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Review Article

Comparison of feasibility, safety and oncological efficacy of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) with conventional two-stage hepatectomy (TSH): a systemic review and meta-analysis

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Abstract: The clinical application of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) is controversial. Thus, we conducted a systemic review and meta-analysis of studies comparing ALPPS to conventional two-stage hepatectomy (TSH). This review aims at summarizing and assessing studies on this topic, and using meta-analysis to provide data support regarding the feasibility, safety and oncological efficacy of ALPPS by comparing with conventional TSH. Articles comparing ALPPS with TSH were identified by searching Medline, Embase and Cochrane library, using pre-specified criteria. Newcastle-Ottawa scale was used for quality evaluation. Chi's test was used for heterogeneity exploration among eligible studies. Random and fixed effect models were used to synthesize the outcomes regarding feasibility, safety and oncological efficacy. A total of 6 studies were eligible for systemic review and meta-analysis, involving 502 patients (118 in ALPPS group, 384 in TSH group). Patients underwent ALPPS experienced more overall morbidities and major morbidities (Clavien-Dindo ≥ IIIa) than patients received TSH did (58% vs. 42.8%, P = 0.04; and 23.4% vs. 15.3%, P = 0.002). R0/R1 resection rates were 86.4% and 71.5% in ALPPS and TSH groups, respectively (P = 0.014). One study reported similar 1-year recurrence free survival (RFS) in both groups. While another study including only patients with colorectal liver metastases observed similar 1-year overall survival in both groups, but higher 1-year RFS in TSH group. Our systemic review suggests that ALPPS induces faster future liver remnant (FLR) hypertrophy, larger FLR increase, and achieves higher completion rate of major hepatectomy than TSH does. Even though mortality rate is similar in these two surgical techniques, overall and major complication rates are higher in ALPPS group. The initial oncological efficacy of ALPPS seems to be encouraging. Yet, R0 status should be paid more attention to in future studies. Controlled trials with extreme caution and carefully selected patients are needed to further assess the advantages and disadvantages of ALPPS.

Keywords: Associating liver partition and portal vein ligation for staged hepatectomy, ALPPS, conventional two-stage hepatectomy, portal vein occlusion, systemic review, meta-analysis

Introduction

Hepatectomy provides crucial curative opportunities for patients with primary or secondary liver malignancies. However, its clinical application is limited by the volume and function of the patient's postoperative liver remnant. Normally, future liver remnant (FLR) volume is estimated before surgery to determine whether it is safe to perform hepatectomy, especially in cases where major hepatectomy is needed. Generally speaking, major hepatectomy is recommended when FLR volume is at least 20% of the total liver volume (TLV) in patients with a healthy liver, and at least 30% of the TLV in patients with a history of extensive chemotherapy, and at least 40% of the TLV in patients with compensated cirrhosis [1-3]. Post-hepatectomy liver failure (PHLF) is the major cause of morbidity and mortality after major hepatectomy [4], and patients with inadequate FLR are in high risk of PHLF [5-7]. In order to provide curative opportunities for patients with insufficient FLR and to improve the safety of major hepatectomy, several approaches were introduced to induce the hypertrophy of FLR.

The latest method proposed for inducing FLR hypertrophy is associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). It was created by chance in 2007 by Dr. Hans Schlitt [8] and first formally introduced as case series in 2012 by Schnitzbauer [9]. Before the innovation, conventional two-stage hepatectomy (TSH) with portal vein occlusion (such as percutaneous portal vein embolization, PVE or portal vein ligation, PVL) was considered standard therapy for patients with small FLR [10, 11]. In conventional TSH, portal vein occlusion is performed in the first stage to induce FLR hypertrophy followed by second-stage hepatectomy after a 2-8 weeks' interval. The major difference between ALPPS and conventional TSH is the extra in-situ split (ISS) of liver parenchyma in the first stage. ALPPS shows not only potential in inducing rapid FLR hypertrophy in a short time interval but also high successful rate of the second stage. However, high morbidity and mortality rates are also observed, raising debates on the advantages and disadvantages of ALPPS [9, 12, 13].

Since the introduction of ALPPS, there have been several studies comparing ALPPS with conventional TSH. However, most of them are not sufficiently powered to detect the differences between these two procedures in feasibility, morbidity, mortality as well as oncological efficacy due to small sample sizes. Hence, our systemic review aims at summarizing and assessing studies on this topic, and using meta-analysis to provide data support on the evaluation of feasibility, safety and oncological efficacy of ALPPS by comparing with conventional TSH.

Materials and methods

Search strategy

A systemic electronic literature search was performed using Medline, Embase and Cochrane library databases, basing on combinations of the following key terms: ALPPS, ALTPS, RALPP, two-stage hepatectomy, in-situ split, liver transection, and portal vein ligation. The search was limited to human and articles reported in English language since January 1st 2007. We set no restrictions regarding publication type or publication status. Detailed search strategy was provided online (see Text, Supplemental Content). The last search was performed on January 11th, 2016.

Study selection

Two researchers (YZ and ML) independently screened the title and abstract of the primary records identified by the electronic search. Duplicates were removed. Articles comparing ALPPS with conventional TSH were considered candidates for this systemic review. Full texts were reviewed for eligibility when necessary. Exclusion criteria were established as 1) articles unrelated to ALPPS or conventional TSH; 2) articles reported in non-English language; 3) animal experiments; 4) inappropriate article types, such as conference abstracts, comments, editorials, letters to the editor; 5) furthermore, articles based on the same patient population were carefully reviewed before the latest report or the one with highest quality was preserved. Group consensus was attained when disagreement existed.

Data extraction

All relevant texts, tables and figures of eligible articles were carefully reviewed for data extraction and an excel form was applied for managing data. Biases of the individual studies were categorized based on the study design. Outcomes of interest were categorized as follows: 1) article characteristics and patients' features such as: author, article type, year of publication, institute, number of patients, tumor type and age; 2) data items referring to feasibility: the degree of FLR hypertrophy, the time interval (days) between stages, the completion rate of stage 2. The degree of FLR hypertrophy is calculated by the following formula: (FLR before stage 1-FLR before stage 2) × (100%/FLR before stage 1); 3) outcomes reflecting safety: overall morbidity rate, major morbidity rate (major complication is defined as Clavien-Dindo classification grade IIIa and IIIb or higher), liver insufficiency rate after major hepatectomy and 90-day mortality rate; 4) outcomes indicating oncological efficacy: R0 resection rate, overall survival and disease-free survival.

Statistical analysis

The mean value difference with 95% confidence interval (CI) was calculated for continuous data, and the odds ratio (OR) with 95% CI for binary variables. When the study reported median and range instead of mean and standard deviation, the latter ones were calculated

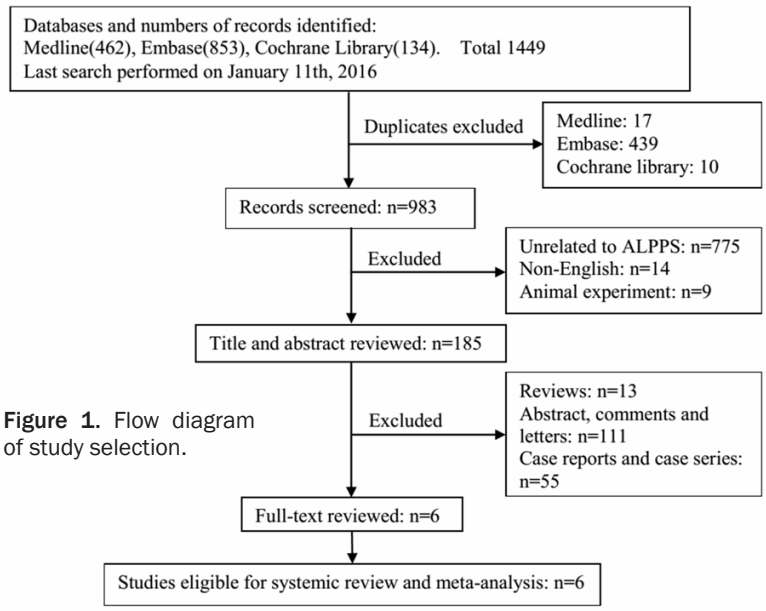

Figure 1. Flow diagram of study selection.

according to Hozo SP's formula [14]. Standard deviation was calculated based on the method described in Cochrane guidelines if needed. Chi's test was used to explore the heterogeneity among eligible studies. *P* value more than 0.05 and I^2 lower than 50% were defined as low heterogeneity. Random and fixed effect models were used to synthesize the outcomes. Random effect model was adopted in the setting of high heterogeneity. All other *P* values were two-sided and *P* values lower than 0.05 were considered statistically significant. Forest graphs were used to present the results. Newcastle-Ottawa scale was used for quality evaluation of eligible articles [15]. Statistical analysis was performed by STATA 14.0 (MP-Parallel Edition. Stata Corp.).

Results

Study selection and quality evaluation

Study selection process is described in **Figure 1**. The electronic literature search yielded 1449 articles, and six studies comparing ALPPS with conventional TSH were eligible for systemic review and meta-analysis [16-21]. These six studies involved 502 patients, of whom 118 and 384 patients underwent ALPPS and conventional TSH, respectively. Risk for bias was mainly determined by their retrospective nature. Half of the included studies were multi-institutional, however, most of them were based on small samples, which confined these studies to low Oxford evidence level with the highest one classified as IIIb.

Basic characteristics of the patients

The mean or median age of patients underwent ALPPS ranged from 55.9 to 68 years [16, 21], while that of patients underwent TSH ranged from 58 to 63 years [20, 21]. Colorectal liver metastases (CRLMs) were the most common indications in both groups. After excluding Knoefel's study for absence of relevant information, CRLM accounted for 68.5% (76/111) and 71.8% (265/369) of the patients in the ALPPS group and the TSH group, respectively (See **Table 1**).

Feasibility of ALPPS

Comparison of FLR hypertrophy and median interval between ALPPS and TSH: Heterogeneity existed among the included studies (Chi^2 = 18.95; d.f. = 5; P = 0.002; I^2 = 73.6%). The mean FLR hypertrophy rates were 74.8% and 46.5% in the ALPPS group and the TSH group, respectively. In a random effect model, the pooled mean difference of FLR hypertrophy rate between ALPPS group and TSH group was 31.1% (95% CI 17.4-44.7%, P = 0.00) (See **Figure 2**). Additionally, the pooled mean difference remained statistically significant after excluding Croome's data from the analysis (point estimated as 24.2%, 95% CI 15.3-33.0%, P = 0.00).

The second stage was performed in a median of 6-11 days and 31-39.9 days in ALPPS group and TSH group, respectively. ALPPS induced higher FLR increase in a shorter time than TSH did, the speed of FLR hypertrophy was obviously faster in ALPPS group than that in TSH group.

Comparison of completion rate of both stages between ALPPS and TSH: There was no heterogeneity among the included studies (Chi^2 = 3.99; d.f. = 5; P = 0.55; I^2 = 0.0%). One hundred percent and 76.6% of the patients in the ALPPS

Table 1. Basic characteristics of eligible studies and data extracted

Characteristics	Knoefel et al. (2013)		Shindoh et al. (2013)		Croome et al. (2014)		Schadde et al. (2014)		Ratti et al. (2015)		Tanaka et al. (2015)	
	ALPPS	TSH	ALPPS	TSH	ALPPS	TSH	ALPPS	TSH	ALPPS	TSH	ALPPS	TSH
Number of cases, Stage 1	7	15	25	144	15	53	48	83	12	36	11	53
Stage 2	7	12	25	104	15	42	48	54	12	34	11	48
Tumor type, n (%)	CRLM, 10 (45)		CRLM, 14 (56)	CRLM, 91 (63)	CRLM, 14 (93)	CRLM, 37 (70)	CRLM, 26 (54)	CRLM, 48 (58)	CRLM, 12 (100)	CRLM, 36 (100)	CRLM, 10 (91)	CRLM, 53 (100)
	HCC, 1		HCC, 3	HCC, 14	GISTLM, 1	HCC, 2	HCC, 3	HCC, 7			NETLM, 1	
	IHCC, 5		IHCC, 2	IHCC, 4		IHCC, 3	IHCC, 8	IHCC, 5				
	PHCC, 3		PHCC, 2	PHCC, 8		PHCC, 3	PHCC, 2	PHCC, 11				
	GBCA, 2		GBCA, 1	GBCA, 3		GBCA, 1	NCRLM, 7	NCRLM, 12				
	NETLM, 1		Others, 3	NETLM, 14		NCRLM, 7						
				Others, 10								
Age, y	67 (55-81)		63 (32-75)	58 (33-79)	55.9 (12.1)	59.5 (11.3)	57 (48.5-65)	61 (54-69)	59 (51-79)	59 (42-66)	68 (50-78)	63 (35-76)
FLR hypertrophy, %	63 (29)	37 (29)	74 (21-192)	62 (0.3-379)	84.3 (7.8)	36 (27.2)	77.4 (IQR 52.8-101.7)	34.1 (IQR 17.4-55.7)	47 (38-133)	41 (29-79)	54 (18)	40 (43)
Time interval, days	6 (4-8)	35 (13-98)	9 (5-28)	34 (12-385)[a]	7.8 (1.1)[a]	39.9 (14.2)[a]	NA	NA	11 (7-12)	31 (25-39)	1 week	4 weeks
Completion of stage 2, %	100	80	100	72.2	100	79	100	65	100	94.4	100	88.9
R0, %	NA	NA	96	NA	NA	NA	83	66	NA	NA	11[b]	80[b]
Overall morbidity, %	71.4	40	64	57.7	NA	NA	43.8	25.3	58.3	11.1	18	33
							72.9	74.1	83.3	38.2	46	44
Morbidity ≥ IIIa, %	NA	NA	40	33	NA	NA	14.6[c]	2.4[c]	0	2.8	9	8
							27.1[c]	14.8[c]	41.7	17.6	27	17
Liver insufficiency, %	0	0	NA	TB > 7 mg/dl	50-50	50-50	50-50	50-50	ISGLS 0	ISGLS 5.9	ISGLS	ISGLS
				12.5	13	29	13	9			18	2
											36	33
90-day mortality, %	NA	NA	12	8.6	0	5	15	6	8.3	2.9	9	2
Follow-up, median (range)	NA	NA	180 (50-776) d	43 (1-127) m	NA	NA	NA	NA	12 (6-18) m	37 (8-72) m	NA	NA
1-year RFS, %	NA	NA	NA	NA	NA	NA	46	48	67	80	NA	NA
1-year OS, %	NA	NA	NA	86%	NA	NA	NA	NA	92	94	NA	NA
Study characteristics												
Article type	Single center, retrospective		Single center, retrospective		Multi-center, retrospective		Multi-center, retrospective		Multi-center, retrospective		Single center, retrospective	
Oxford evidence level	IV		IV		IV		IIIb		IV		IV	

Notes: NA, not available; ALPPS, associating liver partition and portal vein ligation for staged hepatectomy; TSH, two-staged hepatectomy; CRLM, colorectal liver metastases; HCC, hepatocellular carcinoma; IHCC, intrahepatic cholangiocarcinoma; PHCC, perihilar cholangiocarcinoma; GBCA, gallbladder cancer; NET, neuroendocrine tumor; GIST, gastrointestinal stromal tumor; NCRLM, non-colorectal liver metastasis; IQR, Inter Quartile Range); Continuous variables were described as mean (SD) or median (range) and binary data were presented as percentage. [a]Time interval between two stages were unavailable, thus time of the last CT performed before stage 2 were extracted. [b]The article reported the number of patients achieved R0/R1 resection. [c]Only morbidity ≥ IIIb was reported.

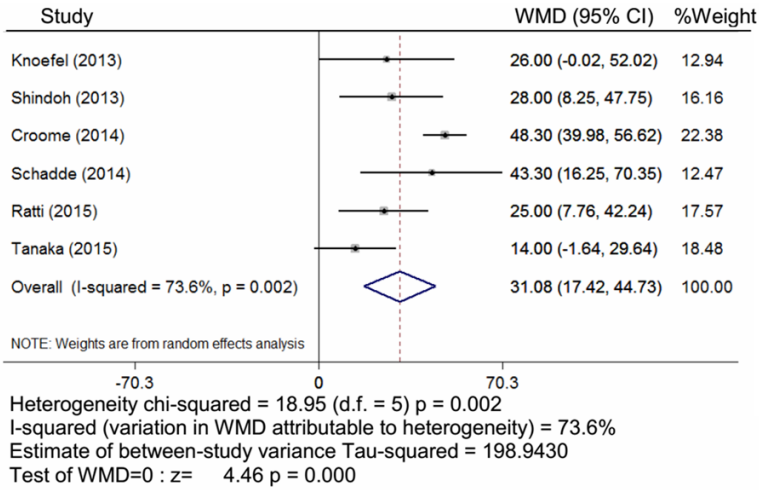

Figure 2. Comparison of FLR hypertrophy between ALPPS and TSH.

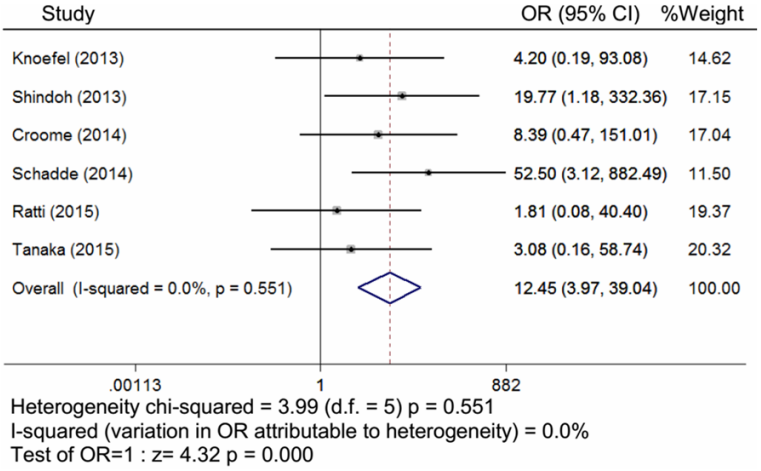

Figure 3. Comparison of completion rate of both stages between ALPPS and TSH.

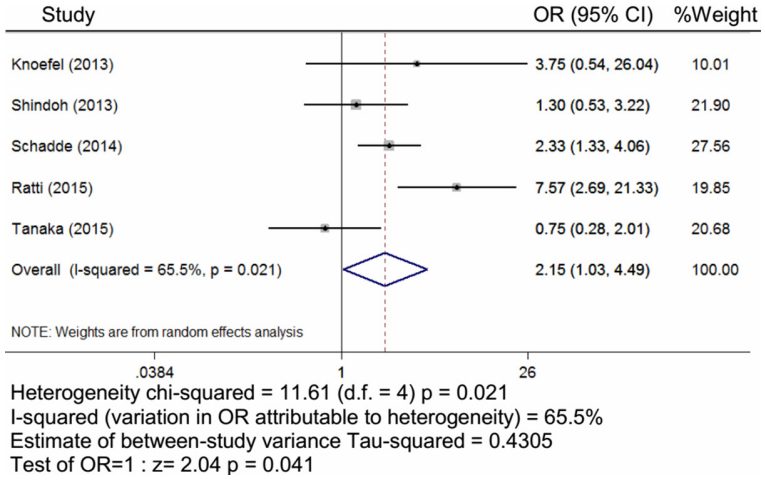

Figure 4. Comparison of overall morbidity between ALPPS and TSH.

group and the TSH group completed the second stage. In a fixed effect model, there was statistical difference between the completion rate of both stages between ALPPS and TSH (Z = 4.32, P = 0.00) (See **Figure 3**).

Safety of ALPPS

Comparison of overall morbidity between ALPPS and TSH: There was heterogeneity among the included studies (Chi^2 = 11.61; d.f. = 4; P = 0.02; I^2 = 65.5%). Fifty-eight percent of patients in the ALPPS group and 42.8% in the TSH group experienced morbidities. In a random effect model, there was statistical difference (Z = 2.04, P = 0.04) (See **Figure 4**).

Comparison of major morbidity between ALPPS and TSH: No heterogeneity was showed among the included studies (Chi^2 = 2.28; d.f. = 3; P = 0.52; I^2 = 0.0%). The morbidities ≥ IIIa were experienced in 23.4% of the patients in ALPPS group and 15.3% in TSH group. In a fixed effect model, there was significant difference (Z = 3.12, P = 0.002) (See **Figure 5**).

Comparison of liver insufficiency rate between ALPPS and TSH: There was no heterogeneity among the included studies (Chi^2 = 1.76; d.f. = 3; P = 0.62; I^2 = 0.0%). Fourteen percent of patients in ALPPS group and 20% in TSH group developed liver insuffiency after major hepatectomy. In a fixed effect model, no statistical difference was found (Z = 0.34, 95% CI, P = 0.73) (See **Figure 6**).

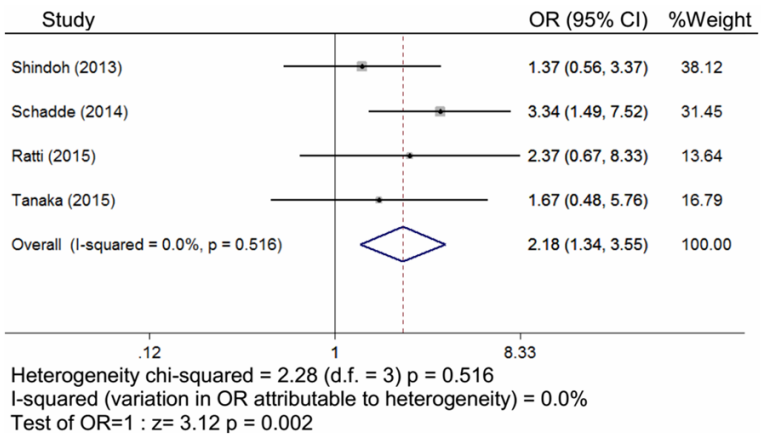

Figure 5. Comparison of major morbidity between ALPPS and TSH.

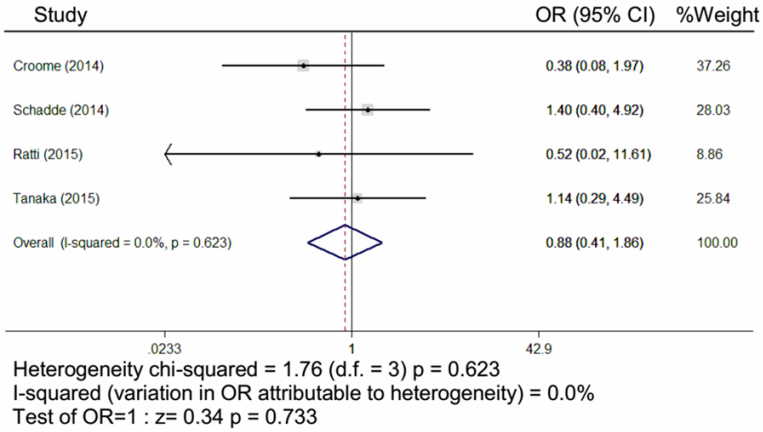

Figure 6. Comparison of liver insufficiency rate between ALPPS and TSH.

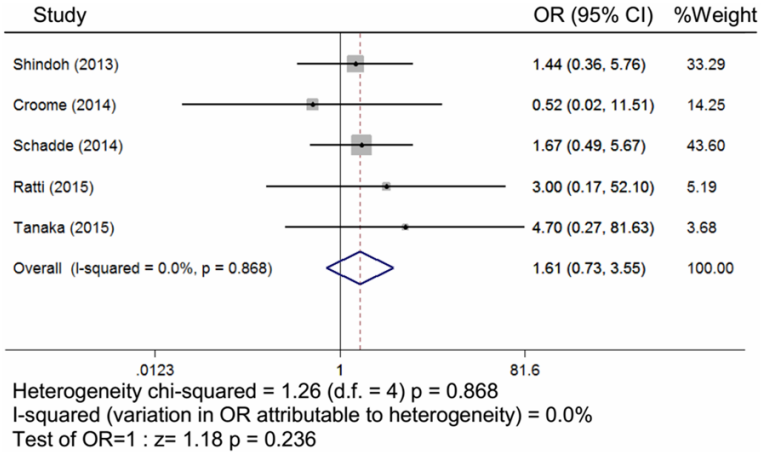

Figure 7. Comparison of 90-day mortality between ALPPS and TSH.

Comparison of 90-day mortality between ALPPS and TSH: No heterogeneity was revealed among the included studies (Chi^2 = 1.26; d.f. = 4; P = 0.87; I^2 = 0.0%). The mean 90-day mortality were 10.8% in ALPPS group and 6.4% in TSH group. In a fixed effect model, no statistical difference was found. (Z = 1.18, 95% CI, P = 0.24) (See **Figure 7**).

Oncological efficacy of ALPPS

Survival data and comparison of R0 resection rate between ALPPS and TSH: Schadde et al. [19] observed similar 1-year recurrence free survival (RFS) in ALPPS group and TSH group (46% and 48%, respectively). While in Ratti et al.'s study which included only CRLM patients, the 1-year RFS was higher in the TSH group (80%) than that in the ALPPS group (68%), however, similar 1-year overall survival (OS) was reported (ALPPS 92%, and TSH 94%) [18].

Only two studies reported the R0 status. There was no heterogeneity between the two studies (Chi^2 = 0.33; d.f. = 1; P = 0.57; I^2 = 0.0%). Approximately 86.4% of the patients in the ALPPS group achieved R0/R1 resection, while only 71.5% in the TSH group achieved R0/R1 resection. In a fixed effect model, there was statistical difference. (Z = 2.45, 95% CI, P = 0.014) (See **Figure 8**).

Discussion

As a newly developed procedure, ALPPS is still in its early exploration phase. Whether the pros outweigh the cons remains controversial. And as time went by, early survival data became available, which may help further evaluate this novel procedure. Therefore, we performed a systemic review and meta-analysis of studies comparing ALPPS with

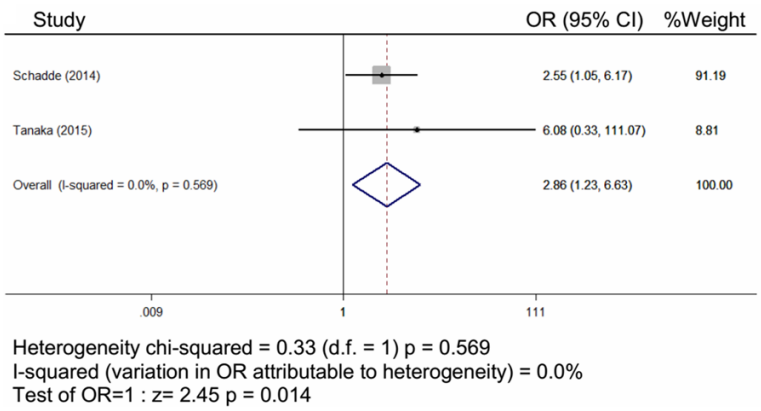

Figure 8. Comparison of R0 resection rate between ALPPS and TSH.

conventional TSH to summarize and synthesize the existing evidence and to provide data support on feasibility, safety and oncological efficacy of ALPPS.

In general, the level of evidence supporting or opposing ALPPS against conventional TSH remains low (with the highest one of IIIb). Hence, solid evidence can't be established. Most of the comparative studies are retrospective and single-centered, causing biases in our systemic review. Small sample sizes undermine their power in detecting differences in feasibility, morbidity, mortality as well as oncological efficacy between these two techniques.

Our systemic review confirms faster FLR hypertrophy and higher completion rate (100% vs. 76.6%) of ALPPS than those of conventional TSH, which is in consistent with previous studies [9, 22]. The mechanism remains unknown. Researchers suggest that the additional in-situ split (ISS) of liver parenchyma may be responsible for the rapid hypertrophy, because ISS prevents formation of vascular collaterals to liver segments with occluded portal flow [23, 24]. Additionally, animal experiment implied that circulating factors played an important role in mediating accelerated liver regeneration [25]. Rapid hypertrophy in short time interval assures the approximately 100% completion rate of ALPPS [22, 26]. Generally, it takes only 1 week for FLR to grow sufficiently for subsequent hepatectomy in ALPPS [27] but at least 2-8 weeks in TSH [28, 29]. However, the longer we wait, the more likely that the patients may fail the second stage due to tumor progression. According to a systemic review of TSH including a total of 459 patients, the completion rate of the second stage was 77% and disease progression accounted for 88% of the patients who failed the second stage [30]. Some researchers argued that the patients who failed the second stage because of disease progression might have worse oncological outcomes even after successful liver resections [20].

Several studies suggested similar degree of FLR hypertrophy between ALPPS and TSH [18, 20], however, our meta-analysis suggests that ALPPS has higher ability in inducing FLR hypertrophy than conventional TSH does (74.8% vs. 46.5%), and this difference remains significant after excluding Croome's study in which the conventional TSH group has a relatively larger standard FLR before surgery. And standard FLR is reported to be negatively correlated to FLR hypertrophy degree [31]. It is noteworthy that Tanaka et al. observed smaller functional FLR increase in ALPPS than that in TSH in spite of greater liver growth in ALPPS group [21], which suggests an asynchronous growth in function and volume of FLR. Even though the incidence of PHLF shows no significant difference after ALPPS and TSH, close attention still needs to be paid to functional liver growth of ALPPS in order to help determine the proper time of performing the second stage and to avoid PHLF.

Ever since the first case series of ALPPS was reported, concerns about high morbidity and mortality of ALPPS have always accompanied its possible advantages. Our meta-analysis shows higher overall and major morbidity rate in ALPPS group than those in TSH group (58%, 23.4% vs. 42.8%, 15.3%). However, mortality rates are not significantly different in these two groups. The largest case series reported by the ALPPS registry involved 202 patients, 28% of the patients experienced severe complications (≥ IIIb) and the 90-day mortality was 9%, which are in accordance with our results. Other large case series reported various overall and major morbidity rates ranging from 53.0 to 80.5% and 40.3 to 59%, respectively [9, 33, 34]. And the mortality rate varied from 6.6% to

12.9% [9, 12, 32, 33]. While in a systemic review which included 459 patients underwent TSH with initially irresectable CRLM patients, the morbidity and mortality rates were 40% and 3%, respectively [30]. Efforts were made to increase the safety of ALPPS. It was suggested that patients older than 60 years, non-CRLM, blood transfusions and stage one duration longer than 300 minutes were independent risk factors for severe complications [22]. Hernandez-Alejandro et al. reported considerable overall morbidity rate of 36% and severe morbidity rate of 14% with 0 mortality [34], suggesting that with strict selection of patients, morbidity and mortality rates of ALPPS can be comparable to TSH. International multicentric randomized controlled trial of ALPPS and conventional TSH in CRLM patients is underway (KEK-ZH Nr.: 2015-0024, Local swiss ethics committee/IRB number). The most appropriate indication for ALPPS is still needed to be confirmed. In addition, multiple modifications such as partial ALPPS [32], Tourniquet modification [35], laparoscopic ALPPS [36], robotic ALPPS and associating liver radiofrequency and portal vein ligation for staged hepatectomy (RALPP) [37] were developed, which may provide benefits in increasing safety of ALPPS by following minimal invasive surgery principle.

Regarding to its oncological efficacy, ALPPS provides higher chance at curability and shows similar 1-year RFS as well as OS when comparing to TSH. However, only two comparative studies reported R0 status and early survival data, as a result qualitative synthesis was used. Other studies reported around nine in ten patients with mixed indications undergoing ALPPS achieved R0 resection [22, 32], and the 1, 2-year RFS and OS of ALPPS were 60%, 42% and 73%, 59%, respectively. While for patients undergoing TSH, R0 was 75%, 3-year RFS and OS were 20%, 58%, respectively [30].

Conclusion

Our meta-analysis suggests that ALPPS induces faster FLR hypertrophy, larger FLR increase, and achieves higher completion rate of major hepatectomy than TSH does. Even though mortality rate is similar in these two surgical techniques, overall and major complication rates are higher in ALPPS group. The initial oncological efficacy of ALPPS seems to be encouraging. Yet, R0 status should be paid more attention to in future studies. Controlled trials with extreme caution and carefully selected patients are needed to further assess the advantages and disadvantages of ALPPS.

Disclosure of conflict of interest

None.

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References

[1] Abdalla EK, Adam R, Bilchik AJ, Jaeck D, Vauthey JN and Mahvi D. Improving resectability of hepatic colorectal metastases: expert consensus statement. Ann Surg Oncol 2006; 13: 1271-1280.

[2] Ribero D, Chun YS and Vauthey JN. Standardized liver volumetry for portal vein embolization. Semin Intervent Radiol 2008; 25: 104-109.

[3] Pulitano C, Crawford M, Joseph D, Aldrighetti L and Sandroussi C. Preoperative assessment of postoperative liver function: the importance of residual liver volume. J Surg Oncol 2014; 110: 445-450.

[4] Ren Z, Xu Y and Zhu S. Indocyanine green retention test avoiding liver failure after hepatectomy for hepatolithiasis. Hepatogastroenterology 2012; 59: 782-784.

[5] Ferrero A, Vigano L, Polastri R, Muratore A, Eminefendic H, Regge D and Capussotti L. Postoperative liver dysfunction and future remnant liver: where is the limit? Results of a prospective study. World J Surg 2007; 31: 1643-1651.

[6] Schindl MJ, Redhead DN, Fearon KC, Garden OJ, Wigmore SJ; Edinburgh Liver Surgery and Transplantation Experimental Research Group (eLISTER). The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. Gut 2005; 54: 289-296.

[7] Kishi Y, Abdalla EK, Chun YS, Zorzi D, Madoff DC, Wallace MJ, Curley SA and Vauthey JN. Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. Ann Surg 2009; 250: 540-548.

[8] de Santibanes E and Clavien PA. Playing Play-Doh to prevent postoperative liver failure: the

"ALPPS" approach. Ann Surg 2012; 255: 415-417.

[9] Schnitzbauer AA, Lang SA, Goessmann H, Nadalin S, Baumgart J, Farkas SA, Fichtner-Feigl S, Lorf T, Goralcyk A, Horbelt R, Kroemer A, Loss M, Rummele P, Scherer MN, Padberg W, Konigsrainer A, Lang H, Obed A and Schlitt HJ. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg 2012; 255: 405-414.

[10] Abdalla EK, Barnett CC, Doherty D, Curley SA and Vauthey JN. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. Arch Surg 2002; 137: 675-680; discussion 680-671.

[11] Pamecha V, Nedjat-Shokouhi B, Gurusamy K, Glantzounis GK, Sharma D and Davidson BR. Prospective evaluation of two-stage hepatectomy combined with selective portal vein embolisation and systemic chemotherapy for patients with unresectable bilobar colorectal liver metastases. Dig Surg 2008; 25: 387-393.

[12] Torres OJ, Fernandes Ede S, Oliveira CV, Lima CX, Waechter FL, Moraes-Junior JM, Linhares MM, Pinto RD, Herman P and Machado MA. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): the Brazilian experience. Arq Bras Cir Dig 2013; 26: 40-43.

[13] Nadalin S, Capobianco I, Li J, Girotti P, Konigsrainer I and Konigsrainer A. Indications and limits for associating liver partition and portal vein ligation for staged hepatectomy (ALPPS). Lessons Learned from 15 cases at a single centre. Z Gastroenterol 2014; 52: 35-42.

[14] Hozo SP, Djulbegovic B and Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5: 13.

[15] Martin B, Paesmans M, Berghmans T, Branle F, Ghisdal L, Mascaux C, Meert AP, Steels E, Vallot F, Verdebout JM, Lafitte JJ and Sculier JP. Role of Bcl-2 as a prognostic factor for survival in lung cancer: a systematic review of the literature with meta-analysis. Br J Cancer 2003; 89: 55-64.

[16] Croome KP, Hernandez-Alejandro R, Parker M, Heimbach J, Rosen C and Nagorney DM. Is the liver kinetic growth rate in ALPPS unprecedented when compared with PVE and living donor liver transplant? A multicentre analysis. HPB 2015; 17: 477-484.

[17] Knoefel WT, Gabor I, Rehders A, Alexander A, Krausch M, Schulte am Esch J, Furst G and Topp SA. In situ liver transection with portal vein ligation for rapid growth of the future liver remnant in two-stage liver resection. Br J Surg 2013; 100: 388-394.

[18] Ratti F, Schadde E, Masetti M, Massani M, Zanello M, Serenari M, Cipriani F, Bonariol L, Bassi N, Aldrighetti L and Jovine E. Strategies to Increase the Resectability of Patients with Colorectal Liver Metastases: A Multicenter Case-Match Analysis of ALPPS and Conventional Two-Stage Hepatectomy. Ann Surg Oncol 2015; 22: 1933-1942.

[19] Schadde E, Ardiles V, Slankamenac K, Tschuor C, Sergeant G, Amacker N, Baumgart J, Croome K, Hernandez-Alejandro R, Lang H, de Santibanes E and Clavien PA. ALPPS offers a better chance of complete resection in patients with primarily unresectable liver tumors compared with conventional-staged hepatectomies: results of a multicenter analysis. World J Surg 2014; 38: 1510-1519.

[20] Shindoh J, Vauthey JN, Zimmitti G, Curley SA, Huang SY, Mahvash A, Gupta S, Wallace MJ and Aloia TA. Analysis of the efficacy of portal vein embolization for patients with extensive liver malignancy and very low future liver remnant volume, including a comparison with the associating liver partition with portal vein ligation for staged hepatectomy approach. J Am Coll Surg 2013; 217: 126-133; discussion 133-124.

[21] Tanaka K, Matsuo K, Murakami T, Kawaguchi D, Hiroshima Y, Koda K, Endo I, Ichikawa Y, Taguri M and Tanabe M. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): short-term outcome, functional changes in the future liver remnant, and tumor growth activity. Eur J Surg Oncol 2015; 41: 506-512.

[22] Schadde E, Ardiles V, Robles-Campos R, Malago M, Machado M, Hernandez-Alejandro R, Soubrane O, Schnitzbauer AA, Raptis D, Tschuor C, Petrowsky H, De Santibanes E, Clavien PA; ALPPS Registry Group. Early survival and safety of ALPPS: first report of the International ALPPS Registry. Ann Surg 2014; 260: 829-836; discussion 836-828.

[23] Tanaka K and Endo I. ALPPS: Short-term Outcome and Functional Changes in the Future Liver Remnant. Ann Surg 2015; 262: e88-89.

[24] Gall TM, Sodergren MH, Frampton AE, Fan R, Spalding DR, Habib NA, Pai M, Jackson JE, Tait P and Jiao LR. Radio-frequency-assisted Liver Partition with Portal vein ligation (RALPP) for liver regeneration. Ann Surg 2015; 261: e45-46.

[25] Schlegel A, Lesurtel M, Melloul E, Limani P, Tschuor C, Graf R, Humar B and Clavien PA. ALPPS: from human to mice highlighting accelerated and novel mechanisms of liver regen-

eration. Ann Surg 2014; 260: 839-846; discussion 846-837.
[26] Schadde E, Schnitzbauer AA, Tschuor C, Raptis DA, Bechstein WO and Clavien PA. Systematic review and meta-analysis of feasibility, safety, and efficacy of a novel procedure: associating liver partition and portal vein ligation for staged hepatectomy. Ann Surg Oncol 2015; 22: 3109-3120.
[27] Bertens KA, Hawel J, Lung K, Buac S, Pineda-Solis K and Hernandez-Alejandro R. ALPPS: challenging the concept of unresectability--a systematic review. Int J Surge 2015; 13: 280-287.
[28] Abulkhir A, Limongelli P, Healey AJ, Damrah O, Tait P, Jackson J, Habib N and Jiao LR. Preoperative portal vein embolization for major liver resection: a meta-analysis. Ann Surg 2008; 247: 49-57.
[29] Jaeck D, Oussoultzoglou E, Rosso E, Greget M, Weber JC and Bachellier P. A two-stage hepatectomy procedure combined with portal vein embolization to achieve curative resection for initially unresectable multiple and bilobar colorectal liver metastases. Ann Surg 2004; 240: 1037-1049; discussion 1049-1051.
[30] Lam VW, Laurence JM, Johnston E, Hollands MJ, Pleass HC and Richardson AJ. A systematic review of two-stage hepatectomy in patients with initially unresectable colorectal liver metastases. HPB (Oxford) 2013; 15: 483-491.
[31] Kokudo N, Tada K, Seki M, Ohta H, Azekura K, Ueno M, Ohta K, Yamaguchi T, Matsubara T, Takahashi T, Nakajima T, Muto T, Ikari T, Yanagisawa A and Kato Y. Proliferative activity of intrahepatic colorectal metastases after preoperative hemihepatic portal vein embolization. Hepatology 2001; 34: 267-272.
[32] Alvarez FA, Ardiles V, de Santibanes M, Pekolj J and de Santibanes E. Associating liver partition and portal vein ligation for staged hepatectomy offers high oncological feasibility with adequate patient safety: a prospective study at a single center. Ann Surg 2015; 261: 723-732.
[33] Truant S, Scatton O, Dokmak S, Regimbeau JM, Lucidi V, Laurent A, Gauzolino R, Castro Benitez C, Pequignot A, Donckier V, Lim C, Blanleuil ML, Brustia R, Le Treut YP, Soubrane O, Azoulay D, Farges O, Adam R, Pruvot FR; e-HPBchir Study Group from the Association de Chirurgie Hépato-Biliaire et de Transplantation (ACHBT). Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): impact of the inter-stages course on morbi-mortality and implications for management. Eur J Surg Oncol 2015; 41: 674-682.
[34] Hernandez-Alejandro R, Bertens KA, Pineda-Solis K and Croome KP. Can we improve the morbidity and mortality associated with the associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) procedure in the management of colorectal liver metastases? Surgery 2015; 157: 194-201.
[35] Robles R, Parrilla P, Lopez-Conesa A, Brusadin R, de la Pena J, Fuster M, Garcia-Lopez JA and Hernandez E. Tourniquet modification of the associating liver partition and portal ligation for staged hepatectomy procedure. Br J Surg 2014; 101: 1129-1134; discussion 1134.
[36] Cai X, Peng S, Duan L, Wang Y, Yu H and Li Z. Completely laparoscopic ALPPS using round-the-liver ligation to replace parenchymal transection for a patient with multiple right liver cancers complicated with liver cirrhosis. [Erratum appears in J Laparoendosc Adv Surg Tech A 2015; 25: 540.]. J Laparoendosc Adv Surg Tech A 2014; 24: 883-886.
[37] Waechter FL, Pinto RD, Koleski F, Sampaio JA and Teixeira UF. Associating Liver Radiofrequency and Portal Vein Ligation for Staged Hepatectomy. Arq Bras Cir Dig 2015; 28: 218.