Evaluation of portal vein occlusion with or without parenchymal splitting in the management of irresectable liver tumors

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Received 10 March 2018
Accepted 18 March 2018

The Egyptian Journal of Surgery 2019, 38:291–300

Background
Portal vein embolization (PVE) has been developed with the principle of inducing hypertrophy of the future liver remnant (FLR) (10–50% after a period of 2–8 weeks). Tumor progression and insufficient hypertrophy of the FLR are the commonest causes that preclude definitive surgery in 10–30% of patients. Recently, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been proposed, with the goal of achieving a faster and magnified hypertrophy (74–87.2% in 9–13 days) for patients with extensive colorectal liver metastases or hilar cholangiocarcinoma. However, introducing ALPPS for hepatocellular carcinoma (HCC) on top of cirrhosis has been questioned and not thoroughly investigated.
Patients and methods
A prospective observational study was conducted on patients who were admitted to the National Liver Institute from 2016 to 2018 with nonresectable liver tumors owing to insufficient FLR. Hypertrophy of the FLR, perioperative morbidity and mortality, overall survival, and other parameters were compared between patients who underwent ALPPS and patients who underwent PVE.
Results
Nineteen patients, of which 17 patients had HCC, underwent first-stage ALPPS, whereas 26 patients, of which 20 patients had HCC, underwent PVE. The mean of the percentage of hypertrophy at 2 weeks for ALPPS group was 41.62±39.7. The mean of hypertrophy after PVE at 2 weeks was 37±5.77%. Fourteen (73.6%) patients could be operated upon for definitive resection in the second stage of ALPPS. Fourteen (54%) patients underwent resection after PVE.
Conclusion
Despite the morbidity and outcomes of ALPPS in patients with cirrhosis, it still can be introduced with strict criteria. Although ALPPS produces more extensive hypertrophy than PVE and less likely progression of the tumor to the FLR, PVE has less overall morbidity and mortality.

Keywords:
associating liver partition and portal vein ligation for staged hepatectomy, embolization, hypertrophy, liver resection

Egyptian J Surgery 38:291–300

1110-1121

Introduction

Liver resection is considered the only curative treatment in most patients with liver malignancies whether primary or secondary. Unfortunately, the rate of resection is ~20–30% in patients with hepatocellular carcinoma (HCC) and 10–20% in patients with colorectal liver metastases [1].

Certainly, the chief factor that hampers resection of large tumors is the future liver remnant (FLR) volume, because of the risk of postoperative liver failure [2].

In case of normal parenchyma, a FLR of 25% should maintain a satisfactory postoperative function, whereas a FLR of 40% is mandatory in presence of underlying liver disease (cirrhosis, prolonged previous chemotherapy, and cholestasis) [3].

Portal vein embolization (PVE) has been developed with the principle of inducing hypertrophy of the FLR (10–50% after a period of 2–8 weeks) [4]. Tumor progression and insufficient hypertrophy of the FLR are the commonest causes that preclude definitive surgery in 10–30% of patients [1].

Since its introduction in 2012, associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) has been contentious. Surprisingly, opponents state that it is not justified, whereas proponents consider it as a striking innovation in liver surgery [5].

The goal of ALPPS is to achieve a faster and magnified hypertrophy (74–87.2% in 9–13 days) for patients with extensive colorectal liver metastases or hilar cholangiocarcinoma [6,7]; however, introducing ALPPS for HCC on top of cirrhosis has been questioned, and not thoroughly investigated [8]. Undoubtedly, major liver resections for HCC can be hazardous given the underlying hepatitis, fibrosis, and cirrhosis [5].

Despite the underlying fibrosis and cirrhosis in patients with HCC, ALPPS induces extensive hypertrophy. However, the high rate of perioperative morbidity and mortality intervenes with the introduction of ALPPS for most patients [8]. Fortunately, the recent modifications of ALPPS, such as radiofrequency-assisted ALPPS (RALPPS) [9], partial instead of complete transection [10], laparoscopic ALPPS [11] as well as hybrid ALPPS [8], result in less surgical trauma than classic ALPPS; therefore, they may offer a better overall survival for patients with large HCC when compared with the nonsurgical management [8].

Patients and methods

This is a prospective observational study that was conducted on patients who were admitted to Surgery and Radiology Departments, National Liver Institute, Menoufia University, with nonresectable liver tumors, owing to insufficient FLR, for preoperative PVE, or ALPPS, as the estimated FRL, based on computed tomography (CT) volumetry, is less than 30% in case of normal liver parenchyma and less than 40% in patients with compromised liver parenchyma owing to steatosis, cholestasis fibrosis or cirrhosis, between May 2016 and January 2018. After taking the approval of our institutional reviewers (IRB); we did this cohort study.

Patients

There were two groups: PVE group and ALPPS group.

(1) Inclusion criteria:
    (a) All sex and age groups.
    (b) Hepatic lesions that require major resection whether malignant or benign lesions.
    (c) Normal, fibrotic, or cirrhotic liver.
    (d) Child A patients.
(2) Exclusion criteria:
    (a) Child B and C patients.
    (b) Advanced portal hypertension.
    (c) Extrahepatic metastasis.
    (d) Bilobar lesion in cases of HCC.

Methods

Data was collected regarding the following:

Preoperative data

(1) Demographic data.
(2) Diagnosis: benign or malignant lesions, primary or secondary lesions, and unilobar or bilobar lesions.
(3) Preoperative assessment of the patients in terms of general condition and liver condition such as the cause of cirrhosis, laboratory assessment of liver functions including MELD and Child-Pugh scores along with assessment of fibrosis and cirrhosis using Fibroscan.
(4) Fibroscan was performed for selected patients to determine the degree of fibrosis, with subsequent studying its relation with liver hypertrophy. Results are presented as a number in kilopascals (kPas). A higher number indicates more liver damage according to Metavir scoring system.
(5) Premaneuver FLR estimation by CT volumetry.

Triphasic CT was performed immediately before PVE or ALPPS at 2, 4, and 6 weeks after PVE, or ALPPS to determine the changes of hepatic lobes volume (Fig. 1).

The following formulae were calculated:

(a) FLR%=[FLRV/(total liver volume−tumor volume)]×100%.
(b) Percentage of increase of FLRV= (FLR% postmaneuver−FLR% premaneuver/%FLR premaneuver)×100%.
(c) DH (degree of hypertrophy) of FLR=FLR% postmaneuver−FLR% premaneuver.

Techniques

PVE was performed using percutaneous transhepatic approach. Then follow-up of liver hypertrophy was done after 2, 4, and 6 weeks by CT volumetry, to assess the response of liver hypertrophy to PVE. If no response by sufficient liver hypertrophy after 8 weeks, the patient should be dropped out.

ALPPS was done by different techniques according to the accessibility of the following different modalities:

(1) The classic technique.
(2) Radiofrequency ablation along Rex-Cantlie's line instead of splitting liver.
(3) Laparoscopic right portal vein ligation combined with in-situ radiofrequency ablation between the two lobes.

Then follow-up of liver hypertrophy was done every 2 weeks by CT volumetry, to assess the response of liver hypertrophy; if the volume was sufficient, we proceeded to liver resection in a second operation, and if no response by sufficient liver hypertrophy after 4 weeks and finally at 6 weeks, the case was canceled from resection.

Postoperative data

The following postoperative data were collected:

(1) Postoperative course: morbidity, particularly postoperative liver failure.
(2) Hospitals stay in days.

Follow-up

At least 6 months from the last case of resection was the follow-up period (range: from date of first procedure 20 months).

Survival and mortality

Analysis of survival and cause of death was done.

Statistical analysis

Data were collected and entered to the computer using SPSS (statistical package for the social sciences; SPSS Inc., Chicago, Illinois, USA) program for statistical analysis.

Two types of statistics were done:

(1) Descriptive statistics.
(2) Analytical statistics:
    (a) *P* value is considered statistically significant when it is less than 0.05.
(3) Sample size:
    (a) Follow-up of 18 cases for each group has been planned.
    (b) The proportion of mortality among ALPPS is 7%, and the mortality rate among PVE is 2%.
    (c) To achieve power of 80% and assuming that error level *P* value of 0.005, the calculated sample size will be 36.

Power and sample size calculation version 3, 2011, software programme was used to calculate the sample size for the study.

Results

From May 2016 to January 2018, 19 patients underwent ALPPS for large liver tumors and 26 patients underwent right PVE, in the National Liver Institute, Menoufia University, as a preoperative preparation for major hepatectomy in patients with large liver tumors.

Demographic and preoperative data of the patients

ALPPS group

Sixteen (84.2%) patients were males and three (15.8%) were female patients, with mean age of 56±8.25 (range: 35–70 years). Thirteen (68.4%) patients showed liver cirrhosis, four (21%) patients had early cirrhotic changes, and the remaining two (10.5%) patients with noncirrhotic liver. Fibroscan study for the degree of liver fibrosis showed two (10.5%) patients with F1, four (21%) patients with F2, two (10.5%) patients with F3, and 11 (57.9%) patients with F4. The degree of fibrosis was ranging between 4 and 35 kPa, with mean of 18.53±9.74 kPa.

PVE group

Twenty-one (80.7%) patients were males and five (19.3%) patients were females. The age of the patients included in this study ranged from 35 to 63 years. The mean age was 52.9±7.4 years. Eighteen (69.2%) patients showed liver cirrhosis, six (23.1%) patients had early cirrhotic changes, and the remaining two (7.7%) patients with noncirrhotic liver. Fibroscan study for the degree of liver fibrosis showed two (7.7%) patients with F1, six (23.1%) patients with F2, 10 (38.8%) patients with F3, and eight (30.8%) patients with F4. The degree of fibrosis ranged between 3.8 and 51.4 kPa, with mean of 21.2 ±17.6 kPa.

Tumor characteristics

Tables 1 and 2.

Technique of ALPPS (Fig. 2)

Regarding the first-stage technique, classic technique was done in seven (36.8%) cases, whereas radiofrequency-assisted ALPPS was performed via open surgery in 10 (52.6%) cases. Laparoscopic radiofrequency-assisted ALPPS was performed in two (10.5%) cases.

Table 1 Tumor characteristics of associating liver partition and portal vein ligation for staged hepatectomy group

	Frequency (*n*=19)	Percentage (100%)
Tumor nature		
HCC	17	89.4
Hepatocellular adenoma	1	5.3
Biliary cyst adenoma	1	5.3
Lesion site		
Right lobe	17	89.4
Left lobe	1	5.3
Left lobe+segment V and VIII	1	5.3

HCC, hepatocellular carcinoma.

Regarding the second-stage procedure, 12 (63.2%) patients underwent right hepatectomy, one (5.3%) patient underwent left hepatectomy, and one (5.3%) patient underwent extended left hepatectomy. Blood loss mean in the second stage of ALPPS was 521.43 ±611.65 ml, ranging from nil loss to 2500 ml.

Dropout of the cases

Second stage of ALPPS was not conducted in five (26.3%) patients. Two patients developed moderate ascites after first stage of ALPPS, which did not respond to medical treatment for 6 weeks. One (5.3%) patient developed new focal lesion in the FLR. One (5.3%) patient refused the second stage. One (5.3%) patient had a malignant portahepatis lymph node.

Interval (weeks) between the two stages of ALPPS

Ten (52.6%) patients reached the sufficient volume of the FLR after 2 weeks of the first stage of ALPPS, whereas four (21%) patients reached the sufficient volume of the FLR after 6 weeks.

Table 2 Tumor characteristics of portal vein embolization group

	Frequency (*N*=26)	Percentage (100%)
Tumor nature		
HCC	20	76.9
Giant hemangioma	2	7.7
Adenocarcinoma	2	7.7
Gall bladder carcinoma	2	7.7
Tumor bed		
Right lobe	22	84.6
Right lobe+segment IV	4	15.4

HCC, hepatocellular carcinoma.

Hospital stay first stage (days)

The mean hospital stay after first-stage ALPPS was 3.79±0.92, with range of 3–6 days.

Hospital stay after second stage (days)

The mean of hospital stay after second-stage ALPPS was 8.58±1.93 days, with range of 7–13 days.

Analysis of the data of hypertrophy in correlation the potential factors

The hypertrophy percentage after 2 weeks was correlated with fibrosis grade, as shown in Table 3.

Simple and then multiple linear regression analyses were performed to identify and assess the effect of several potential predictors such as fibrosis score, model for end-stage liver disease (MELD) score, age, Alpha-FetoProtein (AFP), sex, and operation technique at first-stage ALPPS on the percentage of hypertrophy at 2 weeks as a response variable.

This revealed that fibrosis, MELD score, AFP, and age had a highly significant association with hypertrophy percent at the time of 2 weeks. On the contrary, the models for factors as sex and operation technique revealed nonsignificant association with hypertrophy percentage (Table 4).

Table 3 The hypertrophy percentage after 2 weeks in correlation to the fibrosis grade

Fibroscan grades	Hypertrophy mean	SD	*N*
F1	111.1500	0.91924	2
F2	63.6500	45.43791	4
F3	67.6000	31.67838	2
F4	16.2364	10.89553	11
Total	41.6158	39.74430	19

Table 4 Simple linear regression analysis models for hypertrophy percentage at 2 weeks as a dependent variable associated with potential predictors

Variables	Univariable analysis (*n*=19)				
	Coefficient (*B*)	*t*	*P* value	95.0% CI for B	Adjusted R^2
Fibrosis score	–3.223	–5.315	<**0.001 (HS)**	–4.50 to –1.94	0.602
Age (years)	–2.217	–2.137	**0.047 (S)**	–4.41 to –0.03	0.165
MELD score	–13.590	–2.465	**0.025 (S)**	–25.22 to –1.96	0.220
AFP	–3.526	–2.340	**0.032 (S)**	–6.71 to –0.35	0.199
Gender		2.59[a]	0.126 (NS)[b]		0.081
Male (*n*=16)	–38.575	–1.609	0.126 (NS)	–89.15 to 11.00	–
Female (*n*=3)	Reference (0)	–		–	–
First stage techniques (*n*)	–	0.57[a]	**0.578** (NS)[b]	–	–0.051
Classic (*n*=7)	6.364	0.195	0.848 (NS)	–62.87 to75.60	–
Open RFALPPS (*n*=10)	24.550	0.778	0.448 (NS)	–42.34 to 91.44	–
Laparoscopic RFALPPS (*n*=2)	Reference (0)	–	–	–	–

Adjusted R^2, assessment of goodness of model fit; AFP, Alpha-FetoProtein; CI, confidence interval; HS, highly significant; MELD, model for end-stage liver disease; RFALPPS, radiofrequency associating liver partition and portal vein ligation for staged hepatectomy; S, significant. $P \geq 0.05$, nonsignificant. $P < 0.05$, significant. $P < 0.01$, highly significant. [a]*F*-value for all levels of factor. [b]*P*-value corresponds to *F* statistics.

Table 5 Multiple linear regression analysis of hypertrophy percentage at 2 weeks as a dependent variable predicted by fibrosis score and age

Variables	Multivariable analysis (n=19)				
	Coefficient (B)	t	Adjusted P value	95.0% CI for B	Adjusted R^2
Model 1					0.635
Fibrosis score	–2.922	–4.781	**<0.001 (HS)**	–4.22 to –1.63	
Age (years)	–1.146	–1.587	**0.132 (NS)**	–2.68 to 0.39	
Model 2					0.589
Fibrosis score	–2.957	–4.032	**0.001 (HS)**	–4.51 to –1.40	
MELD score	–3.189	–0.670	**0.513 (NS)**	–13.28 to 6.91	
Model 3					0.589
Fibrosis score	–2.973	–4.139	**0.001 (HS)**	–4.50 to –1.45	
AFP (ng/ml)	–0.851	–0.676	**0.508 (NS)**	–3.52 to 1.82	

Adjusted R^2, assessment of goodness of model fit; AFP, Alpha-FetoProtein; CI, confidence interval; HS, highly significant; MELD, model for end-stage liver disease; S, significant. $P \geq 0.05$, nonsignificant. $P < 0.05$, significant. $P < 0.01$, highly significant.

Table 6 The changes in the hypertrophy degree (HD) of the future liver remnant (FLR) at 2 weeks and 6 weeks after portal vein embolization (PVE) according to the degree of liver fibrosis F (HD of FLR=FLR % after PVE–FLR % before PVE)

	F2 (n=6)	F3 (n=8)	F4 (n=4)	Kruskal–Wallis test	P value	Post-hoc test
HD FLR 2 weeks	24.2±10.6	13.6±1.2	11.3±6.03	6.94	0.006	1=0.005* 2=0.003* 3=0.48
HD FLR 6 weeks	37.7±1.4	25.3±7.9	21.7±1.3	10.86	0.001	1=0.001* 2<0.001** 3=0.28

FLR, future liver remnant; HD, hypertrophy degree. *Statistically significant. **High statistical significance.

Table 7 Hypertrophic changes of the future liver remnant after portal vein embolization

FLR/TLV% before PVE (n=24)	FLR/TLV% after PVE (2 weeks) (n=24)	FLR/TLV% after PVE (6 weeks) (n=24)	HD of FLR 2 weeks (n=24)	HD of FLR 6 weeks (n=24)	Wilcoxon signed ranks test	P value
44.8±10.9	62.6±12.1	65.6±12.1	15.7±7.6	27.5±8.3	1=3.93 2=3.93 3=6.39	1<0.001** 2<0.001** 3<0.001**

FLR, future liver remnant; HD, hypertrophy degree; PVE, portal vein embolization; TLV, total liver volume. **High statistical significance.

Finally, in Table 5, on introducing the previous covariates at a time and performing a stepwise automatic selection procedure for multiple regression analysis, the results suggested that the prediction of hypertrophy percentage at 2 weeks should be limited to fibrosis score as the best-fit model.

PVE technique

Technical success of PVE

Technical success was confirmed in 24 of the patients (92.31%); however, in two (7.69%) patients, the procedure was not completed as collaterals appeared on angiographic images.

Regarding the correlation between the degree of fibrosis and the hypertrophy, it was found that all the patients with F1 and F2 liver fibrosis (100%) got the target FLR volume at 2 weeks after PVE; only 75% of patients with F3 got it at 2 weeks, but all of them (100%) got it at 6 weeks; and 66.67% of patients with F4 reached the target FLR volume at 2 weeks, but the remaining 33.33% did not reach it even after 6 weeks (Table 6).

(1) Comparison between FLR % before PVE and FLR % after PVE (2 weeks).
(2) Comparison between FLR % before PVE and FLR % after PVE (6 weeks).
(3) Comparison between hypertrophy degree (HD) FLR % after PVE (2 weeks) and HD FLR % after PVE (6 weeks) (Fig. 3).

Table 7 shows the hypertrophic changes of the FLR after PVE in the form of highly significant increase of the mean FLR/TLV% 2 weeks and 6 weeks after PVE compared with the preprocedure percentage (P<0.001). The mean percent increase (HD) at 6 weeks after PVE was highly significant compared with 2 weeks after PVE (P<0.001) (Table 8).

Surgery after PVE

Only 14 (70%) patients underwent subsequent formal right hepatectomy. Causes of cancellation are shown in Table 9.

Complications

ALPPS group

Regarding the complications of first-stage ALPPS, 13 (68.4%) patients did not experience postoperative complications. However, five (26.3%) patients

Table 8 Percentage of patients who got the future liver remnant target volume after portal vein embolization in relation to the degree of liver fibrosis F (*N*=22)

Degree of fibrosis	Sufficient volume at 2 weeks [*n* (%)]	Sufficient volume at 6 weeks [*n* (%)]
F1 (*n*=2)	2 (100)	2 (100)
F2 (*n*=6)	6 (100)	6 (100)
F3 (*n*=8)	6 (75)	8 (100)
F4 (*n*=6)	4 (66.67)	4 (66.67)

Table 9 Causes of canceling surgery

Causes	*N*=12 [*n* (%)]
Not done PVE due to presence of collateral	2 (16.7)
Patient refused surgery	2 (16.7)
Failed growth of FLR after leakage of glue and occlusion of LT PV	2 (16.7)
FLR not reached the target volume	2 (16.7)
Tumor enlargement and new focal lesions appeared in FLR	4 (33.4)

FLR, future liver remnant; LT PV, left portal vein; PVE, portal vein embolization.

experienced ascites postoperatively, and the tumor has spread to the counterlateral lobe in one (5.3%) patient.

Regarding the complications of the second-stage ALPPS, six (31.6%) patients had had a smooth postoperative course, whereas four (21.1%) patients experienced postoperative liver decompensation in the form of ascites and jaundice. Three (15.8%) patients experienced ascites, and one (5.3%) patient had bile leak postoperatively. However, six (31.5%) patients have improved by conservative treatment, whereas two (10.6%) patients died early postoperatively.

Regarding recurrence after ALPPS, one (5.3%) patient has experienced recurrence of HCC after 2 years of the second stage of ALPPS.

Regarding survival and mortality after ALPPS, 16 (84.2%) patients have survived after ALPPS, whereas two (10.6%) patients died early postoperatively owing to massive intraoperative bleeding, which resulted in multiorgan failure and death.

Complications of the PVE

Minor complications were detected at 12 (49.9%) patients. Major complications occurred in four (16.6%) patients in the form of internal bleeding in two (8.3%) patients and leakage of the embolic material into the left portal vein leading to its occlusion in the other two (8.3%) patients.

Table 10 The mean features of first-stage associating liver partition and portal vein ligation for staged hepatectomy and portal vein embolization

	First stage ALPPS [*n* (%)]	PVE [*n* (%)]
Number of patients	19	26
Number of patients with cirrhosis (F3 and F4)	13 (68.4)	18 (69)
Hypertrophy 2 weeks	41.62±39.7	37±5.77
Hypertrophy 6 weeks	54.75±21.4	55±5.0
Hepatic decompensation	5 (26)	0
Major complications	0	4 (15)
Tumor progression to contralateral lobe	1 (5)	4 (15)
Mortality	0	0
Definitive surgery (resection)	14 (73.6)	14 (54)

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

Survival and mortality after PVE

All patients (100%) survived after PVE, and there was no mortality.

Highlights of both techniques

This is not a comparative study; however, Table 10 shows the main differences between ALPPS and PVE (Figs 1–3).

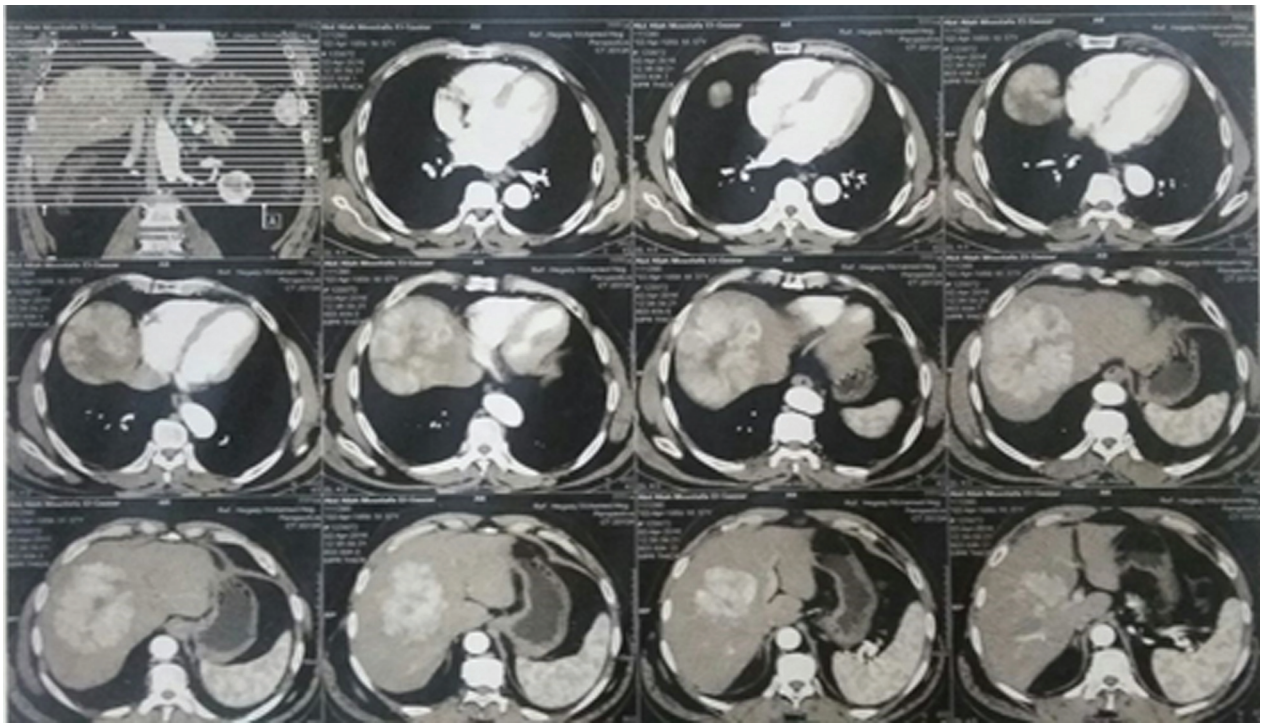
Discussion

Till 2014, the experience of ALPPS for patients with HCC was limited to a few case reports and single-center series demonstrating feasibility, such as reported by Chia *et al.* [12]. Then in 2015, D'Haese and colleagues published a study that evaluated hypertrophy and clinical outcomes for the largest cohort of patients with HCC to that date at 22 centers from 2010 to 2015, who underwent the novel ALPPS. However, their study included 35 patients who underwent ALPPS for HCC and 255 patients who underwent ALPPS for colorectal liver metastasis [8]. Later in 2017, an Asian study was published by Wang and colleagues, which reported 10 patients with cirrhosis who underwent laparoscopic ALPPS for HCC [13].

Our study included 19 patients who underwent ALPPS, 17 of those were cirrhotic and had HCC, and the remaining two patients had normal livers along with hepatocellular adenoma and biliary cyst adenoma. In addition, we evaluated the hypertrophy and outcomes of 26 patients who underwent PVE for different diagnoses; however, 20 patients of those had HCC and 24 patients had cirrhotic liver.

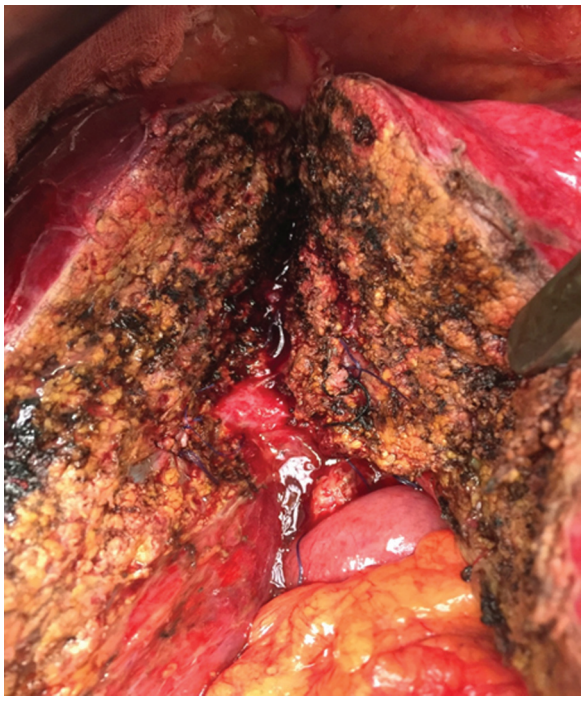
D'Haese and colleagues reported that the hypertrophy of the FLR of patients with HCC was 47% at 8–14

Figure 1



Computed tomography showing large right lobe hepatocellular carcinoma.

Figure 2



Classic technique of associating liver partition and portal vein ligation for staged hepatectomy (complete transection).

days. They also found that hypertrophy was significantly affected by the degree of fibrosis and the age [8]. In the series by Wang and colleagues, the hypertrophy of the FLR was 47% at 2 weeks and 58% at 4 weeks [13].

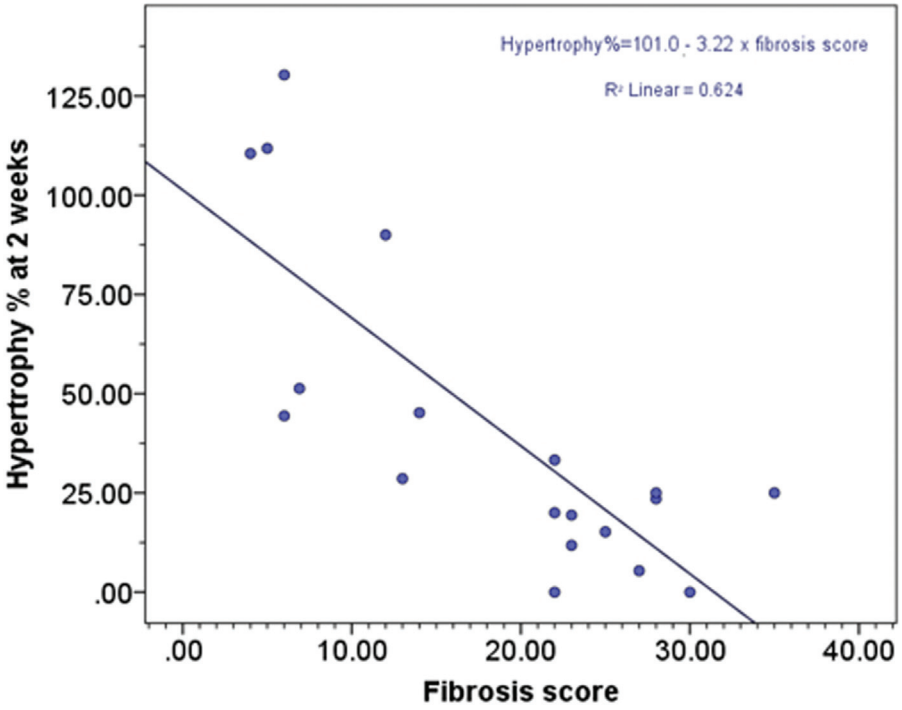
In this study, the hypertrophy of the FLR at 2 weeks was 42%, whereas at 6 weeks was 55%. However, we confirmed the significant effect of the degree of fibrosis on hypertrophy, whereas age was shown to have a meager significance.

The overall morbidity was 63% in D'Haese and colleagues series, and 40% of patients had liver failure postoperative [8]. However, in the series by Wang and colleagues, the incidence of severe complications was 20% after second stage of ALPPS, and 40% of patients experienced mild reversible complications such as reversible liver failure and pleural effusion. In contrast, after the first stage, only one (10%) patient experienced massive ascites and one (10%) patient experienced progression of the HCC to the FLR [13].

In this study, the overall complication rate after the second stage was 42%. On the contrary, 26% of patients had ascites after the first stage of ALPPS; however, it was reversible except for two cases only. Besides, in one (5%) patient, the HCC progressed to the FLR.

The 90-day mortality rate was high for the patients with HCC (31%) in the series by D'Haese and colleagues, where they concluded that the steepest drop in the survival of patients with HCC is within the first 90 days; thus, the high perioperative

Figure 3



Illustrating the multivariable dependent factors of linear regression analysis.

mortality after ALPPS for HCC seems to be the main reason for impaired overall survival [5]. Similarly, in the series by Wang and colleagues, they reported that 30% of patients died within the first 3 months after surgery [13].

In our series, 11% of the patients died early postoperatively, whereas the other 89% patients survived the 90-day period.

In the study by Van Lienden and colleagues, the mean technical success rate of the PVE procedures was 99.3% (range: 86.6–100%). The clinical success rate (successful PVE procedure, inducing enough hypertrophy of the FRL to allow resection), however, was 96.1%. In 70 (3.9%) patients, surgery was not performed. In 51 (2.8%) patients, the hypertrophy response was insufficient to perform the resection, although the embolization procedure was successful. In the other 19 cases, 12 (0.7%) did not technically succeed and seven (0.4%) caused a complication, leading to nonresectability. These complications consisted of severe cholangitis, large abscesses and sepsis, and portal venous or mesentericoportal venous thrombosis [1].

In this study, the time interval between PVE and follow-up CT was 2–4 weeks and repeated 6 weeks after PVE. Technical success rate was 92.31%. The clinical success rate at 2 weeks, however, was 75%. In six (25%) patients, the hypertrophy response was insufficient to perform the resection. The volumetric measurements were repeated 2 weeks later, and the clinical success rate at 6 weeks after PVE was 66.67%. Despite two patients showing increase in the FLR volume to be sufficient for resectability, four (16.67%) patients still not reached the target FLR volume for resection and another four (16.67%) patients showed tumor progression into the FLR despite adequate growth.

In this study, we studied the changes in the HD of FLR according to the changes in the degree of liver fibrosis. Our results showed that the patients with F2 fibrosis had rapid hypertrophy of FLR at 2 weeks with mean HD of 24.2±10.6%, and the hypertrophy continued but with slower rate, so the mean HD at 6 weeks was 37.7 ±1.4%. Patients with F3 and F4 fibrosis showed slower rate of hypertrophy with HD at 2 weeks, with 13.6 ±1.2% for patients with F3 and 11.3±6.03% for patients with F4, which changed to 25.3±7.9 and 21.7±1.3% at 6 weeks, respectively. However, all the patients showed significant increase in the FLR% compared with the pre-PVE values, with the change in the degree of fibrosis.

In the study by Van Lienden and colleagues, 29 studies (1179/1248 patients), the complication rates are summarized, 0.4%, major complications after PVE led

to nonresectability of the patient. These complications consisted of severe cholangitis, large abscesses and sepsis, and portal venous or mesentericoportal venous thrombosis [1]. The only study to describe PVE-related mortality was published by Giraudo and colleagues. In a group of 146 patients, one patient died 20 days after PVE owing to lethal pulmonary embolism. No embolization material was detected in the lung. A second patient developed cholangitis and died of septic shock 39 days after PVE. All other studies reported no PVE-related mortality, resulting in an overall mortality rate of 0.1% [14]. In this study, only 16.6% showed elevated liver enzymes for few days after PVE. Serum total bilirubin remained near pre-embolization concentrations in all patients. Major complications in the form of intra-abdominal bleeding was reported in 8.3%, and migration of the embolization material into the left portal branch causing its occlusion was reported in 8.3% of the cases.

In the study by Van Lienden and colleagues, 20% (358/1791) of the originally planned liver resections after PVE were canceled. In 37 studies (1464 patients), 18.7% of the planned resections were canceled: in 6.1% because of local intrahepatic tumor progression or newly developed metastases in the FRL. In 8.1% of patients resection was canceled because of extrahepatic tumor spread, and in 4.5% by other causes (insufficient hypertrophy of FRL despite PVE, complications of PVE leading to nonresectability, patients refusing further treatment, and preoperative mortality) [2].

The mean period between PVE and liver surgery was 36.9 (range: 21–84) days. In more than 70%, a right hemihepatectomy or extended hemihepatectomy was performed [1].

In this study, surgery was canceled in the other 30% of the cases owing to tumor progression into the FLR in four patients, FLR hypertrophy failed to reach the target volume for resection in two patients, FLR failed to grow owing to migration of the embolizing agent into the left portal vein leading to its occlusion in two patients, two patients refused surgery, and another two patients did not complete the PVE procedure owing to presence of collaterals.

D'Haese and colleagues stated that ALPPS clearly induces more hypertrophy in a shorter period than portal vein ligation or PVE [5]. In systematic review of van Lienden and colleagues, the mean hypertrophy rate of the FLR after PVE was only 37.9±0.1% within a median of 25.9±10.1 days, which is considerably less hypertrophy (72%) within a longer period than we observed in patients after the ALPPS procedure [1].

In this study, the mean hypertrophy at 2 and 6 weeks for the ALPPS group was 42±39.4 and 55±21.42%, respectively. On the contrary, the mean hypertrophy at 2 and 6 weeks for the PVE group was 37±5.77 and 55.3 ±5.0%, respectively.

Conclusion

Cirrhosis and HCC must not be considered as contraindications for the two-staged hepatectomy (ALPPS), as it can be safely done even for grade F4 fibrosis. The degree of fibrosis is the most important factor that affects the hypertrophy of the FLR. Although portal vein emobolization provides less extensive hypertrophy than ALPPS, it acts as the most reliable test of the liver functions. Both normal and diseased livers can grow in response to PVE. Cirrhotic livers regenerate at a slower rate and to a lesser extent than normal livers.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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