PET-CT Standard uptake value predict bevacizumab-containing chemotherapy response and prognosis for unresectable colorectal cancer liver metastasis

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Abstract

Background: Standard uptake value (SUV) of PET-CT is an indicator of tumor metabolic response. In this paper, we aim to explore the clinical value of SUV on the unresectable colorectal cancer liver metastasis (CRLM) patients receiving bevacizumab-containing chemotherapy. Method: This study was performed retrospectively. A total of 185 CRLM patients between April 2011 to December 2015 with complete clinical data were included in this study. All the enrolled patients were assigned into two treatment cohorts (bevacizumab plus first-line chemotherapy cohort and chemotherapy only cohort). A blindly, independent radiologist evaluated images for RECIST and morphologic response. All clinical variables, and various PET/CT parameters were statistically compared with progression-free survival (PFS) and overall survival (OS). Primary and Metastatic tumor SUV were selected for analysis. Results: Among the 185 patients, 101 patients received first line chemotherapy plus bevacizumab (beva cohort), 84 patients only received first-line chemotherapy (CMT cohort). Baseline characteristics of two cohorts showed no statistical difference (P>0.05). Primary SUV level was correlated with primary tumor size, while metastatic SUV was statistically correlated with metastatic tumor number and tumor size (P=0.000). Primary lesion, metastatic lesion SUV and elevation of SUV demonstrated prognostic role for OS (P<0.05). SUV gap were statistically associated with optimal response in bevacizumab cohort (P=0.03) and no-PD status in chemotherapy cohort (P=0.019), respectively. After multivariate analysis, elevated SUV is an independent risk factor for OS (P=0.000). Besides, elevation of SUV between metastatic and primary lesion can be a predictive factor for bevacizumab survival benefit. Conclusion: PET-CT scan is important for CRLM patients. Our study demonstrated that an elevation of SUV was a better prognostic and predictive marker for CRLM patients.

Introduction

Colorectal cancer (CRC), as one of the most common malignancies of the digestive gastrointestinal tract[1], still accounts for approximately one thirds of the estimated new digestive cancer cases and the incidence for this disease is continuously evolving [2]. Approximately 20% to 25% of CRC patients have liver metastases at the time of initial diagnosis and overall prognosis of patients with colorectal cancer liver metastasis (CRLM) is poor. For management of CRLM, recent development of chemotherapy regimens combined with targeted agents demonstrated decent results and increased 5-year overall survival[3]. Bevacizumab, a humanized murine antihuman vascular endothelial growth factor (VEGF) monoclonal antibody, was approved for patients with advanced CRLM in combination with chemotherapy[4]. Many studies demonstrated that treatment with bevacizumab as compared with supportive care alone improved the median duration of survival[5].

For assessing therapeutic responses, the most prevalent way of assessing drug response is to measure volume changes in tumor dimensions based on radiographic criteria such as the Response Evaluation Criteria in Solid Tumors (RECIST)[6]. However, assessing the tumor load with RECIST-defined ORR may be not enough to assess response for bevacizumab with an anti-angiogenic mechanism of action[7]. Thus more accurate response evaluation as a supplementary method during early course of treatment will be

more valuable for patients to receive alternative therapies as soon as possible. In this issue, another evaluation method named computed tomography (CT) morphology criteria has been developed[8, 9] and had a statistically significant association with overall survival.

As CRLM is not common, baseline tests such as computed tomography (CT) and magnetic resonance imaging (MRI) play important roles in patient selection. In addition, fluorodexyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is used to detect CRLM and extra-hepatic metastasis and is now widely used in oncologic evaluation. Bipat et al. reported a meta-analysis showing that PET/CT has greater sensitivity in detecting liver metastases than other noninvasive imaging modalities such as CT or MRI[10]. PET/CT is a powerful and popular tool for imaging tumors as well as to assess the quantity in tumor metabolism during therapy[11]. Assessment of standard uptake value (SUV) is widely adopted for glucose metabolism. Clinical value of SUV applied in prognosis has been explored in many cancers including CRC[12]. However, especially in patients with CRLM, studies reported to date concerning PET response to bevacizumab or chemotherapy are relatively small in terms of sample size. Thus in this study, from two cohorts of CRLM patients receiving chemotherapy with or without bevacizumab, we explored clinical value of early PET/CT scan to facilitate the prediction of treatment response and survival outcomes in CRLM patients.

Method And Materials

Patients and treatment modality

Patients from April 2011 to December 2015 with unresectable CRLM was eligible into this study if the baseline PET/CT scan and SUV of both primary and metastatic site were available. Written informed consent was obtained by each patient. The study was approved by the Ethical Committee of Zhongshan Hospital, Fudan University. For the treatment protocol, patients received either first-line chemotherapy (CMT) plus bevacizumab or first line chemotherapy alone[13, 14].

The follow-up period was as follows: the first follow-up was performed within 2–3 months after the baseline and subsequent follow-up cycles usually ranged from 3 to 6 months or even shorter which depended on the clinical situations and (or) tumor relapse or metastasis being suspected. Data of overall survival (OS) and relapse/metastasis time were also documented. Duration of OS was calculated from the date of baseline to the last follow-up or tumor-specific death. Progression free survival (PFS) was determined from the date of diagnosis to the date of progression under the regular follow-up.

Data acquisition of ^{18}F-FDG-PET/CT

18-FDG PET/CT scans were obtained with a PET/CT scanner (Discovery VCT, GE Healthcare, Milwaukee, Wisconsin, USA). All patients fasted for at least 6 hours before examination. The serum glucose just before PET/CT scanning was less than 10 mmol/dL. Patients were scanned at 50-60 minutes after the

intravenous (i.v.) injection of F-FDG (4.44MBq/kg), typically, patients were scanned from the base of the skull to the mid-thigh. Locations of lesions (Primary and metastatic lesions) were recorded and maximal standardized uptake values (SUVmax) of the lesions were measured.

Imaging analysis

All the enrolled patients were subjected to multiphasic CT at the time of the initial evaluation (baseline status). The image diagnostic reports were all assessed through a double-blinded manner; Radiologist were blinded to pathologic results, patient treatment, and outcomes. Response was evaluated using CT morphologic criteria, assigning each metastasis to 1 of 3 groups (**Table S1**), Morphologic response criteria were defined as optimal if the metastasis changed from a group 3 or 2 to a 1, incomplete if the group changed from 3 to 2, and none if the group had not changed or increased[9]. Another evaluation criterion were RECIST. **Figure S1** demonstrated the specific response status of two evaluation options. Routinely, the changes of all the patients in the post-treatment phase were evaluated from enhanced high-resolution (HR) CT with less than 5-mm slices.

Statistics

Based on baseline characteristics, gender and other clinical data in both cohorts (CMT versus CMT plus bevacizumab) were compared by Chi-square test; age, tumor size, SUVmax values, and follow-up period were compared by Student's t-tests. PFS was assessed using the Kaplan–Meier method, and survival curves were compared using a log-rank test. OS analyses were carried out using the Kaplan–Meier method and the results were compared using a log-rank test. A multivariable Cox proportional hazards model predicting OS was performed using backward stepwise selection. Risk factors were expressed as the hazard ratio [HR, 95% confidence interval (CI)]. Statistical significance was defined as P value less than 0.05. The discrimination of the prognostic model was determined by the Harrell concordance index (C-index) as an index of model performance. Higher C-index values indicate better discrimination.

Results

Baseline clinical characteristics of two cohorts' patients after cases selection

From April 2011 to December 2015, a total of 185 patients with unresectable CRLM (the specific flow graph was demonstrated in **Figure 1**) were enrolled in our study, including 101 patients receiving first line chemotherapy plus bevacizumab (**beva cohort**), 84 patients receiving first-line CMT (**CMT cohort**). Their age range was 24–81 years and their median age was 59 years. The medians for size, CEA, CA199, primary SUVmax and metastatic SUVmax were 4.1 cm, 28.0 ng/L, 91.4 ng/L, 11.6 and 9.9, respectively. Details of other clinical data were demonstrated in **Table 1**. **Table 1** also showed that there is no

difference between two groups for gender, age, primary site, Eastern Cooperative Oncology Group (ECOG) score, number of metastatic site and distribution of liver metastasis.

Correlation between SUV and clinical characteristics

11.6 of primary lesion SUV, 9.9 of liver metastatic lesion were regarded as the cut-off value of primary and metastatic SUV, respectively. Besides, metastatic SUV which is larger than primary lesion SUV was regarded as the elevation of SUV. Table 2 demonstrated the Chi-square test clinical correlation between SUV and clinical characteristics. From the analysis, higher primary SUV was significantly correlated with larger primary tumor size (P=0.000), while metastatic SUV was statistically related with the status of number of metastases and metastatic tumor size (P=0.000). No statistical difference was observed among different Age level, gender group, primary sites, CEA, CA199 level, distribution of liver metastasis (P>0.05).

SUV was clinically correlated with treatment response

Details of treatment response were listed in Table S2, overall objective response rate (ORR) and optimal response rate was 41.6% and 25.9%, respectively. For different treatment protocol cohorts, CMT patients demonstrated a statistically higher rate of progressive disease (PD) rate than bevacizumab plus CMT cohort patients (P=0.014); there is no difference between two cohorts for partial response (PR) and stable disease (SD). Furthermore, to evaluate next efficacy of RECIST and morphologic status on prognosis, among the 185 patients with CRC liver metastasis in two cohorts, those with optimal response by morphologic criteria had significantly better overall survival than patients with incomplete or no response in bevacizumab cohort, with median overall survival of 37 months (95% CI, 28.8-39.2 months) and 25 months (95%CI, 21.4-28.6 months), respectively (P<0.001, Figure S2 (A)). In contrast, response by RECIST was not associated with an improvement in survival in this group (Figure S2 (C)). In addition, Figure S2 (D) also demonstrated that there is no statistically significant difference for duration of OS between optimal group and no optimal group in CMT cohort (P>0.05). To analyze statistical correlation between SUV and treatment response, details of different treatment cohort have been constructed to demonstrate the statistical correlation of separately primary lesion SUVmax, metastatic lesion SUVmax and SUVmax gap between metastatic and primary lesion (Table 3). Compared to primary and metastatic lesions SUV, the gap was determined to have a significant relation with treatment response in both cohorts through different evaluation criteria.

PET-CT SUV were significantly related with PFS and OS

Totally, primary SUV was not a significant prognostic marker for PFS (median survival months: 7.0 months versus 6.0 months, P=0.38, hazard ratio [HR]=1.142, 95%CI: 0.846-1.604). In contrast, higher metastatic lesion SUV (P=0.01) and elevation of SUV (P=0.008) were regarded as a significant factor for PFS. In terms of OS, patients with higher primary lesion SUV had worse survival outcome than patients with lower primary SUV (median survival months: 33.0 months versus 21.0 months, P=0.01, HR=1.799, 95%CI: 1.150-2.816), while metastatic lesion SUV was also regarded as a prognostic factor for OS (median survival months: 35.0 months versus 19.0 months, P<0.001, HR=2.512, 95%CI: 1.605-3.932). Besides, elevation of SUV between metastatic and primary lesion was demonstrated to be a significant OS-related factor with higher HR (P<0.001, HR=3.330, 95%CI: 2.126-5.213). To further determine the prognostic efficacy of primary, metastatic SUV and SUV elevation, C-index of three OS-related prognostic models were evaluated. The performance of elevated SUV model was statistically better than primary SUV (C-index: 0.688 versus 0.638, P<0.001) and metastatic SUV level (C-index: 0.688 versus 0.568, P<0.001). Details were shown in **Figure 2**.

Furthermore, data of all patients were included in univariate and multivariate analysis, which was demonstrated in **Table 4**. From multivariable analysis of OS, CEA level (P=0.031, hazard ratio [HR]= 1.461; 95% confidential interval [CI]: 1.063-1.795), CA199 level (P=0.029, HR=1.806; 95%CI: 1.062-3.072), SUV gap level (P=0.000, HR=2.863; 95%CI=1.645-4.981) and metastatic tumor size (P=0.012, HR=1.631; 95%CI=1.211-2.087) were regarded as independent risk indicators for tumor OS.

PET-CT SUV as a predictive factor for bevacizumab therapy in CRLM

As the PET SUVmax value, a result from semi-quantitative analysis, was often a reflection of metabolic ability on the hepatic and primary lesions, an elevated metastatic SUV may reflect a more progressive tumor metabolic ability. To confirm this hypothesis, we created another two internal controlled groups: high risk group (with elevated SUV) and low risk group (without elevated SUV). among high risk cohort, our data showed that patients receiving the CMT plus bevacizumab has reached a longer duration of PFS (median survival months: 7.0 months versus 5.4 months) and OS (median survival months: 25.0 months versus 18.0 months) than patients receiving CMT only (P<0.05); similar results cannot be reached in the low risk cohort, demonstrating that patients with an elevated SUV should receive a combination treatment of CMT and bevacizumab. Details were shown in **Figure 3**.

Discussion

For management of unresectable CRLM patients, development of clinical imaging devices, surgical techniques, chemotherapeutic agents have been making the diagnosis and treatment of CRLM possible. Beyond oncogene RAS status, bevacizumab was recommended as the effective component of first-line treatment strategy for CRLM[15]. For patients with RAS-mutant tumors and those with RAS wild-type right-sided primaries, first-line therapy with bevacizumab plus chemotherapy gains even greater significance[16, 17]. Besides, exploration of specific survival benefit has become more important for

treatment option selection. As many studies have reported the utility of radiology and nuclear medicine, contrast of pre-treatment and post-treatment radiologic status obtained from CT, MRI and PET-CT was considered as the optimal process for determining response and evaluating prognosis. Based on this, RECIST and PERCIST criteria has been developed and reported as the popular choice for differentiating the response[6, 7].

In addition to RECIST, a novel evaluation criteria called CT morphology criteria based on status of overall attenuation, tumor-liver interface and peripheral rim of enhancement has been reported to be more sensitive than RECIST for evaluating CRLM bevacizumab response[9]. In our study, we performed two treatment response evaluation criteria for both cohorts. The former method, proposed within RECIST, allows that response might be actually calculated comparing 2 different lesions based on tumor volume at baseline and after treatment; this contrasts with a common rule of dimensional response assessment that calls for comparing the same lesion before and after treatment. Besides, we also explored the response through CT morphology criteria. Our results demonstrated that RECIST criteria was more sensitive than CT morphology criteria in CMT cohort, while CT morphology criteria showed preferable prognosis-related performance in beva plus CMT cohort.

PET-CT SUV, as an indicator reflecting metabolic activity of tumor lesion, has also been reported and considered as a prognostic factor in many studies[18-20]. Through the clinical correlation analysis, we found that primary lesion SUV was statistically correlated with primary tumor size, while metastatic SUV level was correlated with liver metastatic tumor size and tumor number. Furthermore, in our study, primary SUV and metastatic SUV have demonstrated the role for survival outcome stratification. Patients with higher SUV showed a worse survival outcome. Elevation of SUV was also proved to be related with optimal response in CT morphology criteria and Progression disease response in RECIST criteria, determining the prediction role of baseline SUV on CRLM lesions. However, in our study, statistical difference of PFS was not shown in different primary SUV level. Since the bevacizumab therapy was targeted for VEGF, Progression disease (PD) of traditional RECIST criteria may not enough to be a study end-point in this group patients. This results were also consistent with many other studies[9]. Even ESMO guideline in 2016 has advised radiologists to pay special attention to the treatment effects if VEGF-targeting antibody bevacizumab is a component of the therapy regimen[13].

Besides, owing to reflection character of SUV on metabolic activity, we hypothesized that a baseline elevation of SUV between hepatic lesion and primary lesion may effectively affect the prognosis of CRLM patients. To further validate the hypotheses, three different SUV models were constructed with respect to clinical utility of primary lesion SUV, metastatic lesion SUV and SUV gap. Among three models, elevation of SUV showed a more promising prognostic performance with a significantly better C-index (0.688). Also, univariate and multivariate analysis of OS proved the prognostic role of SUV elevation indirectly (P=0.000).

Nonetheless, the actual and definitive advantage of baseline PET/CT is that it is capable of quantifying and differentiating between primary and metastatic tissue. Using this quantification method evaluating

the glucose uptake, PET/CT may improve preoperative risk stratification and optimize outcomes[21]. Thus we divided our enrolled patients into two cohorts based on the status of SUV gap (low risk cohort and high risk cohort). Through the analysis, CRLM patients in high risk cohort receiving combination therapy of bevacizumab plus first line CMT had a better survival outcome than their CMT counterparts, demonstrating that an elevation of SUV could be an important factor determining the optimal treatment choice. In contrast, on low risk cohort, similar results were not showed. This may be a reflection of such a phenomenon that tumor lesion with a higher level of metabolism may consist of abundant vessels with positive expression of VEGF receptor, thus those patients with higher SUV may benefit from the VEGF monoclonal antibody therapy.

There are some limitations of this study, including the retrospective design of the study, which may include selection bias, and the small sample size. We believe that well-designed statistical criteria can alleviate this problem. A large scale prospective, randomized controlled study may be warranted to strongly determine the prognostic value of PET-CT. Another limitation is that our study only focused on the CRC live metastasis. Some CRC patients with extra-hepatic metastasis were excluded in this study because bias caused by the anatomical variety can influence the statistical results. Besides, it has been reported in some studies neo-adjuvant chemotherapy was derived as statistically significant risk factor affecting prognosis for CRC liver metastasis, but we could not and did not reveal the correlation. But we believe that further well-organized study would focus on this viewpoint.

In this paper, we adapted CT morphology criteria and RECIST criteria to evaluate treatment response in CRC liver metastasis and found that status of CT morphology criteria is more sensitive evaluating the bevacizumab-containing chemotherapy response. Elevation of SUV obtained from baseline PET-CT scan between metastatic and primary lesion is statistically related with optimal treatment response. Furthermore, elevation of SUV is also statistically related with PFS and OS and demonstrated a better prognostic predictive performance. Besides, CRC liver metastasis patients with elevated SUV receiving bevacizumab-containing chemotherapy had a better survival outcome than their chemotherapy counterparts.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained by all the patients. The study protocol followed the ethical guidelines of the Declaration of Helsinki and was approved by the Ethical Committee of Zhongshan Hospital of Fudan University.

Consent for publication

We have obtained consent to publish from the participant to report individual patient data.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding authors on reasonable request.

Competing interests

The authors declare no conflicts of interest for the publication of this manuscript.

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Authors' contributions

Y.L, QY.F and WT.T collected, analyzed and interpreted the patient data. and Y.L was a major contributor in writing the manuscript. JM.X and GD.H were the corresponding authors in this manuscript and were responsible for the results of this study. YQ.X, SB.L, YH.M, P.Z and LL.Y provided the research ideas and guidance.

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Disclosure statement

The authors declare no conflicts of interest for the publication of this manuscript.

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Figures
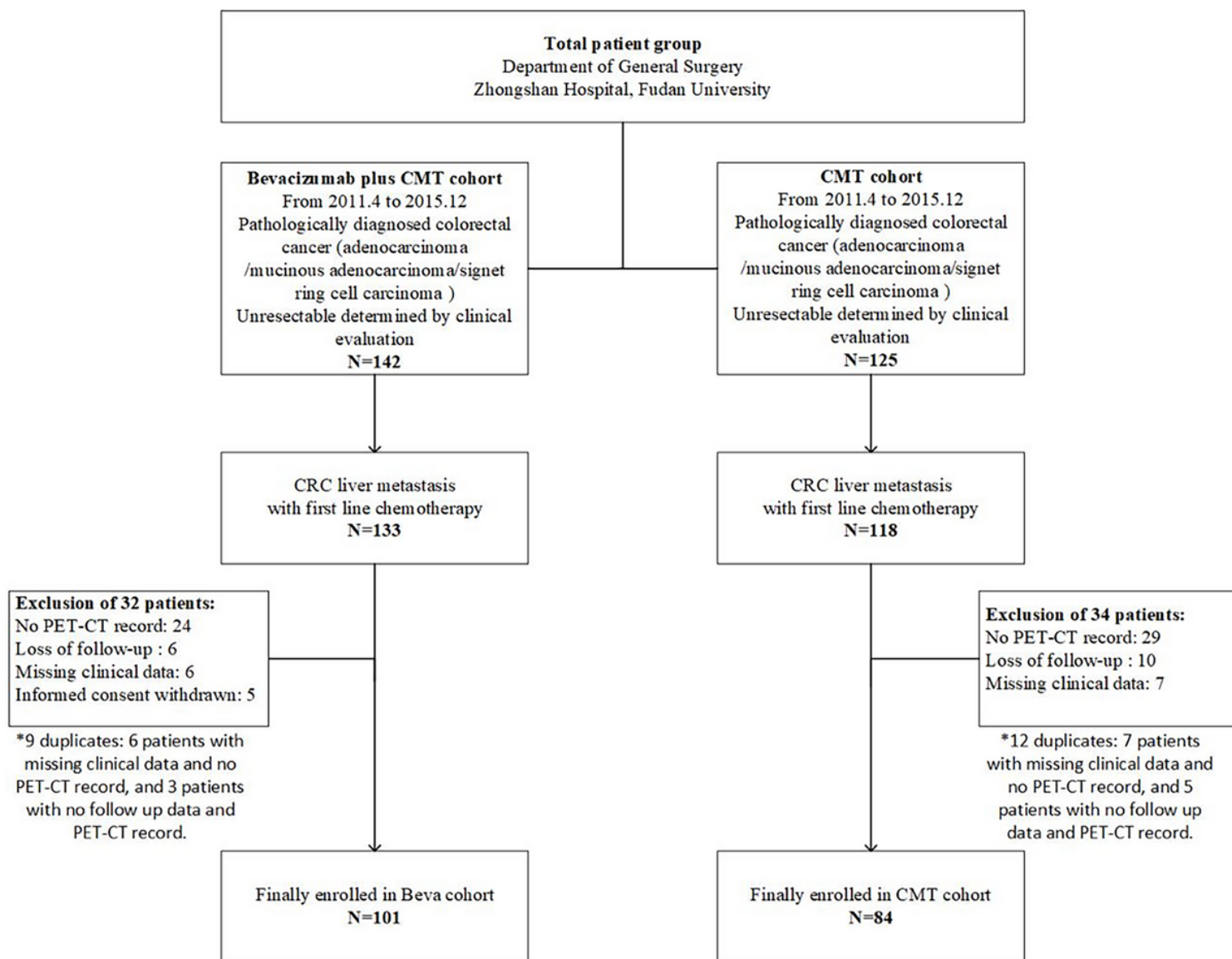
Figure 1

Flow diagram of colorectal cancer liver metastasis patients enrolled from our institution.
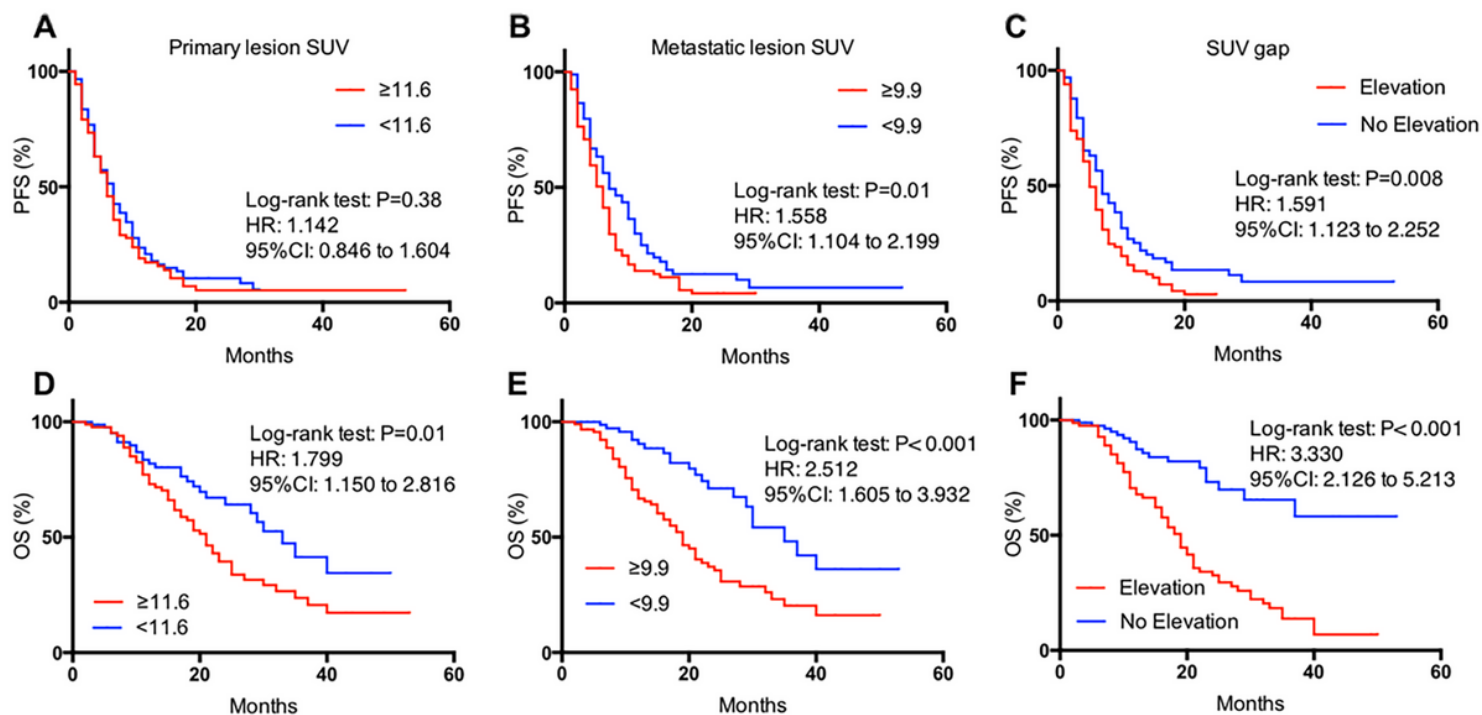
Figure 2

Kaplan-Meier progression-free survival and Overall survival curves for different primary lesion SUV level (A and D), metastatic lesion SUV level (B and E) and SUV elevation (C and F) in CRLM patients. HR, hazard ratio.
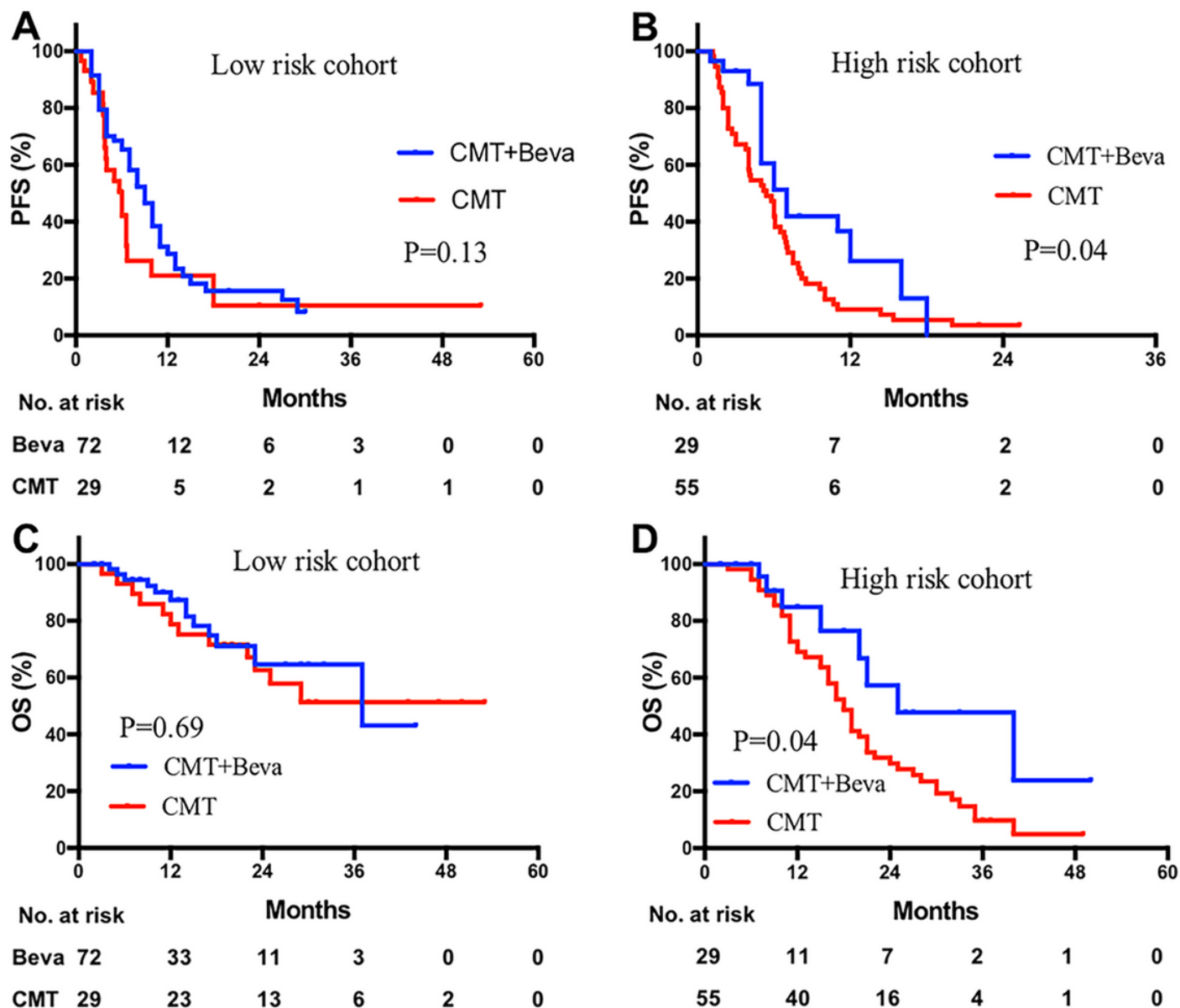
Figure 3

Kaplan−Meier progression free survival (A and B) and overall survival (C and D) curves for patients with different SUV gap level receiving chemotherapy or chemotherapy plus bevazunimab.