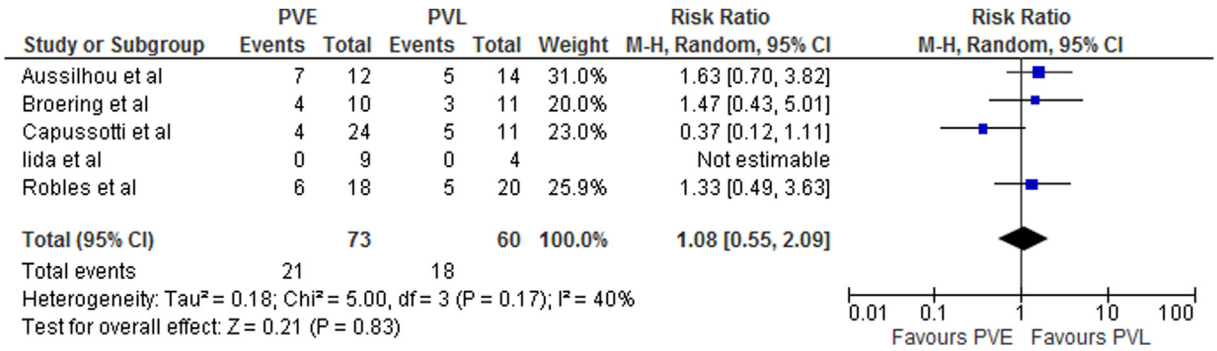

Fig 5. Forest plot showing morbidity after hepatectomy. A Mantel–Haenszel fixed effects model was used for meta-analysis. Risk ratios are shown with 95% CIs.

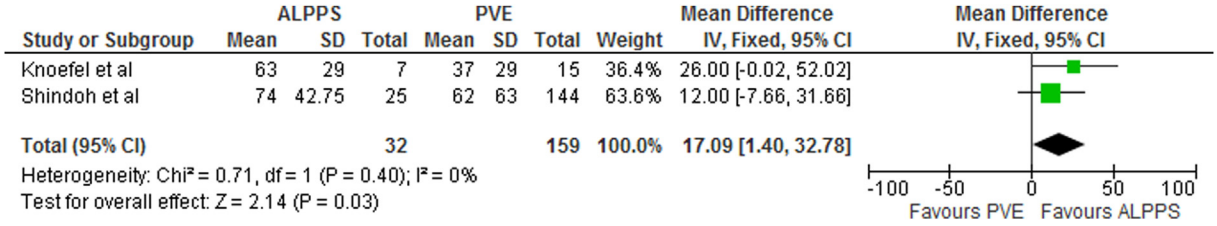

Fig 6. Forest plot comparing percentage increase in future liver remnant (FLR) between portal vein embolization (PVE) and associating liver partition with portal vein ligation for staged hepatectomy (ALPPS). A Mantel–Haenszel fixed effects model was used for meta-analysis. Mean differences are shown with 95% CIs.

patients with liver neoplasms remains challenging, especially those with potentially inadequate FLR.[14,29,30] Over the past few years, PVE and more recently PVL have been employed with varying success to achieve adequate FLR with some studies showing PVL to be less efficient[24,25,30,31] than PVE, whereas others showed comparable results.[15,23] This meta-analysis comparing periprocedural outcomes with PVL and PVE has shown that the mean percentage increase in FLR with PVE was 39% and for PVL 27%, but this difference was not significant. In addition, the morbidity and mortality rates after liver resection, time to hepatectomy, and disease progression are similar between the 2 techniques. In contrast, the ALPPS procedure seems to result in significant percentage increase in FLR compared with PVE (69% vs 50%; $P = .03$).

Obtaining adequate FLR is a prerequisite to minimizing postoperative liver failure after resection for CRLM, especially in patients with bilobar disease requiring staged hepatectomies. An FLR of 20–30% is considered adequate as the minimum safe FLR for patients, depending on whether or not they have had neoadjuvant chemotherapy.[32] It is debatable whether or not branches of segment 4 should be occluded during PVE and PVL, because the volume gain with embolization of segment 4 has been shown to be significantly greater.[33] Only 1 study in this series had patients in both the PVE and PVL groups where the portal vein branches of segment 4 were occluded, which showed a greater increase in FLR with PVE.[14] Dissection in the porta hepatis in cases with branches coming from left portal vein from segment 4, however, can make second stage liver resection difficult technically.[14] An angiographic embolization via a left portal vein entails risk of thrombosis precluding inadvertent reflux of embolic material to the FLR, thereby precluding further resection, albeit with a very low risk.[34-36] In addition, the data in the literature regarding the impact of PVE of segment 4 on the increase in FLR volume of segment 2 and 3 are conflicting. Capussotti et al[23] compared hypertrophy of segments 2 and 3 induced by PVE with and without extension to segment 4 in patients undergoing major hepatectomy and showed no difference in post-PVE volumes of segments 2 and 3 or the rate of increase; they recommended against embolization of segment 4. In contrast, Kishi et al[35] showed marked improvement in segment 2 and 3 hypertrophy compared with PVE alone of the right portal vein with a comparable complication rate with and without embolization of segment 4. It has been suggested that the conflicting outcomes

between these 2 studies may reflect a difference in technical experience and sample size. Nevertheless, in our unit it is a policy to consider embolization of segment 4 if there is inadequate FLR, and segment 4 is to be resected. Portoportal collateral vessels have been shown to affect the increase in FLR,[31] with patients undergoing PVL demonstrating a hepatoportal flow in the occluded lobe compromising the increase in FLR, which was less after PVE.[10] In some experimental models,[37] however, the increase of liver volume after PVL was not restrained by the formation of portoportal collaterals. The increased portal blood flow induced by portal vein occlusion seems to normalize in 2 weeks, with early peak of hepatocyte proliferation after portal occlusion, suggesting that liver hypertrophy is induced early after portal occlusion.[37-39] Then, later formation of portoportal collaterals would not impact on the induced liver hypertrophy. This process may explain the comparable increase in FLR with both techniques in the majority studies.

The decision to proceed with a PVL over PVE is often made preoperatively, especially in patients with neoplasms in the FLR (Table). The comparable increase in FLR with both techniques thereby provides the option to the surgeon to employ PVE in patients who do not require a staged resection by undertaking PVL for patients with bilateral neoplasms requiring a staged approach. PVL does not seem to affect the overall morbidity and mortality rates despite the need for 2 laparotomies compared with PVE. Recently, the ALPPS procedure has been used increasingly to induce faster hypertrophy than the conventional 2-stage hepatectomy. Although there were initial concerns of greater morbidity and mortality,[40] more recent data from the ALPPS registry has shown better outcomes in patients with Colorectal Liver Metastasis (CRLM).[41] In this meta-analysis, the ALPPS procedure seems to result in significant increase in FLR compared with PVE, and has been used as a rescue strategy in patients with insufficient FLR after PVE.[42] Shindoh et al[8] have shown recently a comparable increase in FLR with both the ALPPS procedure and PVE with embolization of segment 4 with the major difference between the 2 techniques being the timing of major hepatectomy. The present meta-analysis did not specifically look at the FLR increase with and without embolization of segment 4 owing to the lack of comparable data from the included studies.

Both PVE and PVL stimulate tumor growth within both embolized and nonembolized liver parenchyma.[43,44] In this review, all the included studies individually as well as the pooled analysis showed no difference in the number of patients with disease progression with each technique. PVL ligation, however, has the benefit of allowing resection of metastases in the FLR.

There are several limitations to our meta-analysis. All the included studies were retrospective in nature and included several indications for resection, although colorectal cancer was the predominant indication. It was not possible to assess the impact of chemotherapy on percentage increase in FLR after PVE and PVL owing to lack of comparable data, and included studies had a variable number of patients with and without chemotherapy (Table). There were no long-term data available to assess the impact of PVE and PVL on survival and recurrence, although PVE alone has not shown to have a detrimental effect on long-term outcomes.[45] Although the studies included in this review were all nonrandomized, the majority of studies were of high quality and provide comparable data for analyzing the majority of primary and secondary outcomes.

Patients with synchronous colorectal cancer and multiple, bilateral liver metastases requiring a 2-stage hepatectomy may be best suited for PVL, because contralateral metastases can be resected during the first operation. PVE should be considered in scenarios where contralateral neoplasms are not present and the only concern is FLR size and function. The recently introduced ALPPS procedure seems to induce greater hypertrophy of the FLR; however, the number of patients reported to date is small, and the ALPPS procedure seems to be associated with increased surgical morbidity. The present meta-analysis shows early comparable results with PVE and PVL.

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