International Journal of Surgery 36 (2016) 8–12

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Original Research

The role of perioperative inflammatory-based prognostic systems in patients with colorectal liver metastases undergoing surgery. A cohort study

Leonardo Solaini, Bambang T. Atmaja, Prabhu Arumugam, Robert R. Hutchins, Ajit T. Abraham, Satyajit Bhattacharya, Hemant M. Kocher*

Barts and the London HPB Centre, The Royal London Hospital, Barts Health NHS Trust, London E1 1BB, UK

HIGHLIGHTS

- GPS and CAR have been shown to be strong prognostic factors.
- Preoperative GPS>0 predict poor prognosis in colorectal liver metastases patients.
- The prognosis of patients with GPS = 0 could be further stratified by CAR.
- Early postoperative inflammatory prognostic systems may be of limited utility.

ARTICLE INFO

Article history:
Received 20 August 2016
Accepted 10 October 2016
Available online 11 October 2016

Keywords:
Colorectal liver metastasis
Inflammatory-based prognostic system
Survival
C-reactive protein
Albumin

ABSTRACT

Background: We aim to evaluate the prognostic value of preoperative and postoperative inflammatory systems in patients who had undergone surgery for colorectal liver metastases, focusing our analysis on the role of C-reactive protein-to-albumin ratio (CAR) and Glasgow prognostic score (GPS).

Methods: A total of 194 patients were enrolled onto this study. Demographics, tumor-related variables, preoperative and postoperative (day 1) inflammatory variables were analyzed as potential prognostic factors.

Results: For the whole cohort three and 5-year survival were 68% and 53% respectively. Median follow up was 27 months (IQR 10-42). At multivariate analysis only preoperative GPS (HR 12.06, 95% CI 2.82–51.53; $p = 0.0008$) was an independent risk factor for poor survival. Patients with a preoperative GPS = 0 had a 3-years survival of 70% while it was 33% for those with GPS = 1 ($p < 0.0001$).

In patients with preoperative GPS = 0 preoperative CAR (HR 1.19, 95%CI 1.05–1.35; $p = 0.0059$) could identify a sub-population at risk for reduced survival. The optimal cut-off for preoperative CAR (preCAR) was 0.133 (HR 7.11 95% CI 1.37–36.78, $p = 0.0063$). 3-years survival was 75% and 21% for patients with preCAR>0.133 and $\leq$ 0.133, respectively ($p = 0.0005$).

The immediate postoperative inflammatory status did not have a significant impact on survival.

Conclusion: GPS is a significant prognostic factor in patients with colorectal liver metastases undergoing surgery. CAR could be a valuable tool to further stratify patients with preoperative GPS = 0 according to their prognosis.

1. Introduction

Inflammatory-based prognostic systems have proven to be valuable prognostic factors in colorectal cancer. In particular, Glasgow prognostic score (GPS) [1,2], its modified version (mGPS) [3] and neutrophil to lymphocyte ratio (NLR) [4–6] were shown to be strong predictors. Nevertheless, most of the reports investigated the preoperative status and data about the prognostic role of the systemic inflammatory response in the early postoperative period has not been studied yet.

A few authors [7,8] focused their research in C-reactive protein/albumin ratio (CAR) as a further tool in predicting survival in patients with colorectal cancer; in their conclusion they consider CAR

* Corresponding author.
E-mail address: h.kocher@qmul.ac.uk (H.M. Kocher).

http://dx.doi.org/10.1016/j.ijsu.2016.10.010

as a factor with a prognostic strength similar to the one of the previously reported inflammation-based prognostic score.

However, no reports have been published about the importance of this factor in predicting the prognosis of patients with colorectal liver metastases undergoing surgery.

In this paper, we aim to evaluate the prognostic value of pre-operative and postoperative inflammatory systems in patients who had undergone surgery for colorectal liver metastases, focusing our analysis on the role of CAR.

2. Material and methods

All patients referred to undergoing liver resection for metastases of colorectal origin between January 2005 and April 2015 were included in the analysis. Laparoscopic liver resections were excluded from the analysis. A major hepatectomy was defined as resection of four or more liver segments [9].

Information about the patients' pre-existing medical comorbidities was used to calculate the Charlson Comorbidity Index (CCI) [10]: the score associated with the presence of a malignant metastatic tumor was ignored as it was the same for all patients.

Full blood count including Hemoglobin (Hb), white blood cell (WBC) count, lymphocytes and neutrophils counts, serum C-reactive protein levels and albumin were recorded preoperatively and on postoperative day 1 (POD1). Biochemical analyses were carried out using Cobas 8000 module c702 (Roche, Basel, Switzerland). Full blood counts were carried out using hematology automated analyzer xe2100 (Sysmex, Kobe, Japan).

Peri-operative neutrophil to lymphocyte ratio (NLR) and CAR were calculated. Glasgow prognostic score (GPS) was also calculated as described elsewhere (2). The difference between the pre-operative and postoperative value of albumin (ΔAlb), CRP (ΔCRP), WBC (ΔWBC) and neutrophils (ΔNTR) and lymphocytes (ΔLNF) counts was also obtained. Primary outcome variables were overall survival (OS) and disease-free survival (DFS).

OS was defined as the period from liver resection to the date of death. DFS was defined as the period from liver resection to the date of the first sign of local or distant disease progression on imaging.

Risk factors analyzed for OS and DFS included: age, sex, CCI, synchronous vs. metachronous, number of liver lesions, Colon vs rectum primary, primary TNM stage, major vs. minor resections, postoperative morbidity and perioperative (preoperative and on POD1) Hb (preHb and Hb1), Albumin (preAlb and Alb1) WBC (preWBC and WBC1), NLR (preNLR and NLR1), CAR (preCAR and CAR1) and GPS (preGPS and GPS1).

2.1. Statistical analysis

Continuous variables were presented as median and interquartile range (IQR). Mann-Whitney *U* test was used to compare continuous variables while Chi-square test was used to compare categorical variables. Multiple regression analysis was used to verify whether the difference between the preoperative and postoperative value of inflammatory markers (ΔAlb, ΔWBC, ΔCRP, ΔLNF, ΔNTR) and operative variables (major vs minor and synchronous resections) were significantly correlated. Kaplan-Meier survival analysis was used to determine survival variables. Follow-up was calculated using Kaplan-Meier function as suggested by Schemper and Smith [11]. The cases of in-hospital mortality were excluded from the survival analysis. Cox proportional-hazards regression was performed to determine predictors of OS and DFS. Hazard ratios (HR) and 95% confidence interval (95% CI) were calculated when required. When a continuous variable was found significant at Cox proportional-hazards regression the optimal cut-off was calculated using the freeware "Cut Off Finder" as described by Budczies et al. [12]. The remaining analyses were performed with MedCalc for windows.

3. Results

Two hundred and eighteen liver resections were performed in 194 patients. Patients' characteristics are shown in Table 1.

Seventy-eight patients underwent right hepatectomy, 12 left hepatectomy and one central hepatectomy. Eighteen patients underwent left lateral segmentectomy while the remaining 109 had segmentectomy and/or non-anatomical wedge resections.

Nineteen patients required a second resection. One patient underwent three liver resections and another one had four during the study period.

Preoperative biochemical serum markers values were significantly different from the postoperative ones (Table 2).

At multiple regression analysis no significant associations were found between ΔAlb, ΔWBC, ΔCRP, ΔLNF and ΔNTR and major or synchronous resections.

3.1. Survival analysis

For the whole cohort three and 5-year survival were 68% and 53% respectively. Median follow up was 27 months (IQR 10-42).

At multivariate analysis only preoperative GPS (HR 12.06, 95% CI 2.82–51.53; $p = 0.0008$) was an independent risk factor for poor survival (Table 3). Patients with a preoperative GPS = 0 had a 3-years survival of 70% while it was 33% for those with preGPS = 1 ($p < 0.0001$) (Fig. 1).

At Cox regression analysis a number of liver lesions higher than 2 was the only risk factor for poor DFS (Table 3). Kaplan-Meier survival curve (Fig. 2) showed a significant difference in DFS according to the number of lesions (lesions>2 median DFS 12 vs 27 months lesions≤2) ($p = 0.0118$).

In patients with preoperative GPS = 0 preoperative CAR (HR 1.19, 95%CI 1.05–1.35; $p = 0.0059$) could identify a sub-population at risk for reduced survival (Table 4). The optimal cut-off for preoperative CAR was 0.133 (HR 7.11 95% CI 1.37–36.78, $p = 0.0063$) (Fig. 3).

4. Discussion

Our analysis demonstrated the importance of inflammatory markers to predict survival in patients with colorectal liver metastases.

Table 1
Patients' characteristics.

Age – median – (IQR)	66 (59–73)
Male/Female ratio	125/69
Charlson comorbidity – median- (IQR)	0 (0–1)
Primary tumor n (%)	
Colon	113 (58.2)
Rectum	81 (41.7)
Stage of the primary tumor[a] (n = 177) n (%)	
I	9 (5.1)
II	25 (14.1)
III	49 (27.7)
IV	94 (53.1)
Metachronous n (%)	126 (64.2)
Liver metastases ≤2 n (%)	62 (28.4)
Major resection n (%)	91 (41.7)
Postoperative complications n (%)	36 (16.5)
In-hospital mortality n (%)	4 (1.8)

[a] AJCC 7th edition.