Original Article

DOI: 10.5582/bst.2015.01139

A systematic review and meta-analysis of feasibility, safety and efficacy of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) versus two-stage hepatectomy (TSH)

Zhipeng Sun[1,2], Wei Tang[2,*], Yoshihiro Sakamoto[2], Kiyoshi Hasegawa[2], Norihiro Kokudo[2]

[1] *Oncology Surgery Department, Peking University Ninth School of Clinical Medicine (Cancer Centre, Beijing Shijitan Hospital, Capital Medical University), Beijing, China;*
[2] *Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.*

Summary **This meta-analysis aimed to review the regeneration rate of future liver remnant (FLR) and perioperative outcomes after associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) and two-stage hepatectomy (TSH). A web search was performed in "MEDLINE", "EMBASE", and "SCIENCE DIRECT" databases using both subject headings (MeSH) and truncated word to identify all the articles published that related to this topic. Pooled risk ratios were calculated for categorical variables and mean differences for continuous variables using the fixed-effects and random-effects models for meta-analysis. Three studies involved 282 patients, of whom 234 were in the TSH group and 48 in the ALPPS group. Morbidity was experienced in 56.3% patients in the ALPPS group and 36.1% in the TSH group. There was a statistical difference (RR = 1.08; Z = 3.24; 95% CI, *p* = 0.001). Second surgeries were performed successfully in 79.1% patients in the portal vein embolization (PVE) group and 100% in the ALPPS group. There was a statistical difference (Z = 2.48; 95% CI, *p* = 0.01). The mean regeneration rate of FLR in the ALPPS group was 56.4% compared with 52.8% in the TSH group. There was no statistical difference (95% CI, *p* = 0.34). So from the outcome of this meta-analysis, TSH had a similar remnant liver regeneration ability compared to ALPPS while the morbidity and mortality rates were relatively low. Cancer progression while waiting for the staged liver resection after portal vein embolization was a drawback for TSH.**

Keywords: Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS), portal vein embolization (PVE), two-staged Hepatectomy (TSH), liver regeneration

1. Introduction

During the period of associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) surgery promotion, there were always comparisons with conventional Two-Stage Hepatectomy (portal vein embolization and staged hepatectomy, TSH), which don't need laparotomy and liver parenchyma partition in the first surgery. Some researchers found that TSH had a similar remnant liver regenerative effect compared to ALPPS while the morbidity and mortality rates were relatively low (*1-3*). There were already 3 randomized control trials comparing the two surgeries up to now that we have summarized as follows.

The major difference between ALPPS and TSH is the extra liver parenchyma partition in ALLPS, which may result in fast remnant liver regeneration. The procedure of cancer-bearing liver partition may also reduce the chance of tumor invasion to the remnant liver (*4*). The major deficit of conventional two-stage hepatectomy is that the speed of future remnant liver

**Address correspondence to:*
Dr. Wei Tang, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.
E-mail: tang-sur@h.u-tokyo.ac.jp

(FLR) regeneration is not very high. It's rarely over 50% for 4-8 weeks. About 1/10 patients who underwent portal vein embolization as the first surgery of TSH lost the second hepatic resection surgery opportunity while waiting for FLR regeneration (*5*) because of cancer progress. So conventional TSH now is widely used for hilar cholangiocarcinoma, which grows slowly compared with hepatic cancer. The purpose of this systematic review and meta-analysis was to compare ALPPS with TSH to evaluate feasibility, safety and efficacy.

2. Materials and Methods

2.1. *Procedure of data collection*

The databases of "MEDLINE", "EMBASE", and "SCIENCE DIRECT" were searched for articles published up to the date of Oct 15th, 2015 using the medical subject headings (MeSH) terms "portal vein ligation", "PVE", "staged hepatectomy", "staged liver resection", "liver resection", "two-stage hepatectomy", "TSH", "associating liver partition and portal vein ligation for staged hepatectomy" and "ALPPS" (Figure 1). There were no language restrictions. Relevant articles were reviewed and duplicates were removed. Articles unrelated to ALPPS, TSH as well as abstracts were excluded. Full-text articles were assessed for eligibility. Editorials and commentary articles as well as case reports were excluded. Studies reporting on up to three patients were classified as case reports. Patients were carefully screened for double reporting, after exclusion of those patients, a quantitative synthesis and meta-analysis was performed.

All patients who underwent liver resection for malignant tumors in both normal and cirrhotic livers were included. Inclusion criteria for searching were studies evaluating the use of TSH and ALPPS for elective liver resection.

2.2. *Types of outcome measures*

The morbidity rate, second surgery finish rate, FLR regeneration rate of TSH and ALPPS were measured.

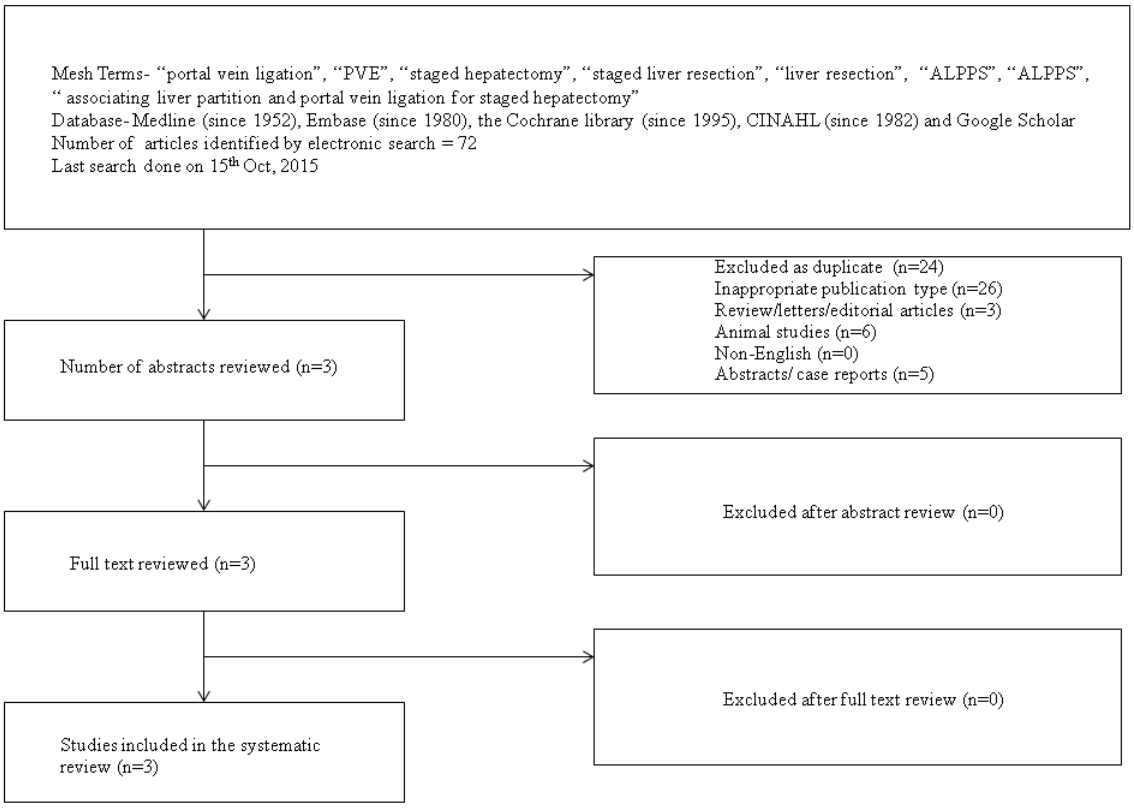

Figure 1. Prisma flowchart of databases searched, strategy used, and exclusions performed for "ALPPS" and "TSH". Randomized and case-controlled studies, irrespective of language, country of origin, hospital, blinding, sample size, or publication status that compared ALPPS and TSH were included in this review. The databases of "MEDLINE", "EMBASE", and "SCIENCE DIRECT" were searched for articles published up to the date of Oct 15th, 2015 using the medical subject headings (MeSH) terms "portal vein ligation", "PVE", "staged hepatectomy", "staged liver resection", "liver resection", "two-stage hepatectomy", "TSH", "associating liver partition and portal vein ligation for staged hepatectomy" and "ALPPS". Relevant articles were reviewed and duplicates were removed. Articles unrelated to ALPPS, TSH as well as abstracts were excluded. Full-text articles were assessed for eligibility. Editorials and commentary articles as well as case reports were excluded. Studies reporting on up to three patients were classified as case reports. Patients were carefully screened for double reporting.

2.3. *Statistical analysis*

Statistical analysis was performed using Review Manager Version 5.2 software (Cochrane Collaboration). The risk ratio (RR) with 95% confidence interval (CI) was calculated for binary data, and the mean value differences with 95% CI for continuous variables. When median and range were reported instead of mean and variance, the mean and variance were calculated based on the methods described by Hozo *et al*. (*6*). Random and fixed effects models were used to calculate the outcomes of both binary and continuous data. 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 $p < 0.05$. Low heterogeneity was defined as $I^2 \leq 33\%$. If the standard deviation was not available, it was calculated according to the guidelines of the Cochrane Collaboration. 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 based on the Newcastle-Ottawa scale (*7*).

3. Results

The strategies of the literature search and the selection of studies are summarized (Figure 1). Three studies comparing ALPPS with TSH procedure met the inclusion criteria (*1,2,8*). All studies were retrospective. These three studies involved 282 patients, of whom 48 were in the ALPPS group and 234 in the TSH group. Pooled data were analyzed by combining the results of these three studies.

3.1. *Comparison of morbidity rate between ALPPS and TSH*

There was no heterogeneity among the included studies ($Chi^2 = 9.97$; df = 2; $p = 0.007$; $I^2 = 80\%$). Morbidities were experienced in 56.3% of patients in the ALPPS group and 36.1% in the TSH group. In a random effects model, there was statistical difference (RR = 1.08; Z = 3.24; 95% CI, $p = 0.001$; Figure 2).

3.2. *Comparison of second surgery finish rate between ALPPS and TSH*

There was no heterogeneity among the included studies ($Chi^2 = 1.54$; df = 2; $p = 0.46$; $I^2 = 72\%$). The staged surgeries were performed successfully in 79.1% of patients in the PVE group and 100% in the ALPPS group. In a random effects model, there was statistical difference. (Z = 2.48; 95% CI, $p = 0.01$; Figure 3).

3.3. *Comparison of FLR regeneration rate after first surgery between ALPPS and TSH*

There was no heterogeneity among the included studies

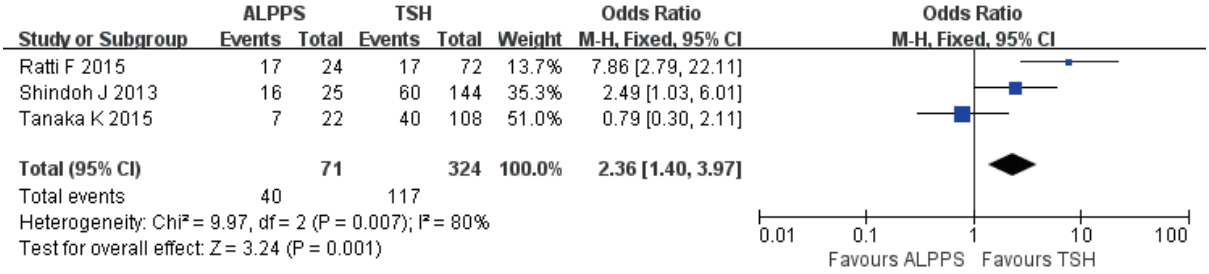

Figure 2. Comparison of morbidity rate between ALPPS and TSH. There studies were included in the analysis. Three was no heterogeneity amongst the included studies ($Chi^2 = 9.97$; df = 2; $p = 0.007$; $I^2 = 80\%$). Morbidity was experienced in 56.3% of patients in the ALPPS group and 36.1% in the TSH group. In a random effects model, there was statistical difference (Z = 3.24; $p = 0.001$).

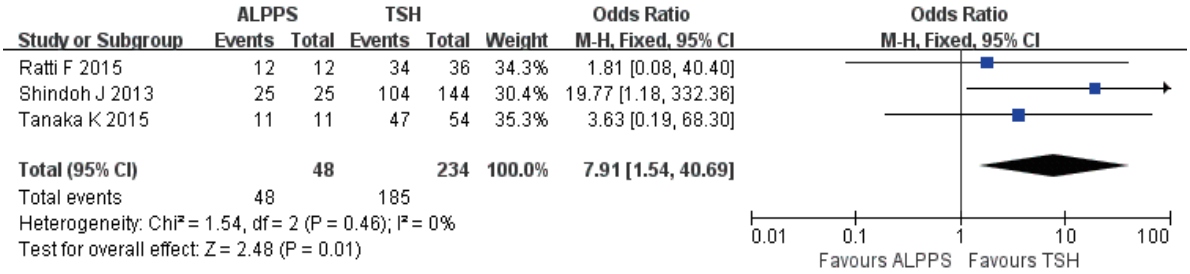

Figure 3. Comparison of second surgery finish rate between ALPPS and TSH. There studies were included in the analysis. Three was no heterogeneity among the included studies ($Chi^2 = 1.54$; df = 2; $p = 0.46$; $I^2 = 0\%$). The secondary surgeries were performed successfully in 79.1% of patients in the PVE group and 100% in the ALPPS group. In a random effects model, there was statistical difference (Z= 2.48; 95% CI, $p = 0.01$).

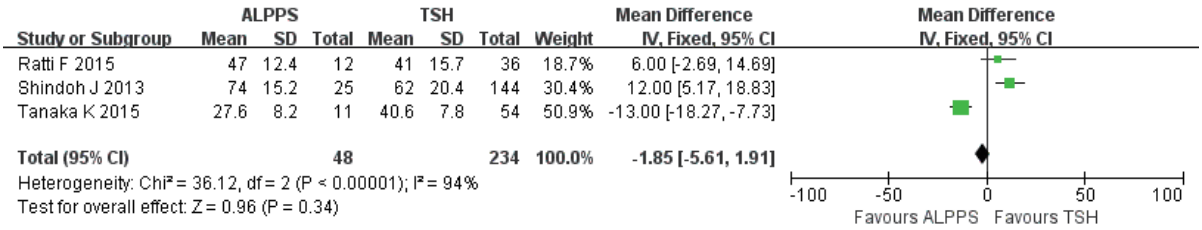

Figure 4. Comparison of FLR regeneration rate after first surgery between ALPPS and TSH. Three studies were included in the analysis. There was no heterogeneity among the included studies ($Chi^2 = 36.12$, df = 2; $I^2 = 94\%$). The mean regeneration rate in FLR in the PVE group was 56.4% compared with 52.8% in the TSH group. In a fixed effects model, there was no difference in the percentage change in FLR increase between ALPPS and TSH (95% CI, $p = 0.34$; Figure 4).

($Chi^2 = 36.12$, df = 2; $I^2 = 94\%$). The mean regeneration rate of FLR in the PVE group was 56.4% compared with 52.8% in the TSH group. In a fixed effects model, there was no difference in the regeneration rate of FLR between ALPPS and TSH (95% CI, $p = 0.34$; Figure 4).

4. Discussion

This meta-analysis shows that about three years after the inaugural publication of the novel ALPPS technique (*4*), the level of evidence supporting its advantages compared with traditional TSH remains low. Studies confirm the high completion rate of 97% for ALPPS, although with the two common biases of single-center and retrospective design. Perioperative mortality rate was 11% and complications grade IIIa or higher occurred in 44% of all patients (*9*).

The reasons for the rapid hypertrophy of the FLR observed in ALPPS and the actual functional growth of the FLR are important clinical questions. Although the rapid growth of the FLR after the ALPPS procedure is very impressive, it remains not so clear that it is better compared with a right hemi-liver plus segment 4 PVE. In our meta-analysis there wasn't any statistical difference between the two types of surgeries in regeneration volume. As reported previously, the hypertrophy of the FLR is negatively correlated with the pre-PVE FLR volume (*10*). Because hepatic parenchyma transection is usually performed along the umbilical fissure (the segmental border between left lateral lobe and segment 4) in ALLPS procedure (*4,11*) while PVE is usually performed on right hemi-liver in TSH procedure (*12,13*). It is incorrect to attribute the reason for the rapid growth of the FLR to hepatic parenchyma partition (*8,11*). Therefore, more prospective studies about FLR regeneration volume comparison between ALPPS and a right hemi-liver plus segment 4 PVE should be performed.

Second, the mechanism explaining how the *in situ* splitting facilitates the regeneration of the FLR needs to be clarified. In animal models, there were no differences between TSH and ALPPS for the quantity of effective regenerative liver cells. The comparison for the quantity of effective regenerative liver cells between ALPPS and PVE was performed in rat models. DNA synthesis was assessed by bromodeoxyuridine (BrdU) and proliferating cell nuclear antigen (PCNA) immunohistochemistry staining on paraffin sections. There were no differences in $BrdU^+$ or $PCNA^+$ hepatocytes. The liver weights were assessed seven days after surgery. The weights of the remnant livers were not significantly different following PVL and ALPPS (*14*). Other research (*15*) also reported similar results that portal vein ligation and portal vein ligation combined with in situ splitting were performed in two groups of mice. The results showed no obvious differences between the two groups were observed at 24 and 48 hours after surgeries.

This systemic review was limited due to the small number of original publications about comparison of ALPPS, which is a very recently introduced technique, with TSH. The reason for this early systematic review was to support the opinion with data about the ongoing debate on the benefits and deficits of ALPPS compared with TSH. At the same time, the quality of studies published currently has not allowed the establishment of solid evidence for safety and efficacy, as shown by this systematic review. More prospective studies about comparison between ALPPS and TSH should be performed to support further assessment of feasibility, safety and oncologic efficacy.

5. Conclusion

TSH has similar remnant liver regeneration ability compared with ALPPS while the morbidity and mortality rates are relatively low. Cancer progression while waiting for the second stage hepatectomy after portal vein embolization is a major shortcoming for TSH.

Acknowledgements

This research was funded by the Japan-China Sasakawa Medical Fellowship, which is a project of the Sasakawa Memorial Health Foundation. The authors wish to thank the Foundation for its support.

References

1. Ratti F, Schadde E, Masetti M, Massani M, Zanello M,

Serenari M, Cipriani F, Bonariol L, Bassi N, Aldrighetti L, Jovine E. Strategies to increase the resectability of patients with colorectal liver metastases: A multi-center case-match analysis of ALPPS and conventional two-stage hepatectomy. Ann Surg Oncol. 2015; 22:1933-1942.
2. Shindoh J, Vauthey JN, Zimmitti G, Curley SA, Huang SY, Mahvash A, Gupta S, Wallace MJ, 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.
3. Tanaka K, Matsuo K, Murakami T, Kawaguchi D, Hiroshima Y, Koda K, Endo I, Ichikawa Y, Taguri M, Tanabe M. Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS): Short-term outcome, fuctional changes in the future liver remnant, and tumor growth activity. Eur J Surg Oncol. 2015; 41:506-512.
4. Schnitzbauer AA, Lang SA, Goessmann H, et al. 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.
5. Okabe H, Beppu T, Nakagawa S, et al. Percentage of future liver remnant volume before portal vein embolization influences the degree of liver regeneration after hepatectomy. J Gastrointest Surg. 2013; 17:1447-1451.
6. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005; 5:13.
7. Martin B, Paesmans M, Berghmans T, Branle F, Ghisdal L, Mascaux C, Meert AP, Steels E, Vallot F, Verdebout JM, Lafitte JJ, 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.
8. Takayasu K, Muramatsu Y, Shima Y, Moriyama N, Yamada T, Makuuchi M. Hepatic lobar atrophy following obstruction of the ipsilateral portal vein from hilar cholangiocarcinoma. Radiology. 1986; 160:389-393.
9. Schadde E, Schnitzbauer AA, Tschuor C, Raptis DA, Bechstein WO, 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.
10. 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, Kato Y. Proliferative activity of intrahepatic colorectal metastases after preoperative hemihepatic portal vein embolization. Hepatology. 2001; 34:267-272.
11. Nagino M, Kamiya J, Kanai M, Uesaka K, Sano T, Yamamoto H, Hayakawa N, Nimura Y. Right trisegment portal vein embolization for biliary tract carcinoma: Technique and clinical utility. Surgery. 2000; 127:155-160.
12. Jaeck D, Oussoultzoglou E, Rosso E, Greget M, Weber JC, 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.
13. Fernandez-Ros N, Silva N, Bilbao J, Inarrairaegui M, Benito A, Avola D, Rodriguez M, Rotellar F, Pardo F, Sangro B. Partial liver volume radioembolization induces hypertrophy in the spared hemiliver and no major signs of portal hypertension. HPB (Oxford). 2014; 16:243-249.
14. Heinrich S, Jochum W, Graf R, Clavien PA. Portal vein ligation and partial hepatectomy differentially influence growth of intrahepatic metastasis and liver regeneration in mice. J Hepatol. 2006; 45:35-42.
15. Yao L, Li C, Ge X, Wang H, Xu K, Zhang A, Dong J. Establishment of a rat model of portal vein ligation combined with *in situ* splitting. PloS one. 2014; 9:e105511.

(Received October 9, 2015; Revised October 21, 2015; Accepted October 24, 2015)