Adverse impact of intermittent portal clamping on long-term postoperative outcomes in hepatocellular carcinoma

S Hao¹, S Chen¹, X Yang², C Wan¹

¹Huazhong University of Science and Technology, Wuhan, China

²Central South University, Changsha, China

ABSTRACT

INTRODUCTION To evaluate the impact of intermittent portal clamping (IPC) on long-term postoperative outcomes in patients with hepatocellular carcinoma (HCC).

METHODS Clinical records of 355 patients underwent curative liver resection for HCC in January 2007 to December 2010 were retrospectively reviewed. According to how portal clamping was performed, patients were grouped as: IPC, n=113; other portal clamping (OPC), n=190; and no portal clamping (NPC), n=52.

RESULTS Median recurrence-free survival (RFS) was statistically significantly shorter in the IPC (39.4 months) than OPC (47.3 months, $p=0.010$) and NPC groups (51.4 months, $p=0.008$). Median overall survival (OS) was also significantly shorter with IPC (46.3 months), versus 52.9 months with OPC ($p=0.022$) and 56.2 months with NPC ($p=0.015$). Kaplan–Meier survival analysis revealed that 5-year cumulative RFS was much lower in the IPC (42.5%) than OPC (50.9%, $p=0.014$) and NPC groups (49.6%, $p=0.013$). Five-year cumulative OS was also much lower in the IPC (44.9%) than OPC (58.0%, $p=0.020$) and NPC groups (57.7%, $p=0.025$). On univariate analysis, tumour grade, size and number, TNM stage, blood transfusion, vascular invasion and IPC were significantly inversely correlated with RFS and OS. On multivariate analysis, tumour size and number, blood transfusion, vascular invasion and IPC remained significant.

CONCLUSIONS Our study suggests that IPC is an independent risk factor for poor long-term postoperative outcomes in patients with HCC.

KEYWORDS

Hepatocellular carcinoma – Hepatectomy – Survival analysis

Accepted 11 January 2016

CORRESPONDENCE TO

Shenghua Hao, E: haoshenghua@126.com

Liver resection remains the curative therapy of choice for hepatocellular carcinoma (HCC).¹ However, the effective control of intraoperative bleeding is crucial to completing the operation and reducing postoperative morbidity and mortality.² Portal inflow occlusion (the Pringle manoeuvre) is the primary approach for reducing operative haemorrhage,³ and intermittent portal clamping (IPC), a modification of the Pringle manoeuvre, is frequently applied in liver surgery.⁴ However, it is unclear whether or not patients undergoing IPC have favorable long-term outcomes. It has been reported that, in comparison with other clamping techniques, IPC maneuver may come with some pitfalls,⁵ such as more intraoperative blood loss, prolonged duration of operation and excessive surgical manipulation.

To address this issue, we reviewed the clinical records of a large cohort of patients who underwent curative liver resection, with the aim of evaluating the impact of IPC on long-term postoperative outcomes in patients with HCC.

Methods

Three hundred and fifty five patients who underwent curative hepatectomy for HCC at the Union Hospital, Tongji Medical College, Huazhong Science and Technology University (Wuhan, China) or at the Third Xiangya Hospital of Central South University (Changsha, China) between January 2007 and December 2010 were included. Two hundred and thirteen patients were male and 142 female. Their mean age was 48.5 ± 10.3 years (range 18–79 years). Written consent was obtained for all patients and the study was approved by the relevant institutional review boards.

Liver resection was carried out using Pean fracture or finger fracture approach, or the Cavitron Ultrasonic Surgical Aspirator (CUSA) technique. A minor hepatectomy was defined as resection of less than three segments of liver, while a major hepatectomy required resection of at least three segments. IPC was performed in 113 patients, which consisted of occlusion of the portal flow via clamping for 15

minutes followed by unclamping for 5 minutes, with the cycle repeated 2–3 times whenever necessary. A further 190 patients received other portal clamping (OPC), consisting of the continuous Pringle manoeuvre, preconditioning portal clamping or selective portal clamping, and 52 patients had the CUSA technique and thus no portal clamping (NPC). The choice over clamping was left to surgeon preference.

Following surgery, patients were followed-up with serum alpha-fetoprotein (AFP) measurements and imaging, comprising ultrasound, computed tomography and magnetic resonance imaging, every 2 months in the first year and every 3–4 months thereafter. Recurrence was defined as rebound AFP levels and the appearance of a new lesion on imaging. Recurrence-free survival (RFS) was defined as the interval between surgery and the date of diagnosis of first recurrence. Overall survival (OS) was defined as the interval between surgery and the date of death or last follow-up.

Statistical analysis

Data are presented as mean (standard deviation), median (range) and percentage. Demographic and clinical factors were assessed on univariate analysis, with between-group differences analyzed using Pearson's chi-squared test. For factors on univariate analysis with a *p* value of <0.05, multivariate analysis was performed to identify those predicting postoperative survival. Survival was compared between the groups using Kaplan–Meier analysis. Statistical analyses were performed using SPSS Statistics, version 19.0 (IBM, Armonk, New York, USA). *p*<0.05 was considered statistically significant.

Results

As shown in Table 1, demographic and clinicopathological features were comparable between the groups. Mean follow-up was 49.7 months (range 6–66 months), and 328 patients had a minimum follow-up of 6 months. Seventeen patients were lost to follow-up within 1–5 months (six in the IPC group, nine in the OPC group and two in the NPC group), and 10 patients died within 3 months of surgery (three IPC patients, six OPC patients and one NPC patient).

The overall perioperative mortality rate was 2.8% (10/355). Among the 328 patients follow-up for a minimum of 6 months, 146 had recurrence (53/104 IPC patients, 75/174 OPC patients and 12/49 NPC patients), and 120 died of cancer-related causes (48 IPC, 65 OPC and 14 NPC patients). Median RFS and OS in the IPC group was 39.4 months and 46.3 months, respectively, which was significantly shorter than that seen in the OPC group (47.3 months, *p*=0.003, and 52.9 months, *p*=0.001, respectively) in the OPC group (51.4 months, *p*=0.009, and 56.2 months, *p*=0.002, respectively).

Five-year cumulative RFS was 42.5% in the IPC group, which was significantly lower than that among OPC patients (50.9%, *p*=0.025) and NPC patients (49.6%, *p*=0.020) (Figure 1). Five-year cumulative OS was also significantly shorter in the IPC than in the OPC and NPC groups, at 44.9% versus 58.0% (*p*=0.014) and 57.7% (*p*=0.012), respectively (Figure 2).

Thirteen clinicopathological factors were evaluated on univariate and multivariate analysis to assess their correlations

Table 1 Demographic and clinicopathologic factors

Variables	IPC (N=113)	OPC (N=190)	NPC (N=52)	P Value
Age (mean, year)	51.7	53.6	55.0	0.665
Sex: Male (male/female)	67.3 (76/37)	68.4 (130/60)	71.1 (37/15)	0.750
Child-Pugh score: A (A/B)	65.5 (74/39)	64.7 (123/67)	67.3 (35/17)	0.700
TNM Stage: I-II (I-II/III)	61.9 (70/43)	67.9 (129/61)	69.2 (36/16)	0.613
Differentiation: H-M (H-M/L-U)	69.0 (78/35)	63.2 (120/70)	61.5 (32/20)	0.486
Tumour size ≤5cm (≤5cm/>5cm)	35.4 (40/73)	40.0 (76/114)	42.3 (22/30)	0.575
Tumour number <2 (<2/≥2)	60.2 (67/46)	61.6 (117/73)	65.4 (34/18)	0.379
Hepatectomy Minor (Minor/Major)	37.2 (42/71)	42.1 (80/110)	48.1 (25/27)	0.323
Virology HBV/HCV(+) [HBV-HCV(+)/(-)]	81.4 (92/21)	78.9 (150/40)	82.7 (43/9)	0.478
All values % (n/n), unless otherwise stated HBV = hepatitis B virus; HCV = hepatitis C virus; H-M = high-moderate; IPC = intermittent portal clamping; L-U = low-undifferentiated; NPC = no portal clamping; OPC = other portal clamping				

with RFS and OS. On univariate analysis, tumour grade (low/undifferentiated), tumour size (>5 cm), tumour number (≥2), TNM stage (III), blood transfusion, vascular invasion, liver cirrhosis, hepatitis B virus (HBV) replication and IPC were significantly negatively correlated with RFS. Tumour size (>5 cm), tumour number (≥2), liver cirrhosis, HBV replication, blood transfusion, vascular invasion and IPC remained significant on multivariate analysis (Table 2).

There were similar results on univariate analysis for factors associated with OS, with tumour grade (low/undifferentiated), size (>5 cm) and number (≥2), and TNM stage (III), blood transfusion, vascular invasion and IPC all significantly negatively correlated with OS. However, multivariate analysis demonstrated that liver cirrhosis, HBV replication, TNM stage and tumour grade were no longer associated with OS, while tumour size/number, vascular invasion, blood transfusion and IPC remained significant (Table 3).

Discussion

HCC is the sixth most common malignancy and the third most common cause of cancer-related death worldwide.⁶ Overall 5-year survival is typically less than 40–60%.^{7,8} A number of factors affect the survival of HCC patients after surgery, and these can be classified as:⁹ tumour-related, including the size and number of tumours, HCC grade, macroscopic or microscopic vascular invasion and TNM stage; patient-related, such as liver cirrhosis, HBV/hepatitis infection

Figure 1 Five-year cumulative recurrence-free survival

Figure 2 Five-year cumulative overall survival

Factor	Univariate			Multivariate		
	95% CI	RR	P	95% CI	RR	P
Sex (M vs F)	0.46, 1.45	0.81	0.55			
Age (≤ 60 vs >60)	0.92, 1.93	0.97	0.232			
Child-Pugh score (A vs B)	0.68, 1.35	0.79	0.361			
TNM stage (I, II vs III)	0.98, 1.12	1	0.023			
Differentiation (H-M vs L-U)	1.77, 4.48	2.6	0.017			
Tumour number (1 vs ≥ 2)	1.86, 5.15	2.83	0.001	2.99, 6.33	4.35	0
Tumour diameter (≤ 5 vs >5 cm)	1.50, 3.90	2.55	0.01	2.21, 4.88	3.66	0.001
Vascular invasion (Yes vs No)	1.28, 3.87	2.63	0.014	2.75, 5.56	3.86	0
Duration of occlusion (≤ 45 vs >45 minutes)	0.95, 1.66	1.05	0.26			
Liver cirrhosis (Yes vs No)	1.90, 3.92	2.85	0.001	3.02, 5.85	3.88	0.001
HBV replication (Yes vs No)	1.88, 4.02	3	0.001	2.95, 6.15	3.5	0.001
Blood transfusion (Yes vs No)	1.10, 2.48	1.76	0.022	2.34, 3.89	3.351	0.001
Portal clamp modality (IP vs OP)	1.47, 2.94	2.05	0.013	2.25, 3.69	2.936	0.001

CI = confidence interval; H-M = high-moderate; HBV = hepatitis B virus; IP = intermittent portal; L-U = low-undifferentiated; OP = other portal; RFS = recurrence-free survival rate; RR = risk ratio.

Factor	Univariable			Multivariable		
	95%CI	RR	P	95%CI	RR	P
Sex (M vs F)	0.46, 1.45	0.81	0.55			
Age (≤ 60 vs >60)	0.92, 1.93	0.97	0.232			
Child-Pugh score (A vs B)	0.68, 1.35	0.79	0.361			
TNM stage (I, II vs III)	0.98, 1.12	1	0.023			
Differentiation (H-M vs L-M)	1.77, 4.48	2.6	0.017			
Tumour number (1 vs ≥ 2)	1.86, 5.15	2.83	0.001	2.99, 6.33	4.35	0
Tumour diameter (≤ 5 vs >5 cm)	1.50, 3.90	2.55	0.01	2.21, 4.88	3.66	0.001
Vascular invasion (Yes vs No)	1.28, 3.87	2.63	0.014	2.75, 5.56	3.862	0
Duration of occlusion (≤ 45 vs >45 minutes)	0.95, 1.66	1.05	0.26			
Liver cirrhosis (Yes vs No)	1.90, 3.92	2.85	0.001			
HBV replication (Yes vs No)	1.88, 4.02	3	0.001			
Blood transfusion (Yes vs No)	1.10, 2.48	1.76	0.022	2.34, 3.89	3.351	0.001
Portal clamp modality (IP vs OP)	1.47, 2.94	2.05	0.013	2.25, 3.69	2.936	0.001

CI = confidence interval; H-M = high-moderate; HBV = hepatitis B virus; IP = intermittent portal; L-U = low-undifferentiated; OP = other portal; OS = overall survival rate; RR = risk ratio.

and impaired liver reserve; and surgery-related, including intraoperative blood loss, blood transfusion and frequent manipulations.

In this cohort of patients, we found that the median RFS and OS was significantly shorter in IPC patients than in the OPC group following liver resection. Moreover, Kaplan–Meier

analysis revealed that 5-year cumulative RFS and OS were much lower in IPC than in OPC patients. Our results indicated that, when compared with OPC, IPC patients experience earlier recurrence and more tumour-related deaths, suggesting that IPC may have promoted tumour recurrence and progression.

Tumour characteristics are highly associated with HCC prognosis,^{10–15} with tumour size, number and differentiation and vascular invasion reported as crucial risk factors for a poor long-term postoperative outcome. In the current study, we found that tumour size, tumour number, and vascular invasion were associated high relative risks in terms of both RFS and OS (all $p < 0.001$).

The evidence for the impact of surgery-related factors on postoperative survival among HCC patients is not quite as definitive. Some authors found that surgery-associated factors such as intraoperative blood loss, operative complications, operative time and the duration of portal occlusion were associated with poor postoperative survival,^{14,15} whereas others did not.^{16,17} Nonetheless, blood transfusion is usually considered as a predictor of poor prognosis in HCC patients,^{18,19} and our study supported the notion that blood transfusion can have an adverse impact on outcomes.

More importantly, the present study revealed that IPC was an independent risk factor associated with poor RFS and OS among HCC patients. The IPC manoeuvre is virtually an ischemia reperfusion injury process.²⁰ Evidence from the literature suggests that liver ischemic reperfusion-injury induced by portal clamping plays a critical role in tumour recurrence and progression in damaged remnant liver, both in animal models,^{21–25} and in clinical practice.^{24,25} This process involves a number of signal pathways and pathological cascades that facilitate tumour cell metastasis and growth.^{26–28}

Taken together, we believe that surgery-related factors can play an important role in postoperative survival in HCC patients. Previous studies have found that hepatectomy manipulations can significant influence the dislodging of cancer cells from the main tumour.^{29,30} Moreover, pressure gradients between tumour vessels and portal vein affect the spread of tumour cells into portal veins.³¹ Indeed, excessive manipulation, prolonged operative times, dramatic pressure fluctuations in the tumourinterstitial space with IPC all can facilitate the shedding of cancer cells from main tumour and their spread along portal system to form metastases. Therefore, in addition to the ‘favourable soil’ produced by ischaemic reperfusion injury with portal inflow occlusion, IPC can enhance the spread of ‘viable seeds’, which ultimately increases the probability of HCC recurrence and progression.

Conclusions

To our knowledge, the current study is the first report with a large cohort of patients to demonstrate a significant, adverse impact of IPC on the HCC recurrence and progression. It suggests that IPC is an independent risk factor for poor long-term outcomes in HCC patients undergoing curative hepatectomy. However, a larger scale, randomised, prospective study is required to elucidate the underlying mechanism by which IPC induces poor postoperative survival among HCC patients.

Acknowledgements

We declare no conflicts of interest and no funding.

References

1. van Gulik TM, de Graaf W, Dinant S *et al.* Vascular occlusion techniques during liver resection. *Dig Surg* 2007; **24**: 274–281.
2. Jarnagin WR, Gonen M, Fong Y *et al.* Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg* 2002; **236**: 397–406; discussion 406.
3. Pringle JH. V. Notes on the Arrest of Hepatic Hemorrhage Due to Trauma. *Ann Surg* 1908; **48**: 541–549.
4. Belghiti J, Noun R, Malafosse R *et al.* Continuous versus intermittent portal triad clamping for liver resection: a controlled study. *Ann Surg* 1999; **229**: 369–375.
5. Nuzzo G, Giuliani F, Giovannini I *et al.* Hepatic resections in normothermic ischemia. *Surgery* 1996; **120**: 852–858.
6. Parkin DM, Bray F, Ferlay J *et al.* Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74–108.
7. Fong Y, Sun RL, Jarnagin W *et al.* An analysis of 412 cases of hepatocellular carcinoma at a Western center. *Ann Surg* 1999; **229**: 790–9; discussion 799.
8. Chang CH, Chau GY, Lui WY *et al.* Long-term results of hepatic resection for hepatocellular carcinoma originating from the noncirrhotic liver. *Arch Surg* 2004; **139**: 320–5; discussion 326.
9. Tung-Ping Poon R, Fan ST, Wong J. Risk factors, prevention, and management of postoperative recurrence after resection of hepatocellular carcinoma. *Ann Surg* 2000; **232**: 10–24.
10. Shah SA, Greig PD, Gallinger S *et al.* Factors associated with early recurrence after resection for hepatocellular carcinoma and outcomes. *J Am Coll Surg* 2006; **202**: 275–283.
11. Regimbeau JM, Abdalla EK, Vauthey JN *et al.* Risk factors for early death due to recurrence after liver resection for hepatocellular carcinoma: results of a multicenter study. *J Surg Oncol* 2004; **85**: 36–41.
12. Imamura H, Matsuyama Y, Tanaka E *et al.* Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. *J Hepatol* 2003; **38**: 200–207.
13. Tandon P, Garcia-Tsao G. Prognostic indicators in hepatocellular carcinoma: a systematic review of 72 studies. *Liver Int* 2009; **29**: 502–510.
14. Kusano T, Sasaki A, Kai S *et al.* Predictors and prognostic significance of operative complications in patients with hepatocellular carcinoma who underwent hepatic resection. *Eur J Surg Oncol* 2009; **35**: 1,179–1,185.
15. Hanazaki K, Kajikawa S, Shimozaawa N *et al.* Survival and recurrence after hepatic resection of 386 consecutive patients with hepatocellular carcinoma. *J Am Coll Surg* 2000; **191**: 381–388.
16. Bruns H, Krätschmer K, Hinz U *et al.* Quality of life after curative liver resection: a single center analysis. *World J Gastroenterol* 2010; **16**: 2,388–2,395.
17. Lei Z, Chang L, Fan-Di M *et al.* Exploration on surgical-related factors influencing HCC patients prognosis. *Hepatogastroenterology* 2012; **59**: 1,541–1,543.
18. Katz SC, Shia J, Liao KH *et al.* Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. *Ann Surg* 2009; **249**: 617–623.
19. de Boer MT, Molenaar IQ, Porte RJ. Impact of blood loss on outcome after liver resection. *Dig Surg* 2007; **24**: 259–264.
20. Petrowsky H, McCormack L, Trujillo M *et al.* A prospective, randomized, controlled trial comparing intermittent portal triad clamping versus ischemic preconditioning with continuous clamping for major liver resection. *Ann Surg* 2006; **244**: 921–8; discussion 928.
21. Wang J, Liu Y, Zhang A *et al.* Inhibitory CpG sequences reduced ischemia/reperfusion-induced hepatic metastases of liver tumor in a murine model. *J Surg Res* 2012; **178**: 248–254.
22. Doi K, Horiuchi T, Uchinami M *et al.* Hepatic ischemia-reperfusion promotes liver metastasis of colon cancer. *J Surg Res* 2002; **105**: 243–247.
23. Nicoud IB, Jones CM, Pierce JM *et al.* Warm hepatic ischemia-reperfusion promotes growth of colorectal carcinoma micrometastases in mouse liver via matrix metalloproteinase-9 induction. *Cancer Res* 2007; **67**: 2,720–2,728.
24. Ishizuka M, Kubota K, Kita J *et al.* Duration of hepatic vascular inflow clamping and survival after liver resection for hepatocellular carcinoma. *Br J Surg* 2011; **98**: 1,284–1,290.
25. Nijkamp MW, van der Bilt JD, Snoeren N *et al.* Prolonged portal triad clamping during liver surgery for colorectal liver metastases is associated with decreased time to hepatic tumour recurrence. *Eur J Surg Oncol* 2010; **36**: 182–188.

26. Man K, Ng KT, Lo CM *et al.* Ischemia-reperfusion of small liver remnant promotes liver tumor growth and metastases—activation of cell invasion and migration pathways. *Liver Transpl* 2007; **13**: 1,669–1,677.
27. Yang Y, Fu SY, Lau WY *et al.* Selective main portal vein clamping to minimize the risk of recurrence after curative liver resection for hepatocellular carcinoma. *Hepatogastroenterology* 2012; **59**: 1,560–1,565.
28. Knudsen AR, Kannerup AS, Dich R *et al.* Expression of genes involved in rat liver angiogenesis after ischaemia and reperfusion: effects of ischaemic pre- and post-conditioning. *HPB (Oxford)* 2010; **12**: 554–560.
29. Yamanaka N, Okamoto E, Fujihara S *et al.* Do the tumor cells of hepatocellular carcinomas dislodge into the portal venous stream during hepatic resection. *Cancer* 1992; **70**: 2,263–2,267.
30. Matsumata T, Kanematsu T, Takenaka K *et al.* Lack of intrahepatic recurrence of hepatocellular carcinoma by temporary portal venous embolization with starch microspheres. *Surgery* 1989; **105**: 188–191.
31. Tanaka T, Yamanaka N, Oriyama T *et al.* Factors regulating tumor pressure in hepatocellular carcinoma and implications for tumor spread. *Hepatology* 1997; **26**: 283–287.