RESEARCH ARTICLE

The metabolic clinical risk score as a new prognostic model for surgical decision-making in patients with colorectal liver metastases

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Abstract

Background and Objectives: Selection for surgery in patients with colorectal liver metastases (CRLM) remains inaccurate. We evaluated if CRLM baseline metabolic characteristics, assessed by [18]F-fluorodeoxyglucose-positron emission tomography/computed tomography (18FDG-PET/CT), could predict postoperative outcomes.

Methods: In a retrospective series of patients undergoing surgery for CRLM, we defined two groups: the long-term survival (LTS) and early relapse (ER) groups, where the postoperative recurrence-free survivals were ≥5 years or <1 year, respectively. We analyzed the patients in whom baseline 18FDG-PET/CT was available. Clinicopathologic parameters, clinical risk score (CRS), and baseline 18FDG-PET/CT characteristics were compared between LTS and ER groups. A metabolic CRS (mCRS) was implemented, adding one point to the standard five-point CRS when the highest tumor standardized uptake values (SUV max)/normal liver mean SUV (SUV mean(liver)) ratios were >4.3, defining low- and high-risk mCRS by scores of 0 to 2 and 3 to 6, respectively.

Results: From a series of 450 patients operated for CRLM (mean follow-up of 58 months), we included for analysis 23 and 30 patients in the LTS and ER groups, respectively. Clinicopathologic parameters and CRS were similar in the LTS and ER groups. Median SUV max/SUV mean(liver) ratios were higher in ER vs LTS (P = .024); 61% of LTS patients had low-risk mCRS and 73% of the ER patients had high-risk mCRS (P = .23).

Conclusions: 18FDG-PET/CT characteristics combined with traditional CRS may represent a new tool to improve selection for surgery in patients with CRLM.

KEYWORDS
18FDG-PET/CT, colorectal liver metastases, prognostic, score, surgery
1 | INTRODUCTION

Surgery remains the only potentially curative treatment in patients with colorectal liver metastases (CRLM), leading to 5-year overall survival (OS) rates ranging from 35% to 50%, and to a cure, defined as recurrence-free survival (RFS) longer than 10 years, in 20% to 35% of patients. Consequently, surgery is recommended in patients with resectable liver-only CRLM, associated or not with perioperative chemotherapy. Accordingly, surgical decision-making in these patients relies primarily on technical resectability and is only marginally influenced by the biological characteristics of the tumor. This leads to poorly effective selection as the majority of patients recur postoperatively, whereas a substantial proportion develops rapid and diffuse relapses, carrying a very poor prognosis. There is, therefore, a strong need for identifying new biomarkers that would help to better individualize therapeutic decision. Several clinicopathologic predictive and prognostic factors and scores have been established in patients with CRLM, and, among them, the Memorial Sloan Kettering clinical risk score (CRS), remains the most widely used. These risk models are useful for prognostication and stratification of the patients, but, due to their limited value for predicting the benefit of surgery in individual cases, they only modestly personalized therapeutic decision.

[18]F-fluorodeoxyglucose positron emission tomography/computed tomography ([18]FDG-PET/CT) is a well-established metabolic imaging modality in oncology for the assessment of initial extension, therapeutic response, and detection of recurrence. [18]FDG-PET/CT allows visualization and quantification of glucose uptake and metabolism, providing in vivo information on the biology of the tumor. The glucose uptake and metabolism of cancer cells is increased by diverse mechanisms (eg increased mitotic activity), that are directly or indirectly related to tumor aggressiveness.

The predictive and prognostic value of metabolic parameters derived from preoperative [18]FDG-PET/CT has already been demonstrated in several cancers including lung, esophageal, and colorectal neoplasms. In CRLM, several studies have also demonstrated the prognostic value of the metabolic parameters measured during preoperative [18]FDG-PET/CT.

In the present study, we analyzed whether baseline [18]FDG-PET/CT metabolic characteristics of CRLM may serve to discriminate between patients who will obtain a significant oncological benefit from surgery and those who will not. In addition, we evaluated the potential predictive value of a new score, combining metabolic data with standard CRS.

2 | PATIENTS AND METHODS

2.1 | Patients

A prospective database including patients who underwent curative-intent resection for CRLM at the Institut Jules Bordet and the Hôpital Erasme between January 2003 and April 2017 was reviewed. Within this population, two groups were retrospectively identified: (1) Patients with long-term survival (LTS), as defined by RFS ≥5 years after the first surgery for CRLM, categorized as patients who benefited from surgery, and (2) patients with early relapse (ER), as defined by the development of unresectable recurrence(s) within or outside the liver during the first postoperative year, categorized as patients who did not benefit from surgery. The inclusion criteria were: Patients ≥18-year old, histologically confirmed CRLM, [18]FDG-PET/CT performed at diagnosis of CRLM and before any preoperative treatment, such as chemotherapy or radiotherapy, and the absence of a second active cancer. As a standard of care, all patients had performed contrast-enhanced abdominal CT and/or magnetic resonance imaging and chest CT at the time of diagnosis of CRLM. This study was approved by Institutional Ethical Committees (CE2841 and P2018/331).

2.2 | Surgery

All patients underwent curative-intent surgery, meaning resection or destruction with radiofrequency (RF) of all metastatic sites. Partial hepatectomy and RF were performed under intraoperative ultrasound guidance, aiming at achieving margin-free resection or destruction. The resections were defined as R0 when resection margins were microscopically healthy, and R1 when resection margins were microscopically invaded. In the case of two-step surgery, the follow-up started from the date of the second intervention.

2.3 | [18]FDG-PET/CT imaging procedure

[18]FDG-PET/CT was performed with four different cameras (GE Discovery Lightspeed, GE Discovery 690, Philips Gemini-16P, and Philips Gemini GXL). Whole-body imaging (skull base or apex of the skull to mid-thigh) was performed according to the standardized practice guidelines. Imaging started 60 to 120 minutes after [18]FDG administration (in 40 patients, images were acquired 60 ± 10 minutes after injection). Patients had to fast for at least 6 hours before examination, with glycaemia ≤170 mg/dL.

2.4 | [18]FDG-PET/CT imaging analysis

Images were analyzed using dedicated commercial software (PET VCAR v.4.6: Advantage Workstation; GE Healthcare). Standardized uptake values (SUV) of reference, specific to each patient, were calculated similarly to PERCIST criteria 1.0. These values were SUVmean(liver) and SUVmean(blood). Corresponding to the average SUV calculated in a spherical region of interest of 3 cm of diameter in healthy liver tissue and the average SUV calculated in a spherical region of interest of 1.2 cm in diameter at the descending thoracic aorta, respectively. Metabolic parameters that were measured included, SUVmax (maximum SUV value within a lesion) and SUVpeak (maximum average SUV within a 1 cm³ spherical volume inside the
lesion) for all observable lesions. In case of multiple hepatic metastases, the highest metabolic value was considered for analysis. The metabolic tumor volume (MTV) corresponded to the sum of the volumes (in cm³) of all hepatic lesions, delineated using a fixed threshold equal to the SUV\textsubscript{mean(liver)} value plus 2 standard deviations. When no lesion was observable, the lesion’s SUV\textsubscript{max} and SUV\textsubscript{peak} values were considered equal to SUV\textsubscript{mean(liver)} and MTV equal to 0. Ratios SUV\textsubscript{peak}/SUV\textsubscript{mean(liver)} and SUV\textsubscript{peak}/SUV\textsubscript{mean(blood)} were calculated to avoid unsuspected errors due to differences between cameras. Images were analyzed by three experienced nuclear physicians blinded to clinical data.

### 2.5 Metabolic CRS

We defined a metabolic CRS (mCRS) by combining metabolic data and CRS, implementing a previously defined prognostic SUV\textsubscript{max}/SUV\textsubscript{mean(liver)} cut-off into the original CRS.\textsuperscript{24} Shim et al identified, using the Contal and O’Quigley method, an SUV\textsubscript{max}/SUV\textsubscript{mean(liver)} cut-off value of 4.3 as the optimum value that best differentiates survival data in the log-rank test. Accordingly, a six-point mCRS was calculated by adding one point to the traditional CRS when the highest SUV\textsubscript{max}/SUV\textsubscript{mean(liver)} ratio of the metastatic hepatic lesion was >4.3. The mCRS was calculated for each patient and categorized as low-risk (score ≤ 2) and high-risk groups (score >2).

### 2.6 Statistical analysis

Statistical analyses were performed using Graphpad (Prism version 7.04 for Windows, GraphPad Software, La Jolla, CA). Clinical, biological, and metabolic variables and scores were analyzed by the Fisher or \(x^2\) tests for categorical variables, and by the Mann-Whitney or the Student t test for continuous variables, depending on the distribution. The intensity of the relationships between measured metabolic parameters was analyzed by a matrix of correlation using a non-parametric Spearman correlation. Variables with a Spearman’s correlation >0.8 were considered as correlated. Parameters that were significantly different between the two groups were tested to predict ER using receiver operating characteristics (ROC) curves. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. A \(P\) value <.05 was considered significant and all tests were two-tailed.

### 2.7 Clinicopathological data

Clinical and laboratory data were analyzed, including demographic characteristics, biological and pathological features of the primary tumor and liver metastases, CEA tumor marker, treatment regimen, and type of surgery. The number and size of liver metastases were defined by anatomical imaging (computed tomography or magnetic resonance imaging). The size of the liver metastases and the CEA were categorized according to CRS categories.\textsuperscript{2} Liver metastases were defined as synchronous or metachronous when diagnosed ≤12 or >12 months after diagnosis of the primary tumor, respectively.

The CRS score, giving one point for primary tumor with nodal invasion, synchronous CRLM, maximal diameter of CRLM ≥ 50 mm, the presence of >1 CRLM and CEA serum level >200 μg/L, was calculated for each patient. CRS was defined as low- and high-risk when scores were ≤2 or >2, respectively.

### 3 RESULTS

#### 3.1 Patient inclusion

An initial population of 450 patients operated for a curative-intent for CRLM was selected. The mean follow-up in this population was 58 months. Among these, 63 and 74 patients were identified in the LTS and ER groups, respectively. From these 137 patients, 84 were excluded, 13 for \(^{18}\)FDG-PET/CT not having been performed at the time of diagnosis of CRLM, 58 who received chemotherapy before \(^{18}\)FDG-PET/CT, and 13 in whom no useable \(^{18}\)FDG-PET/CT data could be recovered. Accordingly, data for a total of 53 patients were analyzed, including 23 patients in the LTS group and 30 in the ER group, corresponding to exclusion rates of 63.5% and 59.5%, respectively.

#### 3.1.1 Clinicopathological and surgical characteristics

Among the 53 patients analyzed, no significant difference was observed between the LTS (\(n = 23\)) and ER (\(n = 30\)) groups, for sex, age, BMI, ASA score, localization of the primary tumor, and the use of preoperative chemotherapy (Table 1). Similarly, no difference was observed in primary T and N stages and degree of differentiation. The rates of multinodular CRLM and of R1 resection were similar between the LTS and ER groups, respectively of 43.5% and 66.7%, \(P = .104\), and 19.1% and 25.0%, \(P = .737\) (Table 2). Of note, a significantly longer time elapsed between \(^{18}\)FDG-PET/CT and surgery in ER patients (median 123 days vs 75 days, \(P = .023\)).

#### 3.1.2 Metabolic parameters of liver metastases

All metabolic parameters, except for MTV, were significantly different between the LTS and ER groups (Table 3). A higher FDG uptake of the liver metastases was observed in ER patients, with the SUV\textsubscript{max}/SUV\textsubscript{mean(liver)} ratio being the most significantly different variable (median ER= 4.21 vs LTS= 2.82, \(P = .008\)).

The correlation matrix showed a high level of correlation between metabolic parameters (eg SUV\textsubscript{max} and SUV\textsubscript{mean}, Spearman \(r = 0.99\)) (Table 3). Only MTV was not correlated to other metabolic parameters. As the SUV\textsubscript{peak}/SUV\textsubscript{mean(liver)} ratio was the most significantly different between the two groups, this parameter was chosen for the ROC curve analysis.

The ROC curve analysis of SUV\textsubscript{peak}/SUV\textsubscript{mean(liver)} ratios is shown in Figure 1. The definition of “positive test” was selected for predicting an ER. The area under the curve was 0.713 (95% CI, 0.572-0.854). Evaluating the cut-off values of >4.0 and >6.5, we
observed specificities of 73.9% and 95.7%, and sensitivities of 56.7% and 16.7%, respectively (PPV of 73.9% and 83.3%, respectively).

Conversely, CRLM with no or low FDG uptake (ratio < 1.43) were only seen in LTS patients (NPV = 100%).

### 3.1.3 Metabolic and CRS

Taken individually, neither CRS nor SUV\textsubscript{max}/SUV\textsubscript{mean(liver)} ratio > 4.3 was significantly different between the LTS and ER groups (P = .120 and P = .159, respectively) (Table 4). In contrast, mCRS values were significantly different between the LTS and ER groups (P = .024). The rates of low- and high-risk mCRS were also significantly distributed among LTS and ER groups. 60.9% of the LTS patients had a low-risk score and 73.3% of the ER group had a high-risk mCRS (P = .023) (Table 4).

### 4 DISCUSSION

Optimally, risk models in patients with CRLM should be able to guide individual therapeutic decision-making by discriminating preoperatively, patients who will or will not benefit from surgery. Defining the benefit of surgery in this setting is a difficult question, ranging from cure to prolonged survival and avoidance or delaying the need for chemotherapy or improved quality of life. However, it is obvious that a clear oncological gain is obtained in patients with postoperative RFS over 5 years whereas no benefit is observed in patients who develop unresectable recurrence within the first postoperative year.\textsuperscript{44} Therefore, as a first approach, we used these cut-offs to evaluate the potential value of baseline \textsuperscript{18}FDG-PET/CT characteristics to predict the benefit of surgery in patients with technically resectable or clearable CRLM. We also hypothesized that the combination of these metabolic criteria with the standard CRS risk
model may improve patient selection for surgery. Indeed, a higher proliferation rate, overexpression of GLUT or hexokinase, hypoxia, and modifications of glucose metabolic pathways,—all factors concurring with the so-called Warburg effect—are responsible for higher glucose uptake in cancer cells, and have been often associated with tumor aggressiveness.17,19,20 It has been shown in various cancers that high FDG uptake is associated with poorer prognosis.21,23 In colorectal cancer and in CRLM, the prognostic value of 18FDG-PET/CT has also been demonstrated, but its value in association with a clinical score has not yet been explored.20,24-28

We first observed that individual preoperative clinicopathological factors, CRS scores, and high- and low-risk CRS were not significantly different between patients who had the opposite postoperative oncological outcomes, confirming the poor prognostic accuracy of traditional clinical surrogates.16,30 In contrast, all metabolic parameters, including SUV<sub>max</sub> and SUV<sub>peak</sub>, with the exception of MTV, were significantly increased in the patients who rapidly relapsed as compared with the patients with prolonged RFS, suggesting that metabolic characteristics could potentially predict the benefit of surgery in individual cases. In addition, according to a recent study showing that CRLM with SUV<sub>max</sub>/SUV<sub>mean(liver)</sub> > 4.3 have a higher risk of recurrence after curative-intent surgery,24 we have proposed a new mCRS, by adding one point to CRS when at least one of the CRLM presented with an SUV<sub>max</sub>/SUV<sub>mean(liver)</sub> > 4.3 at baseline. Our results suggest that this new score may improve patient risk stratification, as we observed a significantly higher proportion of high-risk mCRS (score > 2/6) in patients with early postoperative relapse as compared with patients with prolonged RFS.

In contrast with other reports, MTV did not appear as a strong predictive factor,25,31 even if a tendency toward a higher MTV was observed in ER patients. This could be related to the limited size of the groups but also to the fact that the prognostic impact of tumor burden could be diminished in patients undergoing local therapy, such as surgery, compared with patients treated with systemic therapies. The present data have been obtained with baseline 18FDG-PET/CT, at the time of the diagnosis of CRLM, before any systemic therapy. Accordingly, this study evaluates intrinsic tumor behavior, independent of the response to chemotherapy, as the prognostic value of the response to chemotherapy may vary in patients with CRLM, depending on the number of cycles and on the method used for assessment.32

### TABLE 3

<table>
<thead>
<tr>
<th>A</th>
<th>LTS (n = 23)</th>
<th>ER (n = 30)</th>
<th>P value</th>
<th>B</th>
<th>SUV&lt;sub&gt;max&lt;/sub&gt;</th>
<th>SUV&lt;sub&gt;peak&lt;/sub&gt;</th>
<th>MTV</th>
<th>SUV&lt;sub&gt;max&lt;/sub&gt;/SUV&lt;sub&gt;mean(liver)&lt;/sub&gt;</th>
<th>SUV&lt;sub&gt;max&lt;/sub&gt;/SUV&lt;sub&gt;mean(blood)&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;</td>
<td>6.28 (1.97-16.27)</td>
<td>9.79 (3.54-47.96)</td>
<td>.011</td>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;</td>
<td>0.991</td>
<td>0.678</td>
<td>0.965</td>
<td>0.938</td>
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<tr>
<td>SUV&lt;sub&gt;peak&lt;/sub&gt;</td>
<td>5.15 (1.97-13.58)</td>
<td>7.55 (2.97-44.34)</td>
<td>.021</td>
<td>SUV&lt;sub&gt;peak&lt;/sub&gt;</td>
<td>0.991</td>
<td>0.716</td>
<td>0.949</td>
<td>0.924</td>
<td></td>
</tr>
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<td>MTV</td>
<td>15.99 (0-449)</td>
<td>36.87 (3.89-1494)</td>
<td>.074</td>
<td>MTV</td>
<td>0.678</td>
<td>0.716</td>
<td>0.708</td>
<td>0.701</td>
<td></td>
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<tr>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;/SUV&lt;sub&gt;mean(liver)&lt;/sub&gt;</td>
<td>2.82 (1-6.75)</td>
<td>4.21 (1.77-22.52)</td>
<td>.008</td>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;/SUV&lt;sub&gt;mean(liver)&lt;/sub&gt;</td>
<td>0.965</td>
<td>0.949</td>
<td>0.708</td>
<td>0.953</td>
<td></td>
</tr>
<tr>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;/SUV&lt;sub&gt;mean(blood)&lt;/sub&gt;</td>
<td>4.02 (0.99-9.89)</td>
<td>5.75 (2.11-31.97)</td>
<td>.036</td>
<td>SUV&lt;sub&gt;max&lt;/sub&gt;/SUV&lt;sub&gt;mean(blood)&lt;/sub&gt;</td>
<td>0.938</td>
<td>0.924</td>
<td>0.701</td>
<td>0.953</td>
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</tbody>
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Abbreviations: ER, early relapse; LTS, long-term survival; SUV, standardized uptake value; MTV, metabolic tumor volume.

### FIGURE 1

ROC curve analysis of SUV<sub>max</sub>/SUV<sub>mean(liver)</sub> ratio, AUC = 0.713 (a). Evaluation of different cut-off values of SUV<sub>max</sub>/SUV<sub>mean(liver)</sub> to detect early relapse (b). AUC, area under the ROC curve; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristics; SUV, standardized uptake value
The main limitations of our study are its retrospective nature and the limited number of patients evaluated. The retrospective design also led to a significant difference in time elapsed between $^{18}$FDG-PET/CT and surgery in the ER and LTS groups, surgery being performed later after the $^{18}$FDG-PET/CT in the ER group. The difference in the delay cannot explain the higher metabolic activity observed in the ER group—evaluated at an early stage of their metabolic buildup—compared to the LTS group. However, the difference in delay raises the question of a higher probability that unknown—hepatic or extrahepatic—metastases were present at the time of surgery in the ER group. Prospective studies are mandatory to rule out such questions. Also, a considerable proportion of patients were excluded mostly due to the administration of chemotherapy before baseline $^{18}$FDG-PET/CT. However, the exclusion rates were similar in the two groups and probably does not significantly affect our results but this strongly underlines the need for a prospective validation of these preliminary results.

Taken together, these results may serve as a proof-of-concept that the introduction of simple metabolic parameters into clinical scores may improve the identification of patients with a high risk of early recurrence after surgery. These rapid postoperative recurrences are most probably related to undiagnosed (micro) metastases at the time of surgery, high FDG uptake potentially representing a surrogate marker for higher risk of diffuse occult metastases. This is, to the best of our knowledge, the first study that has implemented metabolic criteria assessed by $^{18}$FDG-PET/CT into a multi-parameter clinical score routinely used in patients with CRLM. Additional modifications of mCRS could most probably further improve its accuracy. More specifically, a binary score based on a single cut-off value may not take full advantage of the quantitative metabolic information provided by $^{18}$FDG-PET/CT. For instance, we observed very low FDG uptake lesions only in the LTS patients and very high uptake values only in the ER patients, indicating that more elaborate computation of the metabolic clinical score should be considered. Finally, other metabolic parameters, such as the heterogeneity of the tumor metabolism, could also be considered to improve the performance of such metabolic clinical scores.

## 5 CONCLUSIONS

In conclusion, this study indicates that baseline metabolic parameters of CRLM assessed by $^{18}$FDG-PET/CT may represent an early biomarker of intrinsic tumor biology, potentially predicting the benefit of surgery. The combination of these parameters with a traditional CRS model may represent a new tool to better individualize the therapeutic decision in these patients.

## ACKNOWLEDGMENTS

The authors acknowledge the contribution of a medical writer, Sandy Field, PhD, for editing and formatting of this manuscript.

## DATA AVAILABILITY STATEMENT

The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## REFERENCES


### TABLE 4 Comparisons between metabolic parameter $SUV_{\text{mean(liver)}}/SUV_{\text{max}}$ ratio, clinical risk score (CRS) and metabolic clinical risk score (mCRS)

<table>
<thead>
<tr>
<th>CRS score, n (%)</th>
<th>LTS (n = 23)</th>
<th>ER (n = 30)</th>
<th>P value</th>
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<tbody>
<tr>
<td>0</td>
<td>3 (13.0)</td>
<td>2 (6.7)</td>
<td>.120</td>
</tr>
<tr>
<td>1</td>
<td>6 (26.1)</td>
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<td></td>
</tr>
<tr>
<td>2</td>
<td>6 (26.1)</td>
<td>10 (33.3)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7 (30.4)</td>
<td>12 (40.0)</td>
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</tr>
<tr>
<td>4</td>
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</tr>
<tr>
<td>5</td>
<td>1 (4.3)</td>
<td>0 (0)</td>
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<table>
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<tr>
<th>CRS risk, n (%)</th>
<th>Low risk (score 0-2)</th>
<th>High risk (score 3-5)</th>
<th>P value</th>
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<tr>
<td>Low risk (score 0-2)</td>
<td>15 (65.2)</td>
<td>14 (46.7)</td>
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<td>High risk (score 3-5)</td>
<td>8 (34.8)</td>
<td>16 (53.3)</td>
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<tr>
<th>$SUV_{\text{max}}/SUV_{\text{mean(liver)}}$</th>
<th>LTS (n = 23)</th>
<th>ER (n = 30)</th>
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<td>$\leq 4.3$</td>
<td>17 (73.9)</td>
<td>16 (53.3)</td>
<td>.159</td>
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<td>$&gt; 4.3$</td>
<td>6 (26.1)</td>
<td>14 (46.7)</td>
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<tr>
<th>mCRS score, n (%)</th>
<th>LTS (n = 23)</th>
<th>ER (n = 30)</th>
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<tr>
<td>0</td>
<td>3 (13.0)</td>
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<td>1 (4.3)</td>
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<th>mCRS risk, n (%)</th>
<th>Low risk (score 0-2)</th>
<th>High risk (score 3-6)</th>
<th>P value</th>
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<td>Low risk (score 0-2)</td>
<td>14 (60.9)</td>
<td>8 (26.7)</td>
<td>.023</td>
</tr>
<tr>
<td>High risk (score 3-6)</td>
<td>9 (39.1)</td>
<td>22 (73.3)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ER, early relapse; LTS, long-term survival.


