Bilirubin kinetics predict survival after ALPPS: results of a multicenter Italian study

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Introduction

When the future liver remnant (FLR) is too small to sustain post-resection liver function, techniques of portal vein occlusion are routinely performed to increase the residual liver volume[1]. In 2012, a new two-step surgical technique combining PVL with in situ splitting of the liver parenchyma, was able to achieve rapid and impressive FLR hypertrophy[2], later popularized with the acronym ALPPS (Associating Liver Partition and Portal vein ligation for Staged hepatectomy)[3]. Despite concerns about its safety, the procedure has quickly found spread since it allows resection of unresectable liver lesions due to the induction of rapid regeneration. The aim of this study was to determine the safety of ALPPS and to analyze perioperative complications and mortality by uni-and multivariate analysis.

Methods & Materials

This study is an observational prospective study of all patients included between March 2012 and February 2014 into a central prospective registry located at the Department of Surgery at Maggiore Hospital (Bologna, Italy). Twelve hepatobiliary centers in Italy partecipated in collection of data. Patients were classified into 3 groups for statistical analysis, according to the indication for surgery: liver metastases (n=22), biliary malignancies (n=20) and hepatocellular carcinoma (n=8). Univariate logistic regression analysis was applied in order to investigate risk factors for 90-day mortality. Survival analysis was performed with Cox Proportional Hazard Model: variables which were found to be statistically significant in univariate analysis for an α-value of 0.10 were included in the multivariate model and then excluded through a backward elimination procedure with α ≤0.05. *Δ-peak* (step1) was defined as the difference calculated between the peak of total bilirubin after step 1 and the baseline value, whereas *Δ-peak* (step2) was calculated as the difference between the peak of total bilirubin after step 2 and the last value before the second operation.

References

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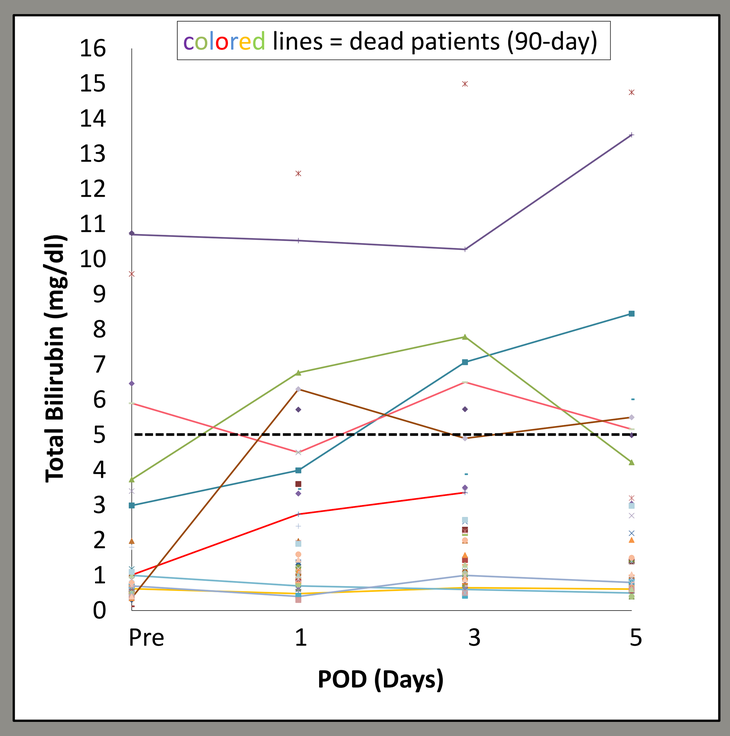
Results

Complications were classified according to the Dindo-Clavien classification of surgical complications. Overall, 160 events were documented but only 51 in 23 patients (46%) were classified as major complications (grade III and IV). PHLF was classified according to the ISGLS definition: 8 PHLF of grade A (n=3 after step 1 and n=5 after step 2), 10 of grade B (n=3 after step 1 and n=7 after step 2) and 5 of grade C were counted. However, no patients developed irreversible liver failure after the first step: two patients died due to sudden cardiac death and septic shock on postoperative day 7 and 5 respectively. The feasibility to proceed to the second stage was 92% (48/50). Mortality after complete resection was 16% (8/50 patients): 5 patients died of hepatic failure, 2 of sepsis and 1 of hemorrhagic shock. 10% of patients underwent a relaparotomy. Patients were discharged after a median hospital stay of 27 days (range 15-127).
The three groups were statistically different for age (p = 0.026), preoperative chemotherapy (p < 0.0001) and biliary stenting (p = 0.006). Baseline bilirubin values were significantly higher in the biliary group (p = 0.016). FLR increase as well as time interval between step 1 and the last CT volumetry were found to be comparable between the three groups. The biliary group experienced more complications after step 1 (p = 0.031) and higher in-hospital mortality after step 2 (p = 0.017).
On univariate analysis, some variables were found to be significantly associated with 90-day mortality: peak bilirubin >5 mg/dl after step 1 (p = 0.004) or step 2 (p = 0.001), biliary malignancy disease (p = 0.018) and age > 65 years (p = 0.006). Multivariate survival analysis revealed that peak bilirubin after step 1 >5 mg/dl and *Δ-peak* (step2) >3 mg/dl were independent prognostic factors for survival (95 % c.i. = 1.008-13.13; HR = 3.64; p = 0.049 and 95 % c.i. = 1.20-31.27; HR=6.12; p = 0.030, respectively).

Variable	95% CI	OR	p-value	95% CI	HR	p-value
Age >65 years	1.08-10.12	3.29	*0.0037*	-	-	-
Sex	0.337-3.67	1.16	0.796			
HCC vs Biliary	0.12-2.80	0.58	0.504			
METS vs Biliary	0.07-1.06	0.28	0.061			
Preoperative Biliary Drainage	0.37-7.59	1.67	0.502			
Total Bilirubin (baseline) >3 mg/dl	0.54-7.30	1.98	0.301			
FLR (preoperative)	0.98-1.002	0.99	0.149			
FLR/TLV (preoperative)	0.83-1.03	0.92	0.178			
FLR/BW (preoperative)	0.0001-5.74	0.03	0.194			
Δ-Peak (step1) >3 mg/dl	1.61-17.97	5.37	*0.006*	-	-	-
Peak Bilirubin (step1) >5 mg/dl	2.38-21.72	7.18	*0.0004*	1.008-13.13	3.64	*0.049*
Right Trisect vs. Right Hepatectomy	0.53-13.12	2.64	0.233			
Bile Duct Ligation vs. Preservation	0.45-7.99	1.90	0.380			
Bile Duct Ext Drained vs. Preservation	0.62-7.45	2.15	0.226			
FLR (precompletion)	0.99-1.003	0.99	0.498			
FLR/BW (precompletion)	0.006-7.32	0.20	0.384			
FLR/TLV (precompletion)	0.88-1.03	0.95	0.270			
Time interval (1st OP-last CT)	0.76-1.25	0.97	0.834			
FLR Increase >60%	0.63-9.001	2.38	0.199			
Δ-Peak (step2) >3 mg/dl	1.99-43.21	9.29	*0.004*	1.20-31.27	6.12	*0.03*
Peak Bilirubin (step2) >5 mg/dl	2.06-44.5	9.57	*0.004*	-	-	-



	Metastases (22 pts)	Biliary (20 pts)	HCC (8 pts)	p-value
Patients characteristics				
Gender M:F	9:13	8:12	6:2	0.261
Age (yr)	59.5 (45-79)	66.0 (54-77)	56.0 (36-74)	*0.026*
BMI	26.4 (19.6-30.4)	24.9 (19.1-19.1)	27.1 (20.8-32.3)	0.098
Diabetes	0 (0%)	2 (10%)	2 (25%)	0.054
Heart Disease	6 (27.3%)	7 (35%)	3 (37.5%)	0.780
COPD	3 (13.6%)	1 (5%)	2 (25%)	0.301
Preoperative chemotherapy	16 (72.7%)	1 (5%)	0	*<0.0001*
Failed PVO	3 (13.6%)	1 (5%)	0	0.504
Biliary stenting	0	6 (30%)	0	*0.006*
Baseline labor values				
Bilirubin (mg/dl)	0.50 (0.12-1.10)	1.49 (0.36-10.7)	0.70 (0.40-0.96)	*0.017*
INR	1.03 (0.85-1.15)	1.01 (0.06-1.18)	1.12 (0.99-1.37)	0.151
Creatinine (mg/dl)	0.84 (0.05-1.16)	0.79 (0.51-1.07)	0.70 (0.49-0.83)	0.119
Liver volumes (preoperative)				
FLR (cc)	328.0 (135-410)	293.5 (173-466)	373.0 (203-593)	*0.033*
FLR/TLV (%)	19.0 (10-27)	20.5 (10-33)	23.5 (15-35)	0.057
FLR/BW (%)	0.40 (0.21-0.58)	0.44 (0.22-0.67)	0.51 (0.31-0.73)	0.059
Liver volumes (precompletion)				
Time interval (1st OP-last CT)	7 (4-11)	7 (3-13)	8.5 (6-15)	0.427
Increase (%)	60.5 (15-227)	76.5 (37-190)	56.5 (14-178)	0.663
FLR/TLV (%)	33 (19-40)	40 (23-59)	39.5 (31-52)	*0.024*
FLR/BW (%)	0.66 (0.39-0.85)	0.89 (0.5-1.22)	0.84 (0.63-1.09)	*0.018*
Intraoperative data (step1)				
Type of resection				
•Right hepatectomy	12 (55%)	3 (15%)	4 (50%)	*0.019*
•Right trisectionectomy	10 (45%)	17 (85%)	4 (50%)	
Associated procedures	17 (77.3%)	2 (10%)	3 (37.5%)	*<0.0001*
Operative time (min)	307.5 (138-510)	350.0 (241-745)	335.0 (258-480)	0.274
Blood transfusions (n°)	0 (0-4)	0 (0-7)	0 (0-5)	0.805
Plasma transfusion(cc)	0 (0-600)	0 (0-900)	0 (0-800)	0.698
Pringle maneuver	8 (36.4%)	7 (35%)	2 (25%)	0.925
Intraoperative data (step2)				
Operative time (min)	183 (50-320)	180 (52-726)	188 (125-720)	0.607
Blood transfusions (n°)	0 (0-4)	0 (0-3)	1 (0-4)	0.929
Plasma transfusion (cc)	0 (0-1600)	0 (0-900)	0 (0-1800)	0.582
Clinical outcomes				
Major morbidity, step1	2 (9%)	8 (40%)	1 (12.5%)	*0.031*
Major morbidity, step 2	8 (36%)	5 (25%)	2 (25%)	0.741
90-day mortality, step 1	0	2 (10%)	0	0.452
90-day mortality, step 2	1 (4.5%)	6 (30%)	1 (12.5%)	*0.017*

Conclusions

ALPPS is a fascinating two-steps technique, able to achieve rapid FLR hypertrophy, thus enabling major liver resection in patients who, otherwise, would not sustain massive removal of liver parenchyma in a single step. ALPPS can be considered as a valid surgical option when performed for bilateral metastatic disease or hepatocellular carcinoma Child A patients, whereas biliary malignancies had an inferior outcome. Especially in these patients, the use of restricting criteria not only in the preoperative assessment but also between the first and second step may be helpful to decrease such a high rate of mortality. Thereby, we looked for some predictive test based on bilirubin levels, which might provide additional information to the current above-mentioned tests and be a reliable predictor of outcome after step 1, either to delay or omit step 2. Longer follow-up are needed to demonstrate the real oncologic advantages as well as potential randomized clinical trials comparing the standard techniques of portal vein occlusion vs. ALPPS procedure.

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