IgG Fc Binding Protein (*FCGBP*) Is Down-Regulated in Metastatic Lesions and Predicts Survival in Metastatic Colorectal Cancer Patients

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Abstract

Background: Liver is the most frequent metastatic spread sites for CRC patients and these patients have much poorer prognosis compared to those without metastasis. Previous studies have shown that IgG Fc binding protein (*FCGBP*) plays important roles in tumorigenesis, progression and prognosis. In this study, we are aimed to explore the significance of *FCGBP* in liver metastatic CRC (LMCRC) patients.

Methods: The expression data of FCGBP was obtained from GEO and TCGA database, *FCGBP* RNA expression was evaluated between primary lesions (PC) and liver metastatic lesion (LM). 135 paired specimens including normal mucosa, primary tumor and liver metastasis tissues were all collected from CRC patients and adopted in Tissue microarrays (TMAs). Immunohistochemical staining was performed on the TMAs slides with FCGBP and the immunohistochemistry score (SI) was calculated by the staining intensity multiplied by the positive rate of stained cells. Survival curves were calculated by Kaplan–Meier method and the log-rank test was used to compare the overall survival (OS) and disease-free survival (DFS). Univariate and multivariate analysis for prognosis were using Cox proportional hazards regression model.

Results: *FCGBP* RNA was down-regulated in PC and LM, and especially lower in LM in database. We also found FCGBP protein was down-regulated in primary lesion and metastatic lesion, especially in metastatic lesion in 135 paired tumor tissues. According to immunohistochemistry score (SI), each cohort (primary lesion and metastatic lesion) was divided into *FCGBP*-positive (SI=4-12) and *FCGBP*-negative (SI=0-3) group. In both groups, the level of CEA (PC group, 3.880 vs 77.049, $p<0.001$; LM group, 3.890 vs 14.239, $p=0.008$) and CA19-9 (PC group, 8.610 vs 111.700, $p<0.001$; LM group, 7.660 vs 19.380, $p=0.037$) was lower than those in *FCGBP*-negative group. *FCGBP*-positive in LM cohort was an independent risk factor both in OS (HR 1.573, 95% CI [1.017-2.433], $p=0.042$) and DFS (HR 1.869, 95% CI [1.256-2.781], $p=0.002$).

Conclusions: This study has found the relationship between *FCGBP* and clinical information of LMCRC patients. FCGBP expression was much lower in liver metastasis tumor tissues compared with primary tumor tissues in liver metastatic CRC patients and associated with the OS and PFS. Our works illustrate that *FCGBP* can be a promising prognostic factor for LMCRC.

Background

Colorectal cancer (CRC), is one of the most common malignant diseases that threaten human's life worldwide. In recent years, survival rates of CRC have increased due to earlier diagnosis with colonoscopy and improved treatment strategies. Global incidence and mortality of CRC could be higher in the next 10 years with more than 2.2 million new cases and 1.1 million cancer deaths annually[1]. According to the newest research data published by CNCC (Chinese National Cancer Center, China), it was estimated that there were more than 376.3 thousand new CRC cases and 191.0 thousand CRC-related deaths in 2015[2]. The treatment strategy mainly depends on TNM staging classification[3]. For metastatic CRC

patients, chemotherapy and neoadjuvant chemoradiotherapy are main therapeutic options. But the efficacy of chemotherapy is greatly limited by individual difference and drug targets. Therefore, to discover significant clinical biomarkers aiming to improve patients' prognoses and provide clinical strategy is our top priority.

IgG Fc binding protein (*FCGBP*) was first discovered as an Fc portion of the IgG molecule binding site in intestinal and colonic epithelia. It plays a crucial part in cell protection and anti-inflammation in tissues[4]. It is a protein and an important component of mucosal immunological defenses[5]. Although the actual function of *FCGBP* is poorly understood, the clinical significance of FCGBP has been reported in some types of cancer. It has been reported that *FCGBP* is down regulated in thyroid carcinoma[6]. Downregulation of IgG binding protein in prostate cancer was found by Mozammel H *et al*[7]. *FCGBP* were identified as being associated with osteosarcoma metastasis and might facilitate the individual management of patients after osteosarcoma treatment[8]. Yasui Y *et al* reported that compared to the normal tissues, *FCGBP* was down-regulated in cancer tissues. A research based on the AOM/DSS chronic bowel inflammation model showed *FCGBP* protein was markedly decreased in the cancerous tissues[9]. All evidences above have indicated that *FCGBP* has been identified as a down-regulated protein in many cancers and suggests that it may play a key role in homeostasis. However, there has no prior studies that have reported *FCGBP* as a biomarker in CRC, especially in metastatic CRC.

In this study, we analyzed the expression of *FCGBP* RNA between CRC primary samples and liver metastatic samples in GEO database. Then we assessed the expression of *FCGBP* RNA in CRC and prognostic significance based on The Cancer Genomic Atlas (TCGA). Next, we assessed the expression of *FCGBP* protein primary CRC (PC) samples and liver metastasis of CRC (LMCRC) samples respectively. At last, we explored the relationship between the expression features and clinicopathological characteristics.

Methods

Patients and Tissue Samples

In this study 135 paired specimens including normal mucosa, primary tumor and liver metastasis tissue were all collected from CRC patients who were diagnosed with no other metastasis according to CT scan. All the patients were taken surgical operation from January 2006 to February 2007 and followed up to December 2012. The diagnosis was all confirmed by Pathology Department of Cancer Institute and Hospital. All cases can provide completely clinical information, including age, gender, the location of tumor, histologic classification, TNM stage, follow-up information and so on. All the patients were followed-up regularly every 3 months until to the 5th year after the resection.

FCGBP Expression Analyses in GEO and TCGA Databases

To evaluate *FCGBP* expression between PC and LMCRC, we summarized the expression profiling microarray data from Gene Expression Omnibus (GEO) database with the accession number GSE41258

and GSE68468 (Affymetrix Human Genome U133A Array). The standardized *FCGBP* expression was divided into Normal (normal tissue), Primary and Metastasis in the datasets above. For data from GEO, the different expression genes were analyzed by limma package in **Supplementary Table 1** and data from TCGA, the different expression genes were analyzed by UCSC XENA in **Supplementary Table 2**. The cohort was divided into four groups, Normal (normal mucosa), Primary, Metastasis and Recurrence.

Tissue Microarray and Immunohistochemistry

Tissue microarrays (TMAs) were adopted after HE staining verification. 1 mm punched samples were measured taken from the tumor center. Different specimen collected from the same patient were placed on the same TMA.

Immunohistochemical staining was performed on the TMAs slides with *FCGBP* (#HPA003564; 1:500; Sigma-Aldrich, United States) rabbit polyclonal antibody. The immunohistochemistry score (SI) was calculated by the staining intensity (0, negative; 1, weak; 2, moderate; 3, strong) multiplied by the positive rate of stained cells (0%-5%, 0; 6%-25%, 1; 26–50%, 2; 51–75%, 3; >75%,4). In this study, SI = 4–12 was defined as positive staining, while SI = 0–3 was defined as negative staining. Positive rate = positive samples/ (positive samples + negative samples). Main point of our study was elucidated as a flowchart in Fig. 1.

Statistical Analysis

The statistical analyses were performed using Student t-test or one-way ANOVA. Survival curves were calculated by Kaplan–Meier method and the log-rank test was used to compare the overall survival (OS) and disease-free survival (DFS). Univariate and multivariate analysis for prognosis were using Cox proportional hazards regression model. The calculations were carried out using SPSS Statistics 23.0 or GraphPad Prism 8.0. *P* value less than 0.05 was considered statistically significant.

Results

1. Immunohistochemical Scores of TMAs Were Evaluated in LMCRC Patients

The demographic characteristics information of LMCRC patients in our study was summarized in Table 1. 270 tumor samples were divided into two cohort, primary CRC tumor cohort (n = 135) and liver metastasis tumor cohort (n = 135). Each cohort was classified into *FCGBP*-negative (SI = 0–3) and *FCGBP*-positive (SI = 4–12) groups. Representative IHC images of FCGBP specimens were shown in Fig. 2. *FCGBP* positive expression (10x) in PC and LM was shown in Fig. 2A, B, negative expression (10x) in PC and LM was shown in Fig. 2C, D. The expression of *FCGBP* protein in LM was much lower than that

in the PC ($p < 0.001$) and it was shown in Fig. 2E. Positive sample number and rate in two cohorts were shown in Table 2.

Table 1
Demographic Characteristics of LMCRC Patients

Factor	Patients, No.
Age, median (range), y	59.500(21.000–78.000)
Gender	
Men	83
Women	52
CEA (range)	30.65(1.400-278.900)
CA19-9 (range)	42.91(2.980–665.90)
Positive nodes (range)	3.000(0–18.000)
Clinical tumor (T) classification	
cT2	5
cT3	72
cT4	58
Clinical nodal (N) classification	
cN0	54
cN1	46
cN2	35
Perineural invasion	
Yes	45
No	90
Venous invasion	
Yes	65
No	70
Lymphatic invasion	
Yes	60
No	75

Table 2
FCGBP expression pattern in different samples by IHC staining

Sample	Total	FCGBP-Negative	FCGBP-Positive	FCGBP Rate %
Primary tumor tissue	135	17	118	87.41
Liver metastasis tumor tissue	135	40	95	70.37

2. *FCGBP* mRNA Was Down-Regulated in Colorectal Liver Metastasis in Colorectal Cancer Based on Public Databases

According to the results of *FCGBP* protein expression in LMCRC TMAs, we then evaluated *FCGBP* mRNA expression in normal tissues, primary tissues and liver metastasis tissues based on two databases form GEO. As shown in Fig. 3A, B, in both GES41258 and GSE68468 dataset, the *FCGBP* mRNA expression was decreased with the progression of the disease. If the GES41258 and GSE68468 dataset were analyzed as a whole, a similar pattern was acquired (Fig. 3C).

To further confirmed *FCGBP* mRNA expression in CRC patients, we then assessed *FCGBP* mRNA expression in TCGA database. 434 colorectal cancer patients were collected and divided into four groups. 51 normal tissues, 380 primary tumor tissues, 1 metastatic tissue and 2 recurrence tissues were compared. The result was consistent with GEO data (Fig. 3D).

3. The Relationship between *FCGBP* Expression and Clinical Features in the Primary Tumor Lesions in Our Cohort

According to the results of public data above, we further analyzed *FCGBP* expression patterns and the clinical information including age, gender, CEA and CA19-9 value, positive nodes number, and TN classification.

As shown in Table 3, in primary tumor cohort, 17 patients were defined as negative and 118 as positive. According to the statistical data in the table, age (60 vs 59, $p = 0.745$) and gender ($p = 0.066$) were not different significantly between two groups. Previous works shown that higher level of CEA and CA19-9 were important biomarkers of CRC patients and predict poor prognosis. In *FCGBP*-positive group, the level of CEA (3.880 vs 77.049, $p < 0.001$) and CA19-9 (8.610 vs 111.700, $p < 0.001$) was lower than that in *FCGBP*-negative group. The number of positive nodes was similar between two groups (3.000 vs 2.000, $p = 0.145$). We also assessed the T classification and N classification in two groups. The percentage of patients in different T classification was similar between two groups. However, the percentage of cN0 in *FCGBP*-positive group was higher (41.5% vs 29.4%) and the percentage of cN2 was lower (19.5% vs 70.6%) than that in *FCGBP*-negative group ($p < 0.001$).

Table 3
Analyses of Relative Clinicopathological Factors and FCGBP expression in the Patients

Factor	Patients, No. (primary)		*p*-value	Patients, No. (metastasis)		*p*-value
	Negative (n = 17)	Positive (n = 118)		Negative (n = 40)	Positive (n = 95)	
Age, median (range), y	60.000 (32.000–72.000)	59.000 (21.000–78.000)	$p = 0.745$	60.500 (21.000–74.000)	58.000 (29.000–78.000)	$p = 0.539$
Gender			$p = 0.066$			$p = 0.315$
Men	7	76		22	61	
Women	17	42		18	43	
CEA (range)	77.049 (1.400-278.900)	3.880 (0.100-322.200)	$p < 0.001$	14.239 (1.360–78.900)	3.890 (0.100-322.200)	$p = 0.008$
CA19-9 (range)	111.700 (2.980–665.90)	8.610 (0.600-827.100)	$p < 0.001$	19.380 (0.600-418.70)	7.660 (0.600-827.100)	$p = 0.037$
Positive nodes	3.000 (0–15.000)	2.000 (0–18.000)	$p = 0.145$	2.000 (0–18.000)	1.000 (0–10.000)	$p = 0.012$
Clinical tumor (T) classification			$p = 0.492$			$p = 0.352$
cT2	0	5		3	2	
cT3	9	63		21	51	
cT4	8	50		16	42	
Clinical nodal (N) classification			$p < 0.001$			$p = 0.003$
cN0	5(29.4%)	49(41.5%)		8(20%)	46(48.4%)	
cN1	0(0%)	46(39.0%)		15(37.5%)	31(32.6%)	
cN2	12(70.6%)	23(19.5%)		17(42.5%)	18(18.9%)	
Perineural invasion			$p = 0.359$			$p = 0.2183$
Yes	4	41		10	35	

Factor	Patients, No. (primary)		*p*-value	Patients, No. (metastasis)		*p*-value
	Negative (n = 17)	Positive (n = 118)		Negative (n = 40)	Positive (n = 95)	
No	13	77		30	60	
Venous invasion			*p* = 0.923			*p* = 0.511
Yes	8	57		21	44	
No	9	61		19	51	
Lymphatic invasion			*p* = 0.417			*p* = 0.643
Yes	6	54		19	41	
No	11	64		21	54	

4. The Relationship between *FCGBP* Expression and Clinical Features in the Liver Metastasis Tumor Lesions in Our Cohort.

As shown in Table 3, 40 metastatic tissues were defined as negative and 95 as positive. There is no significant difference between the two groups with respect to age (60 vs 58, $p = 0.539$) and gender ($p = 0.315$). In *FCGBP*-positive group, the level of CEA (3.890 vs 14.239, $p = 0.008$) and CA19-9 (7.660 vs 19.380, $p = 0.037$) was lower than that in *FCGBP*-negative group. There was significantly different between positive nodes number and patterns (1.000 vs 2.000, $p = 0.012$). The percentage of patients in different T classification was nearly the same between two groups ($p = 0.352$). However, the percentage of cN0 in *FCGBP*-positive group is higher (48.4% vs 20.0%) and the percentage of cN2 is much lower (18.9% vs 42.5%) than that in *FCGBP*-negative group ($p = 0.003$).

5. *FCGBP* -Positive Associated with Better Survival in LMCRC

To identify the prognostic significance of *FCGBP* in LMCRC patients, we analyzed the survival in two cohorts respectively.

In primary tumor cohort, *FCGBP*-positive group had a better OS and DFS (OS $p = 0.011$ and DFS $p = 0.019$; Fig. 4A, B). Univariate Cox analysis demonstrated that *FCGBP*-positive group was a correlative factor for both OS (HR 2.223, 95% CI [1.203–4.109], $p = 0.011$) and DFS (HR 1.842, 95% CI [1.082–3.137], $p =$

0.024). Multivariate Cox analysis shown that *FCGBP*-positive was an independent prognostic factor for OS (HR 2.035, 95% CI [1.052–3.938], $p = 0.035$) but not for DFS (HR 1.570, 95% CI [0.884–2.787], $p = 0.123$) (Table 4, 5).

Table 4
Cox analyses of potential prognostic factors for overall survival in LMCRC

Group	Comparison	Univariate Analysis			Multivariate Analysis		
		HR	95% CI	p-value	HR	95% CI	p-value
Primary tumor cohort	FCGBP-negative vs FCGBP-positive	2.223	1.203–4.109	0.011	2.035	1.052–3.938	0.035
Liver metastasis tumor cohort	FCGBP-negative vs FCGBP-positive	1.611	1.049–2.473	0.029	1.573	1.017–2.433	0.042

Table 5
Cox analyses of potential prognostic factors for disease-free survival in LMCRC

Group	Comparison	Univariate Analysis			Multivariate Analysis		
		HR	95% CI	p-value	HR	95% CI	p-value
Primary tumor cohort	FCGBP-negative vs FCGBP-positive	1.842	1.082–3.137	0.024	1.570	0.884–2.787	0.123
Liver metastasis tumor cohort	FCGBP-negative vs FCGBP-positive	1.874	1.263–2.782	0.002	1.869	1.256–2.781	0.002

In liver metastasis tumor cohort, *FCGBP*-positive group also had a better OS and DFS ($p = 0.007$ for OS and $p = 0.001$ for DFS; Fig. 4C, D). Multivariate Cox analysis illustrated that *FCGBP*-positive was an independent prognostic factor for both OS (HR 1.573, 95% CI [1.017–2.433], $p = 0.042$) and DFS (HR 1.869, 95% CI [1.256–2.781], $p = 0.002$) (Table 4, 5).

Discussion

In this study, immunohistochemical staining was performed in LMCRC TMAs with *FCGBP* antibody. We compared the IHC score of *FCGBP* between primary tumor tissues and liver metastasis tissues and found that *FCGBP* expression was decreased with disease development. We have verified the phenomenon based on TMAs in the GEO and TCGA datasets to confirm that FCGBP mRNA expression was decreased with the progression of the disease. As for clinical information, we found that CEA and CA19-9 level was lower in *FCGBP*-positive group. The percentage of cN0 in *FCGBP*-positive group was higher and the percentage of cN2 was lower than that in *FCGBP*-negative group. In LM cohort, we found that *FCGBP*-positive was an independent risk factor both in OS and DFS. *FCGBP* might be a prognostic factor for LMCRC patients.

Previous studies have found that down-regulated *FCGBP* was associated with lots of malignant diseases and it was known as a prognostic marker in a variety of cancers. Ma R *et al* had performed whole exome-sequencing analysis of 63 CRC cases, and found that with the deficiency of *FCGBP*, CRC developed and showed worse survival rates[10]. At stage I or II CRC, it has reported that *FCGBP* was positively associated with the prognosis of CRC[11]. Onstenk W *et al* measured CTCs of liver metastasis CRC patients and their primary tumor tissues and found that *FCGBP* was down-regulated[12]. Meanwhile in other kinds of cancer, *FCGBP* also has positive effects on prognosis. In HPV-infected patients *FCGBP* expression was upregulated, and it was meaningful to the prognosis of HNSCC patients[13]. The current study indicated that *FCGBP* expressions could be further evaluated as biomarkers for predicting survival of patients with gallbladder cancer and *FCGBP* could be promising targets in the control of gallbladder cancer progression. Xiong L *et al* found that immunohistochemical staining of *FCGBP* was decreased and evaluated it as a biomarker for predicting survival of patients with gallbladder cancer. It would be a potential target in the control of gallbladder cancer progression[14].

As we known, metastasis is the main death reason of CRC patients especially liver metastasis CRC that has much poorer prognosis. Previous works found that *FCGBP* can be evaluated as biomarkers in CRC all stages broadly. But according our present study, we found that *FCGBP*-positive in LMCRC has longer survival. Multivariate Cox analysis illustrated that *FCGBP*-positive was an independent prognostic factor for OS and DFS in liver metastasis cohort but not in primary tumor cohort. We analyzed that *FCGBP* can predict prognosis more adequately in metastasis tumor. We first reported that *FCGBP* can predict prognostic in LMCRC and we thought it could be a biomarker for LMCRC patients. The pattern of FCGBP expression is gradually down-regulated with the cancer development and we speculate that FCGBP may be a tumor suppressor gene. The function of FCGBP and mechanism that FCGBP is down-regulated with cancer development deserve further investigation.

Conclusions

In this study, we discovered *FCGBP* expression was much lower in liver metastasis tumor tissues compared with primary tumor tissues in liver metastatic CRC patients. The expression of FCGBP in liver metastasis is associated with the OS and PFS. In summary, FCGBP may be a potential biomarker to predict the prognosis of CRC.

Abbreviations

FCGBP: IgG Fc binding protein; CRC: Colorectal cancer; LMCRC: Liver metastatic colorectal cancer; GEO: Gene Expression Omnibus; PC: Primary cancer lesion; LM: Metastatic cancer lesion; CNCC: Chinese National Cancer Center, China. TCGA: The Cancer Genomic Atlas. TMAs: Tissue microarrays. OS: Overall survival. DFS: Disease-free survival. SI: Immunohistochemistry score.

Declarations

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Ethics approval and consent to participate:

This article was carried out in accordance with the recommendations of 7th edition of TNM staging system, the Clinical Research Ethics Committee of Cancer Institute and Hospital, Chinese Academy of Medical Sciences with written informed consent from all subjects. IRB number of the study is KY-3019-037. The protocol was approved by the Clinical Research Ethics Committee of Cancer Institute and Hospital, Chinese Academy of Medical Sciences.

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Availability of data and materials:

The data supporting the results of this study are available from TCGA database GEO database, clinical and follow-up information are from Cancer Institute and Hospital.

Author contributions:

ZMY, ZXZ, HQH, TYQ and TYM designed the study, YHZ, WYZ, HYW analyzed the data, ZMY, QCT and RH collected data and drafted the manuscript; FG, CXZ, GYW, XSW revised the content of this manuscript. All authors read and approved the final manuscript.

Consent for publication:

Not applicable.

Conflict of interest:

The authors declare no conflict of interest.

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Figures

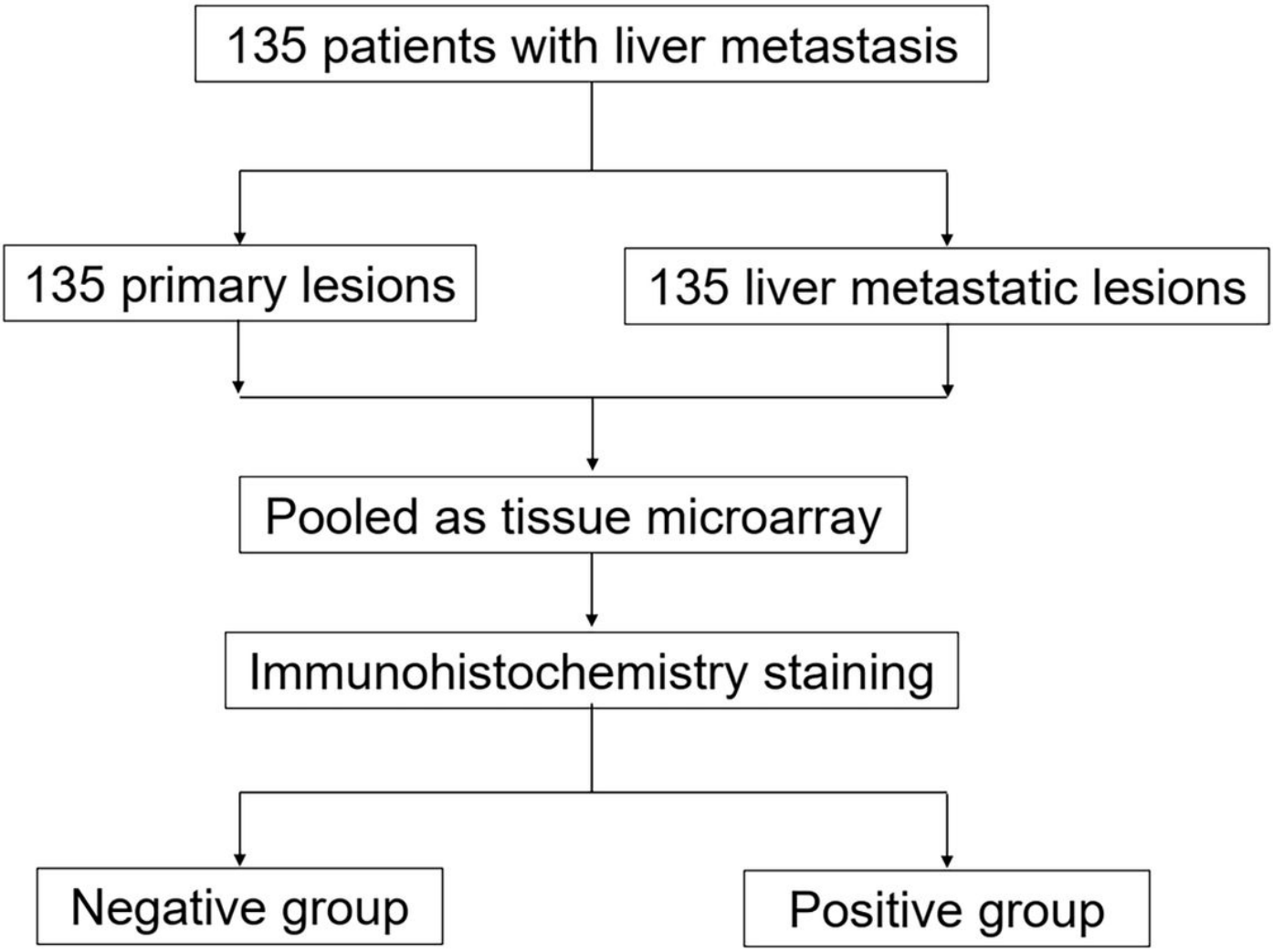

Figure 1

Flowchart of the main point.

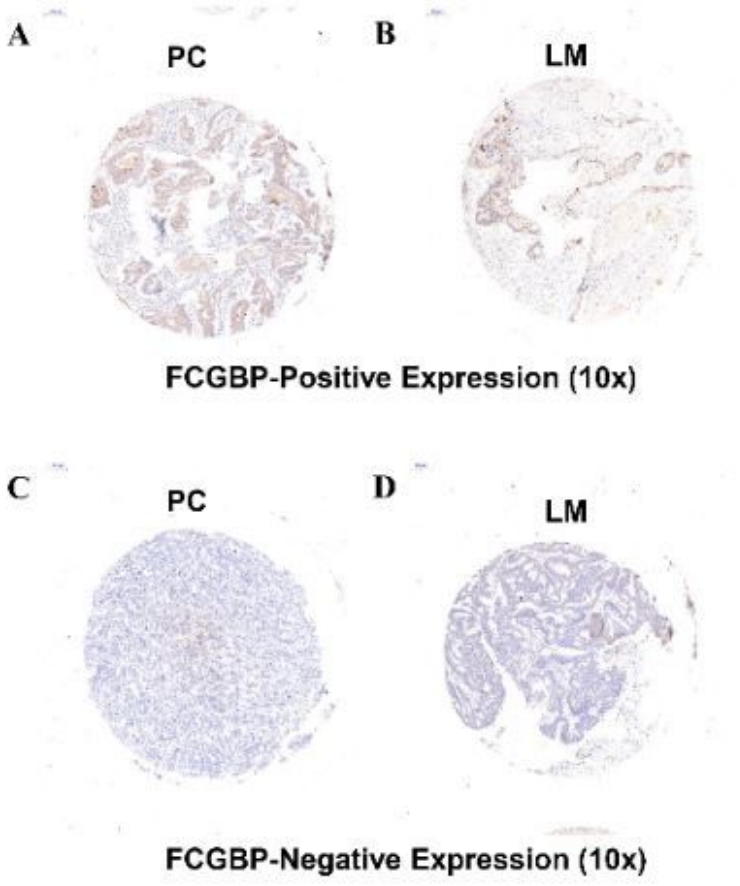

Figure 2

Representative immunohistochemistry staining pictures of FCGBP. High expression in CRC tissue and liver metastatic tissue (10X for A and B) and low expression (10X for C and D) for FCGBP protein were shown.

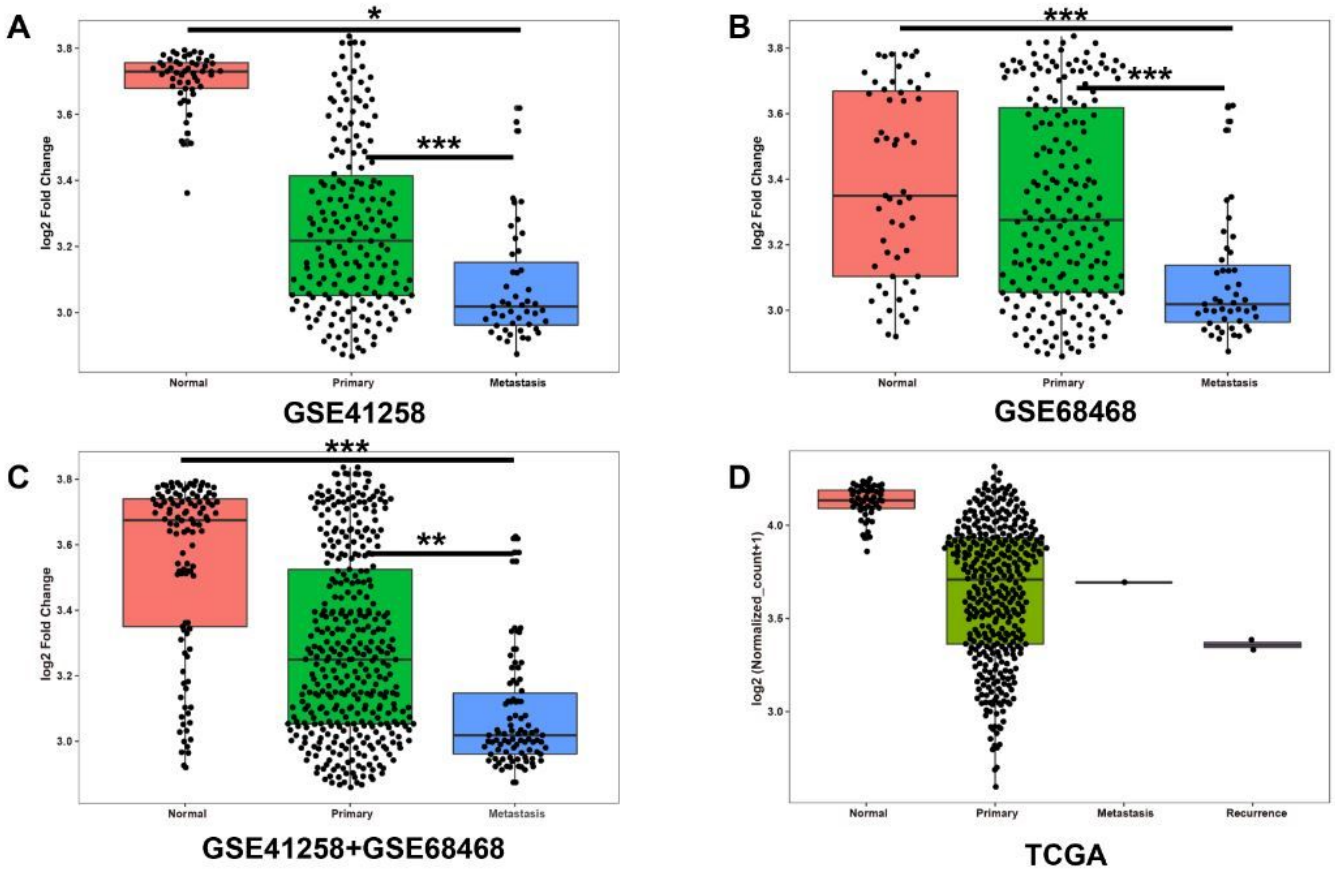

Figure 3

FCGBP expression pattern in normal intestinal tissue, primary tumor, liver metastasis on GEO and TCGA database, recurrence tissue additionally in TCGA. (A) GSE41258, (B) GSE68488, (C) GSE41258+GSE68488 were collected form GEO, (D) summarized from TCGA. * represents p-value<0.05, ** represents p<0.01, *** represents p<0.001.

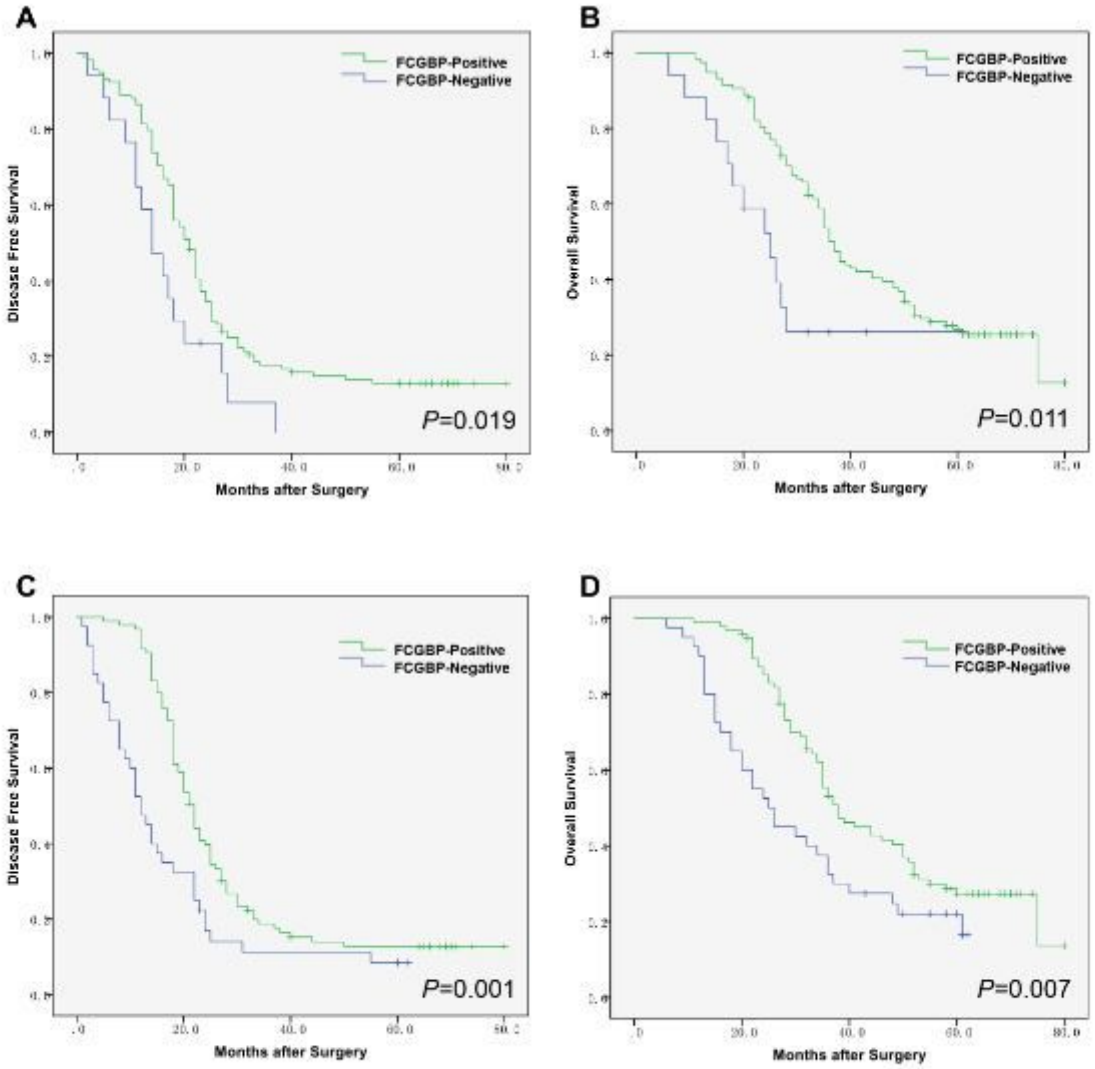

Figure 4

Overall survival and disease-free survival in LMCRC. (A) (B) primary tumor cohort, (C) (D) liver metastasis tumor cohort

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable2.xlsx
- SupplementaryTable1.xlsx