



Original Research

Significance of the Glasgow Prognostic Score for patients with colorectal liver metastasis



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HIGHLIGHTS

- GPS is an important predictor of recurrence following liver resection in patients with CRLM.
- GPS isn't a predictor of survival following liver resection in patients with CRLM.
- We have created a new index that can select patients with poorer prognosis using degree of histologic differentiation, CEA level and GPS.

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ABSTRACT

Background: Systemic inflammation and nutritional status are strongly associated with tumor progression. Inflammation-based prognostic scores, such as the Glasgow Prognostic Score (GPS), reflect these states and are predictive in patients with several types of advanced cancers. The aim of this study was to evaluate the significance of GPS in patients with colorectal liver metastasis (CRLM).

Patients and methods: Study subjects were 134 patients with CRLM who underwent initial radical liver resection at Hiroshima University Hospital between January 2000 and December 2013. Univariate and multivariate analyses were performed to identify variables associated with overall and recurrence-free survival following liver resection in two groups based on GPS.

Results: There was no significant relationship between overall survival and GPS. Recurrence-free survival was significantly poorer in patients with GPS 1–2 than in those with GPS 0 ($p < 0.01$). In multivariate analysis for recurrence-free survival, moderate histologic differentiation, carcinoembryonic antigen level ≥ 10 ng/mL, and GPS 1–2 were identified as independent prognostic factors.

Conclusion: We suggest that GPS is an important predictor of recurrence following liver resection in patients with CRLM, and it should be considered one of the evaluation criteria for liver resection.

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1. Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide and has shown an increasing trend over the last few decades [1,2]. It is known that CRC frequently metastasizes to the liver [3–5]. Recently, prognostic improvement has been observed

in colorectal liver metastasis (CRLM) owing to progress in surgical techniques and perioperative chemotherapy [5,6]. Liver resection remains the gold standard treatment for CRLM, and the combination of liver resection and new perioperative chemotherapy regimens reduces the risk of recurrence and prolongs survival. Nevertheless, overall survival remains poor, and 5-year survival rates following liver resection range from about 30 to 60% [7–10]. Furthermore, because the recurrence rates after liver resection are extremely high, it is difficult to determine the indications for and the timing of liver resection [8,9,11,12]. Therefore, evaluation

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criteria for liver resection for CRLM are necessary.

Recently, there has been increasing evidence that systemic inflammation and nutritional status are associated with tumor progression [13–15]. The systemic inflammatory state increases the levels of circulating neutrophils. Neutrophils continuously release inflammatory cytokines and chemokines, such as interleukin-8 and tumor necrosis factor- α . These cytokines induce not only inflammatory cascades, but also tumorigenesis. Moreover, it is suggested that hypoalbuminemia due to malnutrition results in the suppression of immune responses in patients with tumors [16,17].

Inflammation-based prognostic scores, such as the Glasgow Prognostic Score (GPS), have been shown to be predictive in patients with several types of advanced cancers [18–23]. Although GPS is only based on serum C-reactive protein (CRP) and serum albumin (Alb) levels, this score can reflect systemic inflammation and nutritional status. CRP is a major marker of inflammation, and hypoalbuminemia reflects malnutrition. These factors are associated with an immunosuppressed state in patients with cancer.

The aim of the present study was to evaluate the significance of GPS in patients with CRLM. We also confirmed whether GPS could become one of the evaluation criteria for liver resection.

2. Patients and methods

A total of 134 patients with CRLM who underwent initial radical liver resection at Hiroshima University Hospital between January 2000 and December 2013 were enrolled in this study. All medical records were obtained retrospectively. The median follow-up period was 43 months (range: 3–155 months). Blood samples were acquired prior to surgery, as close as possible to the actual day of the procedure. Perioperative chemotherapy regimens were determined by the medical oncologist based on individual patient characteristics. Treatment with 5-fluorouracil (5-FU) and folic acid or irinotecan was the standard regimen. The local Institutional Review Board approved this study, and all patients provided informed consent.

3. Definitions

Prognostic factors were examined with respect to overall and recurrence-free survival after liver resection.

Histological differentiation of the primary colorectal cancer region was confirmed by examination of a resected specimen. Radical liver resection was defined as R0 resection. Major hepatectomy was defined as the resection of three or more segments, while minor hepatectomy was defined as the resection of less than that.

Although modified inflammation-based prognostic scores are also often used [24], we used GPS in this study. GPS was estimated as previously described. Briefly, patients with both elevated CRP levels (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL) were assigned a score of 2. Patients with only one of these biochemical abnormalities were given a score of 1, while patients with neither elevated CRP levels nor hypoalbuminemia were assigned a GPS of 0.

4. Statistical analysis

Continuous variables are presented as the median and range. For continuous variables, parametric analyses were performed using Student's *t*-test, and non-parametric analyses were performed using the Mann-Whitney *U* test. Categorical variables were compared using the chi-square test. Survival curves were generated using the Kaplan-Meier method, and comparisons between different groups were performed using log-rank tests. A multivariate Cox proportional hazards model was used to determine independent risk factors associated with poor overall and recurrence-free survival. To

validate the predictive value of each of the inflammation-based scoring systems, receiver operating characteristic curves were used. A difference was considered significant if the *p* value was less than 0.05. Statistical analyses were performed using the JMP Genomics statistical software version 12 (SAS Institute Inc., Cary, NC, USA).

5. Results

5.1. Clinicopathological characteristics

Clinicopathological characteristics of the patients are shown in Table 1. The patient population included 90 men (67%) and 44 women (33%). The median age was 63 years (range: 30–87 years). Regarding cancer location, 74 patients (55%) had a colon primary lesion, and 60 patients (45%) had a rectal primary lesion. Regarding liver resection, 37 patients (28%) received synchronous resection of colorectal primary cancer and liver metastases, and 97 patients (72%) received metachronous resection. Regarding histological differentiation of the primary CRC, 89 patients (66%) had a moderately differentiated adenocarcinoma, 37 patients (28%) had a well-differentiated adenocarcinoma, and 8 patients (6%) had others (poorly differentiated adenocarcinoma, mucinous adenocarcinoma, and unknown). The number of liver metastases ranged from 1 to 14; 69 patients (52%) had single and 65 patients (48%) had multiple liver metastases. Sixty-six patients (49%) received neoadjuvant chemotherapy and 101 patients (75%) received adjuvant chemotherapy. The primary drug used for neoadjuvant chemotherapy was 5-FU. Oxaliplatin, irinotecan, and cetuximab or bevacizumab were supplementary medications and were administered to 18 (27%), 13 (19%), and 7 (10%) patients, respectively. The primary drug used for adjuvant chemotherapy was also 5-FU. Oxaliplatin, irinotecan, and cetuximab or bevacizumab were administered as supplementary medications to 35 (34%), 20 (19%), and 11 (10%) patients, respectively. At the time of the study, 87 patients (64%) were alive, while 47 patients (36%) had died. Recurrence was observed in 88 patients (65%), and 52 patients (38%) experienced liver recurrence. The 1-, 3-, and 5-year overall survival rates following liver resection were 92%, 76%, and 60%, respectively. The 1-, 3-, and 5-year recurrence-free survival rates following liver resection were 55%, 36%, and 32%, respectively.

A GPS of 0 was allocated to 106 patients (89%), while a GPS of 1–2 was allocated to 15 patients (11%).

Table 1
Clinicopathological characteristics of the whole patients.

Characteristics	n = 134
Age (year, range)	63 (30–87)
Gender (Male/Female)	90/44
Site of primary lesion (Colon/Rectum)	74/60
Timing (Synchronous/Metachronous)	37/97
Histologic differentiation (Moderate/others)	89/41
Distribution (Unilobar/Bilobar)	97/37
Number of liver metastasis (Single/Multiple)	69/65
Maximum tumor size (mm, range)	33 (8–160)
Liver resection (Major/Minor)	28/106
Neo-adjuvant chemotherapy (Yes/No)	66/68
Adjuvant chemotherapy (Yes/No)	101/33
(Systemic/TAI/Systemic + TAI)	74/14/13
White blood cell (μ l, range)	5840 (2110–12080)
Neutrophil (μ l, range)	3580 (1059–8989)
Lymphocyte (μ l, range)	1620 (371–1134)
CEA (ng/ml, range)	67.8 (0.8–1134)
GPS (0/1/2)	106/13/2
Survival (Alive/Death)	87/47
Recurrence (Yes/No)	88/46

GPS: Glasgow prognostic score, TAI Transcatheter arterial infusion, CEA: carcinoembryonic antigen.

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