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ORIGINAL ARTICLE

Modification of right hepatectomy results in improvement outcome: a retrospective comparative study

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Abstract

Objective: To evaluate any change in the operative and survival outcomes in patients undergoing a right hepatectomy after adoption of the no-clamp technique using a radiofrequency dissecting sealer (TissueLink™) in liver resection.

Methods: In all, 58 consecutive patients who underwent a right hepatectomy from July 2003 to December 2007 (Group 1) were compared with 66 consecutive patients who underwent a right hepatectomy from January 1999 to June 2003 (Group 2). In group 1, a liver transection was performed with a cavitron ultrasonic surgical aspirator (CUSA) and TissueLink™ without hilar clamping whereas in group 2, a liver transection was performed with CUSA and diathermy with routine continuous hilar clamping.

Results: For the operative outcomes, there was significantly less blood loss (median 450 vs. 900 ml, $P < 0.001$) in group 1. The complication rate was also significantly lower in group 1 (22.4% vs. 47.0%, $P = 0.004$). In subgroup analysis for patients with hepatocellular carcinoma (HCC), the overall survival rate was significantly better in group 1; 1-, 3- and 5-year survival rates were 78%, 72% and 57% in group 1 vs. 72%, 44% and 39% in group 2, respectively ($P = 0.048$).

Conclusions: When compared with the retrospective cohort, a right hepatectomy utilizing TissueLink™ without hilar clamping was feasible with potential benefits in surgical outcomes.

Keywords

hilar clamping, hepatectomy, radiofrequency dissecting sealer, hepatocellular carcinoma

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Introduction

Bleeding is an important contributing factor for post-operative morbidity and mortality after hepatectomy.[1,2] The Pringle manoeuver (or hilar clamping) is commonly used in controlling hepatic inflow to decrease blood loss during liver resection.[3–5] Nevertheless, hilar clamping may decrease cardiac output and increase systemic vascular resistance during surgery.[6] Moreover it may cause ischaemic insult to the remnant liver, which is a significant problem in cirrhotic patients.[7,8] Although several studies have analysed the effect on outcome after various methods of hilar clamping during hepatectomy, the results have been inconclusive and hence no consensus exists as to the optimal usage of hilar clamping.[6,9]

In recent years, a number of new dissecting instruments have been developed to facilitate liver resection with less blood loss. TissueLink™ (TissueLink medical Inc., Dover, DE, USA) is a type of saline-linked radiofrequency dissecting sealer. It employs radiofrequency energy, which is transmitted to the target tissue through saline dripping. It seals the intrahepatic vessels through shrinkage of collagen at a temperature below 100°C and thus prevents char formation. It has been shown to achieve better haemostasis than conventional diathermy in hepatectomy.[10,11]

Prior to 2003 at the Prince of Wales Hospital, Hong Kong, it was standard practice for a continuous hilar clamp to be applied during parenchymal dissection for patients undergoing a right hepatectomy. Parenchymal dissection and a transection was then performed using the ultrasonic surgical aspirator (CUSA;

ValleyLab, Boulder, Co, USA) and diathermy. Since early 2003, parenchymal dissection and transection was performed using CUSA and TissueLink™. Starting with a minor hepatectomy, the blood loss during liver resection was noted to be very low even without hilar clamping. Thus the standard technique from July 2003 for parenchymal dissection and transection during major hepatectomy became CUSA and TissueLink™ without routine hilar clamping.[12]

The present study was intended to determine whether these changes in technique resulted in changes in the post-operative outcomes and survival after a right hepatectomy.

Methods

All patients who underwent a right hepatectomy in the Prince of Wales Hospital, Hong Kong during the period from 1st January 1999 to 31st December 2007 were included in the present study. A right hepatectomy was defined as resection of the Couinaud's segments 5 to 8 (±segment 1) according to the Brisbane classification.[13] Patients who underwent a concomitant bile duct resection, bowel resection or extended right hepatectomy which involved resection of segment 4 were excluded from the present study. Patients were divided into two groups according to the method of liver resection. From July 2003 to December 2007, patients underwent a right hepatectomy with the use of a radiofrequency dissecting sealer and CUSA without hilar clamping (group 1) whereas from January 1999 to June 2003, patients underwent a right hepatectomy with the use of CUSA, diathermy and routine hilar clamping (group 2). The baseline characteristic, intra-operative parameters and post-operative outcomes were compared between the two groups. Outcomes of particular interest were post-operative morbidity and mortality, operation time, blood loss, transfusion rate, post-operative liver function, hospital stay and survival. Surgical complications were classified as described by Dindo and colleagues.[14] Post-operative hepatic insufficiency was defined by the 50–50 criteria from Belghiti *et al.*[15] (bilirubin level >50 μmol/l and prothrombin time <50% at post-operative day 5). Hepatic encephalopathy was defined as an altered mental state as a result of impaired liver function, evidenced by a rise in serum ammonia level. Liver failure was defined as progressively increasing hyperbilirubinemia with serum total bilirubin persistently ≥85 μmol/l.[16] Operative mortality was defined as death within the same admission for surgery or death occurred within 30 days after surgery. A blood transfusion was given if there was haemodynamic disturbance as a result of a massive blood loss or when the haemoglobin level dropped below 8.0 g/dl. Any blood given during surgery or within the same admission after surgery was counted as a peri-operative transfusion.

Surgical technique

All surgical procedures were performed by consultant-grade surgeons specialized in hepato-biliary surgery at a university hospital. Operations were performed with a right subcostal incision with an upward midline extension, and in selected patients this was extended by a left subcostal incision. Intra-operative ultrasound (Aloka, Tokyo, Japan) was used in all patients to define the tumour, to exclude pre-operatively undetected lesions and to mark the plane for a liver parenchymal transection. The central venous pressure was ideally kept below 5 cm H_2O.[17–19] The approach to liver mobilization was variable and left to the discretion of the surgeon.

In group 1, hilar dissection was performed to ligate the right hepatic artery and right portal vein if possible before liver transection. Otherwise, the hepatic artery and portal vein branches were ligated intra-hepatically during parenchymal transection. Liver transection was performed with CUSA and a radiofrequency dissecting sealer (TissueLink™) without hilar clamping. In group 2, continuous hilar clamp was applied during liver transection. The right hepatic artery and portal vein were divided intra-hepatically during liver transection either by a endovascular stapler or using a knife between clamps with over sewing of both ends. A liver parenchymal transection was performed with CUSA and diathermy. Larger vessels and the bile duct were ligated separately in both groups. Right hepatic veins were usually divided by endovascular staplers. In most patients, tissue glue (Tisseel; Baxter, Vienna, Austria) was sprayed onto the liver transection surface to augment haemostasis and to decrease bile leak, although a recent study showed that its routine use might not be justified.[20] The decision to place abdominal drains was left to the operating surgeons.

Statistical analysis

Data were expressed in mean ± standard deviations (SD) or median (range). Continuous variables were compared using Student's *t*-tests or Mann–Whiney *U*-test as appropriate; whereas categorical variables were compared with χ^2 test or Fisher's exact test as appropriate. Survival curves of disease-free survival and overall survival were calculated using the Kaplan–Meier method and compared with a two-sided log-rank test in univariate analysis. Multivariate analysis was performed by stepwise Cox regression in prognostic factors with $P < 0.050$ during univariate analysis for survival analysis in patients with a hepatocellular carcinoma. A statistically significant result was defined as $P < 0.05$. All statistical calculations were performed using SPSS 15.0 software (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

In all, 124 patients were included in the analysis: 58 (47%) patients belonged to group 1 whereas 66 (53%) patients belonged to group 2. The baseline characteristics between the two groups are shown in Table 1.

Table 1 Baseline characteristics table

	Group 1 (n = 58)	Group 2 (n = 66)	P-value
Age	51.5 (17–72)	54 (33–76)	0.174
Gender (M : F)	78% : 22%	89% : 11%	0.090
ASA score			0.254
I	21 (36%)	26 (39%)	
II	33 (57%)	30 (45%)	
III	4 (7%)	10 (15%)	
Number of medical co-morbidity	1 (0–5)	0 (0–5)	0.607
Liver cirrhosis	14 (24%)	24 (36%)	0.141
Child's grading in cirrhotic patients (A/B)	14/0	23/1	1.000
Tumour size (cm)	6.9 ± 3.3	6.0 ± 2.8	0.117
Resection margin (cm)	1.6 ± 1.3	1.4 ± 1.4	0.623
Pathology			
Hepatocellular carcinoma	36 (62%)	50 (76%)	
Colorectal metastasis	14 (24%)	11 (17%)	
Cholangiocarcinoma	4 (7%)	0 (0%)	
Undifferentiated carcinoma	0 (0%)	1 (2%)	
Metastatic gastrointestinal stromal tumour	1 (2%)	0 (0%)	
Benign liver conditions	3 (5%)	4 (6%)	

ASA, American Society of Anesthesiologists; medical co-morbidity included diabetes, hypertension, hyperlipidaemia, gout, ischaemic heart disease, history of stroke, chronic obstructive pulmomary disease; Benign liver conditions included recurrent pyogenic cholangitis, focal nodular hyperplasia, hepatic haemangioma and adenoma.

Table 2 Operative outcomes

	Group 1 (n = 58)	Group 2 (n = 66)	P-value
Total operative time (min)	318 ± 64	185 ± 45	<0.001[a]
Clamp time (min)	NA	20 ± 8	
Placement of the abdominal drain	28 (48.3%)	41 (62.1%)	0.122
Blood loss (ml)	450 (100–2400)	900 (186–11745)	<0.001[a]
Transfusion rate	6 (10.3%)	17 (27.0%)	0.020[a]
Complications rate	13 (22.4%)	31 (47.0%)	0.004[a]
Hospital stay (days)	8 (5–36)	10 (6–69)	0.004[a]
Operative mortality	1 (1.7%)	4 (6.1%)	0.370

[a]Statistically significant result ($P < 0.05$).

Operative outcomes

The operative outcomes are summarized in Table 2. In summary, group 1 had less blood loss, a lower transfusion rate, a lower complication rate and shorter hospital stay than group 2. The list of complications according to Dindo's description[14] is shown in Table 3.

Post-operative liver function

There was no significant difference in the pre-operative international normalized ratio (INR), albumin and bilirubin levels between the two groups. The mean bilirubin, INR and albumin level at post-operative day 5 (D5) were used as surrogate markers for post-operative recovery of liver function. The D5 albumin level (g/l) was significantly higher in group 1 (group 1 vs. group 2 = 30.4 ± 4.9 vs. 27.7 ± 3.8, $P = 0.002$). The D5 INR, bilirubin level and rate of hepatic insufficiency (group 1 vs. group 2 = 6.1% vs. 12.2%, $P = 0.487$) were also higher in group 2, although results did not reach statistical significance.

Subgroup analysis on heptocellular carcinoma

A total of 36 patients in group 1 and 50 patients in group 2 were included for analysis. Baseline comparison between the two groups is shown in Table 4. The median follow-up durations were 38.4 (0.8–80.1) and 25.7 (0.2–124.3) months in group 1 and 2, respectively. The overall survival rate for patients with heptocellular carcinoma (HCC) was significantly higher in group 1. The

Table 3 List of complications

	Group 1 (n = 58)	Group 2 (n = 66)
Hepatic encephalopathy	0	4
Bile leakage	1	2
Liver failure	1	2
Renal failure	0	2
Pneumonia	0	2
Post-operative bleeding	0	2
Pleural effusion	1	9
Intra-abdominal collection	6	4
Wound infection	6	14
Others complications[a]	1	3

[a]Other complications included urinary tract infection, urinary retention, incisional hernia, soleal vein thrombosis.

1-, 3- and 5-year survival rates were 78%, 72% and 57% in group 1 and 72%, 44% and 39% in group 2, respectively (P = 0.048). (Fig. 1a) The disease-free survival rate was also significantly higher in group 1. The 1-, 3- and 5-year disease-free survival rate was 73%, 61% and 57% in group 1 and 47%, 31% and 26% in group 2, respectively (P = 0.009) (Fig. 1b). Univariate and multivariate analysis on survival in HCC patients is shown in Table 5. Group 2 and the presence of a satellite nodule were independent prognostic factors for overall survival in HCC patients.

Effect of transfusion on complication and survival in HCC patients

The complication rate was significantly higher in patients who received a blood transfusion vs. those who did not receive a transfusion; 14 (60.9%) vs. 30 (29.7%), P < 0.005. The wound infection rate was also higher in patients who received a transfusion 7 (30.4%) vs. those who did not 16 (12.9%), although it did not reach statistical significance, P = 0.057. Excluding the patients who received a transfusion in group 2, there was no statistical significance in the complication rate between group 1 and 2; 13 (22.4%) vs. 19 (38.8%), P = 0.066. With regards to survival in HCC patients, after excluding the patients who received a transfusion in group 2, the overall survival rate was still significantly better in group 1; 1-, 3- and 5-year survival rates were 78%, 72% and 57% in group 1 vs. 69%, 39% and 36% in group 2, P = 0.028.

Discussion

Pringle's manoeuver is a traditional method used to reduce blood loss during a hepatectomy. However, a surgeon's main concern for hilar clamping is the ischaemic–reperfusion injury to the remnant liver and subsequent development of post-operative liver failure, especially in cirrhotic patients. In order to preserve the liver function, some surgeons advocate a hepatectomy without hilar clamping,[10,21] especially in a live donor hepatectomy.[22–24] The present study showed that a right hepatectomy without hilar clamping was feasible and safe when combined with the use of CUSA and a radiofrequency dissecting sealer. When compared with the retrospective cohort of routine hilar clamping with CUSA and diathermy, it resulted in significantly less blood loss, less post-operative complications, shorter hospital stay and even better survival in patients treated for HCC.

A formal right hepatectomy was chosen for comparison in the present study because it is commonly performed. As the surgical anatomy and the magnitude of surgery were standardized, it allowed a fair comparison between the two techniques. In addition, all consecutive patients undergoing a right hepatectomy from a single centre were studied, strengthening the validity of this study and the comparative data. It should be acknowledged that several other factors may have contributed to the observed differences.

These factors would include changes in the CVP, the method of hepatic mobilization or indeed simply the extrahepatic ligation of the right portal pedicle. However, given the retrospective nature of this study, these were not able to be studied in detail.

Contrary to the most common belief, an interesting finding of the present study was a significantly higher blood loss in the group 2 (median 900 vs. 450 ml, P < 0.001). It is the authors' belief that the likely explanation is the improvement in surgical technique and the use of a radiofrequency dissecting sealer. From the authors previous experience of 248 consecutive patients undergoing partial hepatectomy, the radiofrequency dissecting sealer was effective in hemostasis during a partial hepatectomy, even without hilar clamping.[12] Other studies also showed that a radiofrequency dissecting sealer is effective in controlling bleeding during a hepatectomy.[10,11,21,24] Besides, without hilar clamping, there would not be any time constraint with regard to ischaemic insult to the remnant liver. As a result, surgeons would have more time for meticulous haemostasis in group 1. In addition the TissueLink™ needs time to achieve secure haemostasis on the liver transection surface. These were the main reasons for longer operating time in group 1.

Previous studies showed that a cirrhotic liver can tolerate up to 30–45 min of ischaemia at a normal body temperature.[25,26] As the mean clamping time was just 20 min in group 2, the effect on post-operative liver function was expected to be small. This short clamp time would also explain the insignificant change in the post-operative liver function between the two groups.

Possible explanations with regards to post-operative complications were a significantly higher blood loss and transfusion rate in group 2. When we compared patients who received a transfusion to patients who did not, the complication rate was significantly higher in the former group. Besides, after exclusion of patients receiving a transfusion in group 2, there was no statistical significance in the complication rate between group 1 and 2. The significant difference in the complication rate also explained the longer hospital stay in group 2.

In subgroup analysis for patients with HCC who underwent a right hepatectomy with curative intent, there was a significant

Table 4 Baseline characteristics and tumour recurrence in hepatocellular carcinoma (HCC) patients

	Group 1 (n = 36)	Group 2 (n = 50)	P-value
Baseline characteristics			
Number of medical co-morbidity	0 (0–5)	0 (0–5)	0.320
Cirrhosis	13 (36.1%)	24 (48.0%)	0.272
Child's grading in cirrhotic patients (A/B)	13/0	23/1	1.000
Median blood loss (ml)	462 (100–1700)	930 (200–11745)	<0.001[a]
Transfusion rate	4 (11.1%)	14 (29.8%)	0.041[a]
Tumour characteristics			
Tumour size (cm)	6.3 ± 2.7	6.5 ± 3.3	0.713
Vascular invasion	11 (36.0%)	10 (20.0%)	0.171
Satellite lesions present	7 (19.4%)	9 (18.0%)	0.865
Resection margin (cm)	1.5 ± 1.0	1.0 ± 0.9	0.022[a]
Tumour differentiation			0.153
Well	9 (25.0%)	14 (28.5%)	
Moderate	26 (72.2%)	28 (57.1%)	
Poor	1 (2.8%)	7 (14.3%)	
TNM staging			0.868
I	21 (58.3%)	32 (64.0%)	
II	5 (13.9%)	6 (12.0%)	
III	10 (27.8%)	12 (24.0%)	
Tumour recurrence			
Recurrence rate	13 (36.1%)	27 (54.0%)	0.101
Treatment for recurrence			
Surgical resection	2	2	
Trans-arterial therapy	1	4	
Systemic chemotherapy	8	6	
Local ablative therapy	1	1	

[a]Statistically significant result ($P < 0.05$).
TNM, tumour node metastasis.

improvement in overall and disease-free survival in group 1. The 3- and 5-year survival rates for HCC patients were 72% and 57% in group 1, which were comparable to that around 60% and 40% as reported from the literature with various surgical techniques.[27–29] The difference in blood loss and transfusion rate may contribute to the survival difference between the two groups. Univariate analysis from the present study showed that a blood loss of more than 500 ml was a significant risk factor for survival. Other studies also showed that operative blood loss and peri-operative blood transfusion were important prognostic factors on tumour recurrence and overall survival.[30–33] However, after excluding the patients who received a transfusion in group 2, the survival rate was still significantly lower than in group 1. The result suggested that factors other than blood transfusion would also contribute to the survival difference between the two groups. In fact, results from the univariate and multivariate analysis showed that HCC patients in the group using continuous hilar clamping had a significantly poorer survival. From the literature, data on the effect of ischaemic–reperfusion injury to tumour recurrence and survival is still lacking. The authors postulate that it might be because of the improvement in the peri-operative management between the two groups. Undoubtedly, there were significant improvements in the surgical technique and peri-operative management during the time interval between group 1 and 2. It was a major confounding factor for survival difference between the two groups. Besides, the differences in complication rate and post-operative liver function may also contribute to the difference in survival between the two groups.

Conclusions

With the improvement in dissecting instruments and surgical technique, a change in practice from routine hilar clamping to no clamping occurred for patients undergoing a right hepatectomy. The change was made possible by adopting better haemostatic instruments (CUSA and radiofrequency dissecting sealer) and a meticulous technique of dissection. When compared with the ret-

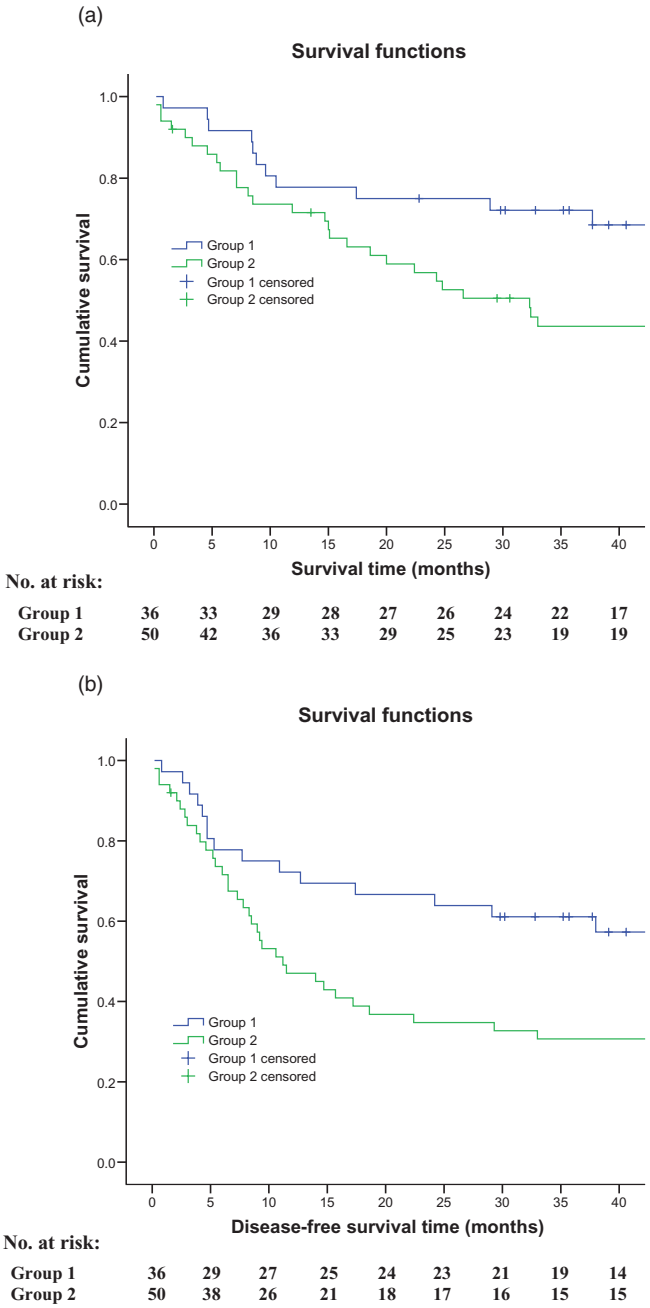

Figure 1 Kaplan–Meier analysis on survival in hepatocellular carcinoma (HCC) patients. (a) Overall survival in HCC patients, log-rank test $P = 0.048$. (b) Disease-free survival in HCC patients, log-rank test $P = 0.009$.

rospective cohort, a right hepatectomy utilizing TissueLink™ without hilar clamping was feasible with potential benefits in surgical outcomes.

Conflicts of interest

None declared.

Table 5a Univariate analysis on prognostic factors for survival in hepatocellular carcinoma (HCC) patients

		P-value[a]
Surgical technique	Group 1	0.048[b]
	Group 2	
Operative blood loss	≤500 ml	0.047[b]
	>500 ml	
Blood transfusion	No	0.680
	Yes	
Tumour size	<5 cm	0.137
	≥5 cm	
Resection Margin	<1 cm	0.423
	≥1 cm	
Presence of satellite nodule	No	0.005[b]
	Yes	
Tumour differentiation	Poor	0.495
	Moderate	
	Well	
TNM staging	I	0.057
	II	
	III	

TNM, tumour node metastasis.

Table 5b Multivariate analysis on prognostic factors for survival in HCC patients

		Hazard ratio	*P*-value[a]
Surgical technique	Group1	1.00 (reference)	
	Group2	2.00 (1.04, 3.86)	0.037[b]
Presence of satellite nodule	No	1.00 (reference)	
	Yes	2.68 (1.36, 5.29)	0.004[b]

[a]Log rank test.
[b]Statistically significant result ($P < 0.05$).

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