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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Received July 17, 2016; Accepted September 5, 2016; Epub November 15, 2016; Published November 30, 2016

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...
Comparison of ALPPS with TSH

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, this was also true, with 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

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<td>NETLM, 14</td>
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<td>Age, y</td>
<td>67 (55-81)</td>
<td>63 (32-75)</td>
<td>74 (21-192)</td>
<td>58 (33-79)</td>
<td>55.9 (12.1)</td>
<td>59.5 (11.3)</td>
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<td>FLR hypertrophy, %</td>
<td>63 (29)</td>
<td>37 (29)</td>
<td>74 (21-192)</td>
<td>62 (0.3-379)</td>
<td>84.3 (7.8)</td>
<td>36 (27.2)</td>
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<td>Time interval, days</td>
<td>6 (4-8)</td>
<td>35 (13-98)</td>
<td>9 (5-28)</td>
<td>34 (12-385)</td>
<td>39.9 (14.2)</td>
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<td>80</td>
<td>100</td>
<td>100</td>
<td>79</td>
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<td>R0, %</td>
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<td>NA</td>
<td>83</td>
<td>66</td>
<td>NA</td>
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<td>Overall morbidity, %</td>
<td>71.4</td>
<td>40</td>
<td>64</td>
<td>57.7</td>
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<td>43.8</td>
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<td>Morbidity ≥ IIIa, %</td>
<td>NA</td>
<td>NA</td>
<td>40</td>
<td>33</td>
<td>NA</td>
<td>14.6</td>
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<tr>
<td>Liver insufficiency, %</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>TB &gt; 7 mg/dl</td>
<td>50-50</td>
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<td>90-day mortality, %</td>
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<td>NA</td>
<td>12</td>
<td>8.6</td>
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<td>15</td>
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<td>NA</td>
<td>NA</td>
<td>180 (50-776) d</td>
<td>43 (1-127) m</td>
<td>NA</td>
<td>12 (6-18) m</td>
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<td>1-year DFS, %</td>
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<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>Study characteristics</td>
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<td>IIIb</td>
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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. aTime interval between two stages were unavailable, thus time of the last CT performed before stage 2 were extracted. bThe article reported the number of patients achieved R0/R1 resection. cOnly morbidity ≥ IIIb was reported.
Comparison of ALPPS with TSH

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

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 (Chi² = 11.61; d.f. = 4; P = 0.02; I² = 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 (Chi² = 2.28; d.f. = 3; P = 0.52; I² = 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 (Chi² = 1.76; d.f. = 3; P = 0.62; I² = 0.0%). Fourteen percent of patients in ALPPS group and 20% in TSH group developed liver insufficiency after major hepatectomy. In a fixed effect model, no statistical difference was found (Z = 0.34, 95% CI, P = 0.73) (See Figure 6).
Comparison of ALPPS with TSH

Table 1. Comparison of 90-day mortality between ALPPS and TSH

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>%Weight</th>
</tr>
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<tbody>
<tr>
<td>Shindoh (2013)</td>
<td>1.37 (0.66, 3.77)</td>
<td>38.12</td>
</tr>
<tr>
<td>Schrade (2014)</td>
<td>3.34 (1.49, 7.52)</td>
<td>31.45</td>
</tr>
<tr>
<td>Ratti (2015)</td>
<td>2.37 (0.67, 8.33)</td>
<td>13.64</td>
</tr>
<tr>
<td>Tanaka (2015)</td>
<td>1.67 (0.48, 5.76)</td>
<td>16.79</td>
</tr>
<tr>
<td>Overall</td>
<td>2.18 (1.34, 3.55)</td>
<td>100.00</td>
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</table>

Heterogeneity chi-squared = 2.28 (d.f. = 3) p = 0.516
I-squared (variation in OR attributable to heterogeneity) = 0.0%
Test of OR = 1: z = 3.12 p = 0.002

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

Table 2. Comparison of liver insufficiency rate between ALPPS and TSH

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>%Weight</th>
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<tbody>
<tr>
<td>Crome (2014)</td>
<td>0.38 (0.08, 1.97)</td>
<td>37.26</td>
</tr>
<tr>
<td>Schrade (2014)</td>
<td>1.40 (0.40, 4.92)</td>
<td>28.03</td>
</tr>
<tr>
<td>Ratti (2015)</td>
<td>0.52 (0.02, 11.61)</td>
<td>8.66</td>
</tr>
<tr>
<td>Tanaka (2015)</td>
<td>1.14 (0.29, 4.40)</td>
<td>25.54</td>
</tr>
<tr>
<td>Overall</td>
<td>0.88 (0.41, 1.96)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Heterogeneity chi-squared = 1.76 (d.f. = 3) p = 0.623
I-squared (variation in OR attributable to heterogeneity) = 0.0%
Test of OR = 1: z = 0.34 p = 0.733

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

Table 3. Comparison of 90-day mortality between ALPPS and TSH

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>%Weight</th>
</tr>
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<tbody>
<tr>
<td>Shindoh (2013)</td>
<td>1.44 (0.36, 5.76)</td>
<td>33.29</td>
</tr>
<tr>
<td>Crome (2014)</td>
<td>0.52 (0.02, 11.51)</td>
<td>14.25</td>
</tr>
<tr>
<td>Schrade (2014)</td>
<td>1.67 (0.49, 5.67)</td>
<td>43.60</td>
</tr>
<tr>
<td>Ratti (2015)</td>
<td>3.00 (0.17, 52.10)</td>
<td>5.19</td>
</tr>
<tr>
<td>Tanaka (2015)</td>
<td>4.70 (0.27, 81.63)</td>
<td>3.68</td>
</tr>
<tr>
<td>Overall</td>
<td>1.61 (0.73, 3.55)</td>
<td>100.00</td>
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</table>

Heterogeneity chi-squared = 1.26 (d.f. = 4) p = 0.868
I-squared (variation in OR attributable to heterogeneity) = 0.0%
Test of OR = 1: z = 1.18 p = 0.236

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 (Chi² = 1.26; d.f. = 4; P = 0.87; I² = 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 (Chi² = 0.33; d.f. = 1; P = 0.57; I² = 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
Comparison of ALPPS with TSH

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 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
Comparison of ALPPS with TSH

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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