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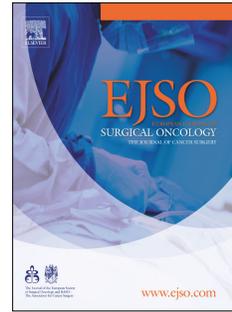
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Prolonged portal triad clamping during liver surgery for colorectal liver metastases is associated with decreased time to hepatic tumour recurrence

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ABSTRACT

AIMS: The aim of this study was to evaluate the oncological outcome of portal triad clamping during hepatectomy in colorectal cancer patients.

METHODS: 160 patients with colorectal liver metastases underwent a partial hepatectomy with curative intent. Data were collected in a prospective database and were retrospectively analyzed for time to liver recurrence (TTLiR) and time to overall recurrence (TTR). The prognostic significance of portal triad clamping of any type and severe ischemia due to prolonged portal triad clamping was determined by Cox regression models.

RESULTS: TTLiR was reduced after clamping of any type, although not statistically significant ($p=0.061$). Severe ischemia due to prolonged portal triad clamping significantly decreased TTLiR ($p=0.022$), but not TTR. Furthermore, severe ischemia independently predicted TTLiR in a multivariable analysis ($p= 0.038$).

CONCLUSIONS: Severe ischemia due to prolonged portal triad clamping during hepatic resection for colorectal liver metastases appears to be associated with decreased TTLiR. Further research remains necessary to determine the causative effect of prolonged vascular clamping on liver tumour recurrence.

Key words: colorectal liver metastases, vascular occlusion, portal triad clamping, hepatectomy, tumour recurrence.

INTRODUCTION

Surgical resection is the most effective treatment for patients with colorectal liver metastases, offering 5-year and 10-year survival rates between 36-58% and 23-26%, respectively^[1-4]. However, even after an apparently complete resection, approximately 50% of patients ultimately present with recurrent disease, usually within the first year following resection^[1,3]. The most likely source for recurrences are microscopic tumour residues that are undetectable at the time of surgery^[5,6]. Furthermore, recurrence may also develop from circulating tumour cells that are shed into the circulation during surgery^[7,8]. In the past decades, many prognostic factors of recurrence and survival after hepatectomy for metastatic colorectal cancer have been documented, including both preoperative^[9,10] and peri-operative variables^[11-14].

Temporary clamping of the vascular inflow of the liver is frequently applied in liver surgery. It is predominantly used to reduce peri-operative blood loss during hepatic resections^[15]. A major disadvantage of vascular inflow occlusion is that it causes ischemia/reperfusion injury (I/R) to the liver, which may lead to postoperative liver dysfunction. The adverse effects of I/R on hepatocellular damage and liver function have been well documented^[16]. Nonetheless, Rahbari *et al.* showed recently in a meta-analysis that portal triad clamping had no effect on postoperative overall morbidity and mortality when compared to no portal triad clamping^[17]. However, nothing is known about the effects of vascular clamping during liver surgery on long-term oncological outcome. We have recently shown in a murine model of partial hepatic I/R by temporary blood flow occlusion that the outgrowth of pre-existing colorectal micrometastases in occluded liver lobes was accelerated over 5-6 fold compared to non-occluded lobes^[18]. Based on these results, portal triad clamping during partial hepatectomy may adversely affect oncological outcome in colorectal cancer patients by accelerating the outgrowth of pre-existent hepatic micrometastases.

The aim of the present study was therefore to evaluate the prognostic significance of portal triad clamping and of severe ischemia due to prolonged clamping, on long-term oncological outcome in patients after partial hepatectomy for colorectal liver metastases.

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METHODS AND PATIENTS

Patients and surgical management

All consecutive patients who underwent a partial hepatectomy for colorectal liver metastases with curative intent (1998-2008) at the University Medical Center Utrecht in The Netherlands were selected from a prospectively collected liver database. Selection criteria for entering the study were: no signs of extrahepatic disease on preoperative imaging by routine liver contrast-enhanced four phase CT and thoraco-abdominal spiral CT scan, no untreatable lesions as determined by intraoperative ultrasonography, no gross residual disease (R2) at laparotomy and no simultaneous focal heat destruction by radiofrequency ablation, laser induced thermotherapy or any other local ablative treatment. In addition, patients who had died within 30 days after the hepatic resection were excluded from further analysis. Following these selection criteria, 160 patients were identified from the database and were further analysed.

Three expert hepatic surgeons performed the operations. Portal triad clamping was used consistently by the hepatic surgeons, without specific preoperative indications. As in many other institutions, portal triad clamping was applied only when the surgeons expected, during surgery, that the peri-operative blood loss would exceed 1000 ml in total. When portal triad clamping was applied, intermittent clamping of maximally 15 minutes per cycle was preferred. Blood loss was minimized by maintaining central venous pressure below 5 cm H₂O.

Prognostic factors

Patient and operation characteristics were prospectively collected. Besides clamping type and duration, various factors were extracted from the database for each patient, including age at the time of liver resection, gender, location of the primary tumour, nodal status of the primary tumour, disease free interval between resection of the primary tumour and detection of the liver metastases and synchronicity of metastases, the number, maximal size and

distribution of the hepatic metastases, preoperative carcinoembryonic antigen (CEA), duration of operation, usage of (neo)adjuvant chemotherapy, extent (major defined as 3 segments or more) and type of the resection (anatomical or non-anatomical), aspect of liver parenchyma, resection margins, blood loss and the amount of packed red blood cells transfused.

First, we analyzed the influence of clamping of any type compared to no vascular clamping on outcome. Second, patients were classified according to severity of ischemia during hepatectomy. The first group consisted of patients who had no vascular clamping during liver surgery. The second group of patients had minor ischemia during hepatectomy. This was defined as portal triad clamping for 20 minutes continuously or intermittent clamping of not more than 3 cycles of maximally 15 minutes ischemia time each. The third group, i.e. the severe ischemia group, consisted of patients in whom clamping times exceeded those mentioned for the minor ischemia group. The cut-off points regarding clamping times are based on preclinical observations.^[18,19]

Follow-up

Routine follow-up included at least liver contrast-enhanced four phase CT-scan of the liver, chest X-ray and CEA levels every 6 months, which were prospectively collected in the database. Follow-up data were updated by letters and telephone calls to referring physicians and general practitioners. The duration of the follow-up and the time between hepatectomy and the detection of recurrence were obtained, as well as the site of recurrence and survival data. The end-points of this analysis were the time to develop liver recurrence (TTLiR) and the time to develop recurrence in general (TTR). The influence on overall survival was also determined.

Statistical analysis

Kaplan-Meier survival curves were compared by log rank test statistics. Comparison between groups for the different variables was performed by ANOVA, Kruskal-Wallis test or Pearson

Chi-square test when appropriate. Hazard ratios (HR) of decreased TTLiR, decreased TTR and overall survival were computed for all variables to estimate relative risks and 95% confidence intervals using Cox proportional hazards regression analysis. Multivariable analysis was performed to determine the independent prognostic impact of severity of ischemia on TTLiR, TTR and overall survival while adjusting for possible confounders simultaneously. Therefore, covariables that significantly affected outcome by univariable analysis entered into a multivariable regression analysis. A 95% confidence interval or $p < 0.050$ was considered significant. All statistical analyses were performed using SPSS® for Windows® version 15.0 (SPSS, Chicago, Illinois, USA).

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RESULTS

Patient characteristics

During the study period, 160 patients who underwent a partial hepatectomy for colorectal liver metastases with curative intent were identified from the liver database. Twenty patients with initially non-resectable metastases were down-staged by neo-adjuvant chemotherapy. Three patients had preoperative portal vein embolisation to allow regeneration of the future remnant liver. Two patients had a two-staged resection (because of excessive intraoperative blood loss or R2 resection) and were evaluated for recurrence and survival from the second operation.

Vascular clamping was used in 88 patients. All patients had an inflow occlusion (Pringle Maneuver). Inflow occlusion was performed continuously in 53 patients and intermittently in 35 patients. Ischemic preconditioning was not performed. Median total ischemia time was 21 (range 2 - 69) minutes for continuous clamping and 40 (range 20-90) minutes for intermittent clamping. The “minor ischemia” group was formed by 38 patients. The remaining 50 patients comprised the “severe ischemia” group.

As the indication for vascular clamping is influenced by several factors, the ischemia groups were compared concerning their baseline values. No significant differences concerning the (baseline) prognostic factors were observed between the ischemia groups, including factors influencing the choice for vascular clamping, such as blood loss, extent and type of resection (data not shown).

Long-term outcome

Median follow-up was 2.5 years. Altogether, 112 patients had a recurrence within the study period, of whom 66 had a liver recurrence. Median TTR was 1.3 years, with 38.3% and 23.3% of patients being disease free after 2 and 5 years, respectively. Seven patients underwent repeat hepatectomy for liver recurrence, 10 patients underwent local ablation of hepatic recurrent disease and 4 had lung resection for pulmonary metastases. Adjuvant

chemotherapy was given to 20 patients after hepatic resection. 91 patients died during follow-up. Overall 5- and 10-year survival was 36.5% and 22.3 %.

Effect of vascular clamping and severe ischemia on patterns of recurrence and survival

Decreased time to liver recurrence was observed in patients subjected to vascular clamping of any type ($p=0.061$, figure 1a). Vascular clamping of any type did not affect TTR or overall survival (data not shown). In patients with severe ischemia, TTLiR was significantly shorter when compared to patients undergoing no clamping ($p=0.022$, figure 1b). In the minor ischemia group, TTLiR was not significantly different when compared to both other groups. TTR and overall survival were not affected by either minor or severe liver ischemia (figure 1c and data not shown, respectively).

Severe ischemia is an independent predictor of tumour recurrence in the liver

To evaluate the effect of severe ischemia on tumour recurrence, patients who had severe ischemia due to prolonged vascular clamping were compared to patients who had no clamping at all during hepatectomy. Univariable analysis among all variables examined revealed that synchronous disease, bilobar tumour distribution, positive resection margin and severe ischemia were inversely correlated to TTLiR (Table 1). TTR was inversely correlated to positive lymph nodes of the primary tumour, synchronous disease, type of resection and the use of neoadjuvant chemotherapy. Overall survival was inversely affected by disease free interval between primary tumour and hepatic metastases of less than 12 months and a preoperative CEA value $\geq 200\text{ng/mL}$. None of the other prognostic variables examined were correlated to TTLiR, TTR or overall survival (data not shown).

Subsequent analysis using multivariable regression analysis revealed that positive resection margin and severe ischemia were independent predictors for decreased TTLiR ($p=0.040$ and $p=0.038$ respectively, table 2). In addition, positive lymph nodes of the primary tumour independently predicted decreased TTR ($p=0.017$). Finally, overall survival was

independently predicted by a disease free interval between primary tumour and hepatic metastases of less than 12 months ($p=0.045$).

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DISCUSSION

Overview of literature

In the past decades, many prognostic factors of (hepatic) recurrence and survival after hepatectomy for metastatic colorectal cancer have been documented^[9,11,20]. Although the majority of these studies focused on preoperative criteria for selecting patients with liver metastases that may benefit from surgery, several studies hypothesized a correlation between accelerated tumour recurrence and peri-operative factors, including hypotension^[14], blood transfusion^[12], portal vein embolisation^[21] and morbidity^[13,22]. Surprisingly, very little is known about the effects of vascular occlusion on tumour recurrence and survival. Vascular clamping methods have been traditionally analyzed as a predictor of postoperative morbidity and mortality. Recently, Rahbari *et al.* showed in a meta-analysis that portal triad clamping had no effect on postoperative overall morbidity and mortality when compared to no portal triad clamping^[17]. However, the studies analyzed did not provide any data on long-term (oncological) outcome. Recently, Wong *et al.* reported that time to recurrence and overall survival in patients who received a hepatectomy with or without intermittent clamping of the portal triad were not significantly different^[23]. However, time to *liver* recurrence was not addressed by Wong *et al.*, which was the focus of the present study.

Translation from preclinical results to the clinical setting

A significantly shorter time to liver recurrence was observed in colorectal cancer patients who had been subjected to prolonged periods of portal triad clamping, which appeared to be irrespective of the clamping method used. This is in accordance with our preclinical results, showing that vascular clamping induces a 5-6 fold growth acceleration of pre-established colorectal micrometastases^[18]. Furthermore, comparable results were demonstrated by Ito *et al.*, showing that prolonged ischemia time during liver resection for colorectal liver metastases was associated with reduced progression free survival^[24].

Retrospective study

A disadvantage of the present study is its retrospective nature. As a consequence, one can not entirely exclude the possibility of indication bias. However, as in many other institutions, portal triad clamping was used without specific preoperative indications and applied only when the surgeons expected, during surgery, that the peri-operative blood loss would exceed 1000 ml in total. No differences between the groups were observed in extent and type of the resection, in tumour characteristics, blood loss or red blood cell transfusion. This suggests that the groups may be considered similar concerning the base-line characteristics. As such, the present study enhances our hypothesis that severe hepatic ischemia provides a local tumour growth stimulatory micro-environment.

Nonetheless, a retrospective study is not designed to provide data on the mechanisms for this phenomenon; therefore we can only conclude that the severe ischemia during liver surgery is associated with a shorter time to hepatic recurrence, rather than a causative mechanism. A large randomized controlled trial would be necessary to determine the causative effect of prolonged vascular clamping on liver tumour recurrence. However, in most hospitals, vascular clamping is not a standard procedure, but is only applied in case of (impending) excessive blood loss. Randomization between clamping and no clamping would therefore imply that some patients would unnecessarily be subjected to a procedure which is potentially harmful and on the other hand some patients with accelerating blood loss would be withheld from a maneuver which may be needed to perform a safe resection. A randomized controlled trial on clamping versus no clamping could therefore be considered unethical. Since the data presented here is the only data available until now, it may be advisable to keep the ischemia times as short as possible, whenever clamping during liver surgery is warranted.

Liver ischemia

Since inhibition of hypoxia following I/R resulted in decreased tumour acceleration in a preclinical mouse model^[25], liver *ischemia* was used as a predicting variable, rather than

clamping type (continuous versus intermittent) or clamping duration. The cut-off points between minor and severe ischemia were based on preclinical findings. Concerning continuous clamping, clamping for 30 minutes or 45 minutes resulted in accelerated outgrowth of micrometastases in a murine model, while ischemia up to 20 minutes did not show any difference in tumour growth acceleration^[19]. Furthermore, when the 45 minutes of clamping was performed intermittently by three cycles of 15 minutes, no growth acceleration of the micrometastases was observed as well. Therefore, patients undergoing continuous clamping up to 20 minutes or intermittent clamping for not more than 3 cycles of maximally 15 minutes ischemia time each were designated as patients with minor ischemia.

Implementation

With the introduction of approaches that reduce blood loss during hepatic resection, such as the maintenance of low venous pressure^[26], precoagulation devices^[27,28] and hemostatic biologicals^[29], portal triad clamping can be avoided more frequently^[30]. However, when vascular control is needed in case of excessive hemorrhage, intermittent clamping is preferred and total clamping times should be kept to a minimum. When ischemia times are inevitably long, future strategies that counteract the adverse effects of surgery-induced I/R on tumour growth may include drugs that improve post-operative hypoxia, post-ischemic microcirculation, anti-angiogenic therapies or anti-inflammatory agents. Adjuvant chemotherapy destructing possible residual tumour deposits combined with strategies that protect against accelerated tumour growth may hopefully result in further improvement in long term outcome.

Conclusion

In conclusion, both in pre-clinical mouse models and in this series of colorectal cancer patients, severe liver ischemia due to prolonged vascular clamping during liver resection for colorectal liver metastases *appears to be associated* with decreased time to liver recurrence. In case of inevitable clamping, total ischemia time should be kept to a minimum. In light of

the study characteristics, further research remains necessary to determine the causative effect of prolonged vascular clamping on liver tumour recurrence. Meanwhile, it may be advisable to keep total ischemia times as short as possible whenever vascular inflow occlusion is warranted.

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CONFLICT OF INTEREST

There is no conflict of interest in our study.

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FIGURE LEGENDS**Figure 1.**

Kaplan-Meier curves illustrating the effects of any type of clamping on liver free survival (a, $p=0.061$, log rank test), the effect of severe ischemia on liver free survival (b, $p=0.022$, log rank test) and disease free survival (c, $p=0.173$, log rank test). Severe ischemia is compared to no ischemia.

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Table 1. Univariable analysis for liver recurrence, overall recurrence and overall survival in patients with no ischemia (n=72) or severe ischemia (n=50). Only significant data are shown.

Variable	#	Hazard Ratio (95% Confidence Interval)		
		Liver recurrence	Overall recurrence	Overall survival
N-stadium				
Negative	51			
Positive	71	n.s.	1.81 (1.16-2.82) *	n.s.
Disease free interval (m)				
≥ 12	48			
< 12	74	n.s.	n.s.	1.81 (1.09-3.01) *
Metachronous	53			
Synchronous	69	2.03 (1.12-3.68) *	1.81 (1.17-2.82) *	n.s.
Preoperative CEA (ng/mL) ^a				
< 200	84			
≥ 200	10	n.s.	n.s.	1.06 (1.00-1.12) *
Distribution				
Unilobar	77			
Bilobar	45	1.91 (1.09-3.34) *	n.s.	n.s.
Type				
Anatomical	70			
Non-anatomical	52	n.s.	1.53 (1.00-2.34) *	n.s.
Resection margin				
R0	108			
R1	14	1.94 (1.00-3.96) *	n.s.	n.s.
Chemotherapy ^{b,c}				
None	95			
Neoadjuvant	14	n.s.	2.34 (1.25-4.37) *	n.s.
Vascular clamping				
No ischemia	72			
Severe ischemia	50	1.38 (1.04-1.83) *	n.s.	n.s.

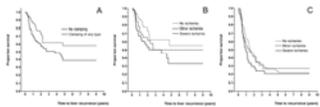
*significant prognostic factor in univariable regression model ($p < 0.05$). n.s. = not significant.

^aCEA 28 (23%) missing values; ^bOne patient in severe ischemia group had both neoadjuvant and adjuvant chemotherapy;

^c14 patients received adjuvant chemotherapy.

Table 2. Multivariable analysis for liver recurrence, overall recurrence and overall survival in patients with no ischemia (n=72) or severe ischemia (n=50).

Variable	Liver recurrence		Overall recurrence		Overall survival	
	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value	HR (95% CI)	<i>P</i> -value
Positive nodal status primary	-	-	1.84 (1.11-3.05)	0.017	-	-
Disease free interval < 12 months	-	-	-	-	1.70 (1.01-2.84)	0.045
Synchronous disease	1.83 (0.99-3.38)	0.053	1.36 (0.85-2.17)	0.202	-	-
Preoperative CEA ≥ 200 ng/mL	-	-	-	-	1.05 (0.98-1.11)	0.117
Bilobar distribution	1.72 (0.93-3.16)	0.084	-	-	-	-
Resection type	-	-	1.25 (0.94-1.74)	0.182	-	-
Positive margin	2.25 (1.04-4.86)	0.040	-	-	-	-
Neoadjuvant chemotherapy	-	-	1.63 (0.85-3.15)	0.144	-	-
Severe ischemia	1.37 (1.02-1.85)	0.038	-	-	-	-



ACCEPTED MANUSCRIPT