Abstract. The aim of the present study was to explore the value of T1 mapping on gadolinium-ethoxybenzyl diethylene-triamine pentaacetic (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI) for grading hepatocellular carcinoma (HCC) and predicting its recurrence rate. A retrosppective study was performed that included 75 patients (66 men and 9 women; mean age, 52.89 years; age range, 23-79 years) with HCC who had undergone Gd-EOB-DTPA-enhanced MRI with T1 mapping before surgery. The T1 relaxation time of the 81 lesions and non-tumorous liver parenchyma in 75 patients with HCC were measured before Gd-EOB-DTPA was injected and then at 5, 10 and 20 min after administration, respectively. T1[lesion (L)-hepatic parenchyma (H)]/H (%) was calculated as the increment rate of the T1 value in the lesions relative to the non-tumorous liver parenchyma. One-way analysis of variance and Spearman's correlation analysis was used to compare the differences and relationship of T1 mapping values among the three grades of HCC. A total of 81 lesions were divided into well-differentiated HCC (grades I; n=21), moderately differentiated HCC (grades II; n=40) and poorly differentiated HCC (grades III; n=20) according to the histopathology. The T1[lesion (L)-hepatic parenchyma (H)]/H (%) value among grades I, II and III HCC on pre-contrast results and on post-contrast results at the 5-, 10- and 20-min hepatobiliary phase (HBP) were significantly different (P<0.05), and T1[lesion (L)-hepatic parenchyma (H)]/H (%) was correlated with the histological grade of HCC at each time point (r=0.637, r=0.554, r=0.499 and r=0.560, respectively, P<0.001). A total of 41 recurrence cases [grade I (n=5), grade II (n=23) and grade III (n=13)] were verified by imaging (CT, MRI or ultrasound) or reoperation. Patients with grade III and grade II HCC had higher recurrence rates compared with that in patients with grade I HCC (P<0.05; median recurrence times were 258 days, 605 days and undefined, respectively). According to the optimal cut-off point for the T1[lesion (L)-hepatic parenchyma (H)]/H (%) of the three grades of HCC, patients with HCC in the low T1[lesion (L)-hepatic parenchyma (H)]/H (%) value group (≤155.15%) had lower cumulative recurrence rates compared with that in the medium (T1[lesion (L)-hepatic parenchyma (H)]/H (%) >155.15% and ≤241.20%) and high (T1[lesion (L)-hepatic parenchyma (H)]/H (%) >241.20%) value groups at the 20-min HBP (P<0.05; median recurrence times were undefined, 530 days and 447 days, respectively). These results indicate that the parameters of T1 mapping would be beneficial for predicting the grading and recurrence of HCC.

Introduction

Primary hepatocellular carcinoma (HCC) is one of the most common malignancies and the third leading cause of cancer-related death worldwide (1). The recurrence rate of HCC 5-years after surgery is >60% in Japan (2). Studies have found that tumor heterogeneity, high degree of differentiation, large size, multicentricity, microvascular invasion, intraoperative extrusion of the tumor, postoperative intervention, macroscopic or microscopic portal venous tumor extension and intrahepatic metastasis were risk factors indicative of poor prognosis after surgery (3-5). Magnetic resonance imaging (MRI) provides valuable imaging information for the preoperative and postoperative evaluation of HCC (6).

Gadolinium-ethoxybenzyl diethylene-triamine pentaacetic (Gd-EOB-DTPA)-enhanced MRI has been widely used in the evaluation of HCC, as it aids in the differential diagnosis, grading and final diagnosis process (7-9). The uptake of Gd-EOB-DTPA in HCC is determined by the expression of
organic anion transporter polypeptide 1B1 (OATP1B1) and OATP1B3, and their activity can predict the signal intensity of Gd-EOB-DTPA-MRI (10). A previous study found that dysplastic nodules (DN) reduced the uptake of Gd-EOB-DTPA and that the enhancement rate of DN in the hepatobiliary phase was higher compared with that in the moderately and poorly differentiated HCC (11). The advantage of Gd-EO-DTPA is that it is taken up by hepatocytes, resulting in the maximal enhancement of normal liver parenchyma in the hepatobiliary phase (HBP) 20 min after injection of the contrast agent (12), thus improving the detection rate of the lesion. A previous study by Zeng et al (13) found that Gd-EOB-DTPA-MRI significantly improved the diagnostic and accuracy rates of the liver focal lesions compared with multislice computed tomography and MRI non-specific gadolinium contrast. However, Gd-EOB-DTPA-MRI is inadequate to detect HCC for clinical treatment. Hence, evaluating the liver background and grading of the tumor are crucial factors for a better treatment. A previous study proved that dynamic contrast-enhanced (DCE)-MRI with Gd-EOB-DTPA as a liver-specific MR contrast agent can improve the sensitivity and accuracy in the detection of small HCC (14). In addition, An et al (9) reported that the enhanced degree of HCC on the early arterial phase was correlated with its histopathological grade by using multi-parameter quantitative analysis based on Gd-EOB-DTPA-enhanced MRI and diffusion-weighted imaging (DWI). However, the specificity of these multi-parameter methods for grading HCC in the aforementioned studies was not significant. T1 mapping based on Gd-EOB-DTPA-enhanced MRI has been increasingly used for qualitatively diagnosing diseases of hepatic fibrosis and liver function, and it has achieved good efficiency for discriminating between different degrees of liver fibrosis (15-17). Previous studies found that it was valuable to evaluate T1 mapping quantitatively at 5-, 10- and 20-min HBP after contrast enhancement for distinguishing interhepatic focal lesions (16,18-20). Previously, retrospective studies demonstrated that T1 mapping before and after Gd-EOB-DTPA administration can benefit HCC grading, since T1 mapping could reflect the microscopic changes associated with the tumor to a certain extent (16,18-20).

Up to now, there have been few T1 mapping studies on HCC grading focusing on the association between T1 mapping and HCC recurrence (21). The aim of the present study was to investigate the correlation between T1 mapping and the histopathological grade of HCC, which subsequently provides more preoperative diagnostic information by calculating the T1 value to predict the recurrence of HCC.

Materials and methods

Patients. Retrospective data collection and analysis was approved by the Institutional Review Board of The First Affiliated Hospital of Guangxi Medical University (Nanning, China). A total of 75 consecutive patients who were diagnosed with primary HCC, confirmed by histopathological examination, between September 2015 and March 2017, were enrolled for the present study. All patients underwent a hepatectomy within 2 weeks of Gd-EOB-DTPA-enhanced MRI. Inclusion criteria were as follows: i) Patients who underwent Gd-EOB-DTPA-enhanced MRI before hepatectomy or liver biopsy; ii) patients who underwent surgical resection treatment; and iii) patients who were confirmed to have primary HCC by histopathological staining. Exclusion criteria were as follows: i) Tumor size >1 cm; ii) previous interventional treatment; iii) metastasis; and iv) diffuse-type HCC. Recurrence was defined as a new lesion that was observed by two experienced radiologists on imaging (CT, MRI and ultrasound) or confirmed by pathology after reh spat ectomy. All the patients were followed up until September 30, 2018, or until mortality. For patients who were unable to undergo reexamination in person at The First Affiliated Hospital of Guangxi Medical University, follow-up was performed 3 months after surgery, via telephone. Written informed consent was obtained from all patients with HCC. For the histopathological examination, the HCC tissues and corresponding non-cancerous were fixed in 4% neutral formaldehyde at 65°C for 2 h and subsequently the paraffin-embedded tissues were cut into 4 μm sections. Following which hematoxylin and eosin staining was performed for 1 h at room temperature. Pathological sections were observed under an Olympus BX53 light microscope (magnification, x100 and x200) and the features of HCC were observed as follows: The hepatocytes were polygonal or round, and arranged as nests or cables; the nuclei were enlarged and its nucleolus was deeply stained and there was an abundance of blood sinuses in the cancer nests.

MRI protocols. All MR scans were conducted on a 3T MRI scanner (Magneton Verio; Siemens Healthineers) with an 8-channel phased-array body coil. Half-fourier acquisition single-shot turbo spin echo sequence, axial turbo spin echo T2-weighted free breathing with fat suppression sequence, and breath-hold axial single-shot echo planar imaging DWI fat-suppressed sequence were performed prior to contrast enhancement. An axial T1-weighted three-dimensional spoiled gradient echo volume interpolated body examination fat-suppressed sequence was performed to acquire DCE-MRI data. A bolus of 0.025 mmol/kg Gd-EOB-DTPA (Bayer AG) was injected at a rate of 2 ml/sec through the cubital vein, followed by a 20-ml saline flush at the same rate. T1 mapping was performed before and at the 5, 10 and 20 min delay phases after Gd-EOB-DTPA administration. The sequence parameters used are listed in Table I.

T1 value measurement. All MRI data obtained from the patients were analyzed to measure T1 relaxation time using operator-defined regions of interest (ROI). The ROI with an area of 1-1.2 cm2 was drawn manually on the lesion and non-tumorous liver parenchyma (1-2 cm distant from the margin of the tumor) by two experienced radiologists, respectively, who were blinded to the histopathological information, and each ROI was taken three times to measure the mean T1 values for further analysis. In case of conflicts, the decision was negotiated. All measurements were performed to avoid bile duct, hemorrhage, necrosis, cystic, fat, blood vessels and bile ducts, artifacts, selecting the maximum tumor cross-sectional area (Fig. 1). Subsequently, the average values were calculated and the T1 value was expressed as the mean ± standard deviation (SD). The increasing rate of T1 value in the HCC lesion \( \frac{\text{T1}_{\text{L-H}}}{\text{H}} \times 100 \), where L indicates the lesion and H indicates the hepatic parenchyma.
The $T_{1(L-H)/H}$ (%) values before and at the 5-, 10- and 20-min HBP after Gd-EOB-DTPA administration for each patient were respectively calculated by the aforementioned equation.

**Statistical analysis.** Analyses were performed using SPSS software (version 22.0; IBM Corp.). Statistical charts were created using GraphPad Prism v5.01 (Graphpad Software, Inc.). Descriptive statistics (mean ± SD), such as mean diameter were provided when no quantifiable data was available. One-way analysis of variance with the least significant difference test were used to compare the differences in the increment rate of the $T_1$ value in the lesions relative to non-tumorous liver parenchyma ($T_{1(L-H)/H}$ (%)) among different grades of HCC. Spearman’s correlation analysis was used to evaluate the correlation between the increasing rate of $T_1$ values and HCC grading. Patients who were lost to follow-up or died (due to an accident unrelated to HCC or from postoperative complications) during the follow-up period were censored. Receiver operating characteristic (ROC) curve analyses were conducted for $T_{1(L-H)/H}$ (%) of grade I, II and III HCC. The cut-off values of $T_{1(L-H)/H}$ (%) between grades I and II, grades II and III HCC were obtained, respectively; and then the cumulative recurrence rates of the three groups rearranged by these two cut-off values of $T_{1(L-H)/H}$ (%) were also evaluated using Kaplan-Meier method and log-rank test. $P<0.05$ was considered to indicate a statistically significant difference.
Results

Patient characteristics. A total of 75 patients (66 men and 9 women; mean age, 52.89 years; age range, 23-79 years) with 81 lesions were included in the present study. According to the Liver Disease Symposium on Barcelona Clinic Liver Cancer (BCLC) staging system for hepatocellular carcinoma (22), the HCC cases were classified as BCLC stage A, B, C and D. A total of 81 lesions with a mean diameter of 4.13±0.32 cm (range 1.2-15 cm) were measured. Pathological diagnosis and grading were made according to the Edmondson-Steiner grading system (23). Due to research population restrictions, Edmondson-Steiner grade IV of HCC was not included in the present study. In our study, 19 patients with 21 lesions (25.93%) were classified as grade I, 37 patients with 40 lesions (49.38%) as grade II and 19 patients with 20 lesions (24.69%) as grade III. Recurrence of HCC was observed in 41 (54.67%) out of 75 patients during the follow-up period (median, 639.00 days; range, 42.00-973.00 days), and 1 patient was lost to follow-up after 490 days from the last reexamination. A total of 3 patients (2 HCC grade II and 1 HCC grade III) died 369, 195 and 398 days, respectively, after hepatectomy. The 41 recurrence cases [grade I (n=5), grade II (n=23), and grade III (n=13)] were verified by imaging (CT, MRI and ultrasound) or reoperation. The baseline characteristics of the patients are shown in Table II.

Comparison of T1 mapping of different grades of HCC at different time points. On pre-contrast, T1(L-H)/H (%) values for grade I, II and III HCC were 31.42±15.77, 56.07±21.42 and 78.21±27.68, respectively; at 5 min after enhancement, T1(L-H)/H (%) values were 85.48±73.06, 132.63±37.27 and 172.82±71.48, respectively; at 10 min after enhancement, T1(L-H)/H (%) values were 115.43±82.25, 190.81±66.58 and 226.13±101.49, respectively; and at 20 min after enhancement, T1(L-H)/H (%) values were 149.46±97.32, 247.59±85.16 and 333.95±134.99, respectively. T1(L-H)/H (%) was moderately correlated with Edmondson-Steiner HCC grading both at pre-contrast, and at 5, 10 and 20 min after administration of Gd-EOB-DTPA, respectively (r=0.637, r=0.554, r=0.499 and r=0.560, respectively; P<0.001). On pre-contrast and on post-contrast at the 5- and 20-min HBP, multiple comparisons of T1(L-H)/H (%) in the three groups of HCC were significantly different (P<0.05). On post-contrast at 10 min, the differences in T1(L-H)/H (%) value between grades I and II, and grades I and III were statistically significant (P<0.05), while T1(L-H)/H (%) values between grades II and III showed no significant differences (P>0.05). The T1(L-H)/H (%) value markedly increased for each grade of HCC at each time point and the T1(L-H)/H (%) of different HCC grades increased after enhancement compared with pre-enhancement (Fig. 2).

Variation of T1(L-H)/H (%) and the T1 relaxation time at each time point. The variation trend of T1(L-H)/H (%) and the T1 relaxation time in HCC lesions and non-tumorous liver parenchyma of differentiation grades at each time point are shown in Fig. 3. The value of T1(L-H)/H (%) after enhancement was higher compared with that pre-contrast, and T1(L-H)/H (%) was significantly increased with increasing delay time after contrast medium administration, with the most significant difference observed at the 20-min HBP (P<0.05). For HCC lesions, the T1 value was lowest at 5 min, but increased gradually from 10 to 20 min, with overlapping results for grades II and III. For liver parenchyma, the higher the malignancy degree of HCC

Table II. Clinical characteristics of the 75 patients with primary hepatocellular carcinoma.

| Characteristic | Value |
|---------------|-------|
| Age, years*   | 52.89±1.38 |
| Sex, n (%)    |       |
| Male          | 66 (88.00) |
| Female        | 9 (12.00)  |
| Mean size, cm*| 4.13±0.32 |
| Underlying disease, n (%) |       |
| HBV           | 66 (88.00) |
| HCV           | 8 (10.67)  |
| HBV + HCV     | 8 (10.67)  |
| Clonorchis    | 9 (12.00)  |
| Cirrhosis     | 44 (58.67) |
| Child-Pugh classification*, n (%) |       |
| A             | 70 (93.33) |
| B             | 5 (6.67)   |
| BCLC stage, n (%) |     |
| A             | 52 (69.33) |
| B             | 17 (22.67) |
| C             | 6 (8.00)   |
| D             | 0 (0.00)   |
| AFP, n (%)    |       |
| Normal <20 ng/ml | 27 (36.00) |
| Abnormal ≥20 ng/ml | 48 (64.00) |

*Mean ± standard deviation; †(33). HBV, hepatitis B virus; HCV, hepatitis B virus; BCLC, Barcelona Clinic Liver Cancer; AFP, α-fetoprotein.
the lower the $T_1$ value, particularly in the pre-contrast imaging. The $T_1$ value of liver parenchyma decreased quickly from pre-contrast to 10 min post-enhancement, and then slowly from the 10- to 20-min HBP, for the three grades of HCC. However, the $T_1$ value of non-tumorous liver parenchyma at each time point showed no statistical differences among the different grades of HCC ($P>0.05$).

**Survival analysis for 3 groups of patients with HCC.** At the 20-min HBP, the optimal cut-off point for the $T_{1(L-H)}/H\%$ of grade I and II, II and III HCC based on the ROC curve analysis were 155.15 and 241.20%, respectively (Fig. 4). The patients were subsequently classified into a low group ($T_{1(L-H)}/H\% \leq 155.15\%$), a medium group ($T_{1(L-H)}/H\% >155.15\%$ and $T_{1(L-H)}/H\% \leq 241.20\%$) and a high group ($T_{1(L-H)}/H\% >241.20\%$). During the follow-up period, 41 out of 75 patients developed recurrence; 5 cases (5/19) were Edmondson-Steiner grade I, 23 cases (23/37) were grade II and 13 cases (13/19) were grade III HCC, and their median recurrence times were undefined, 605 days and 258 days, respectively. The recurrence rates of patients with grade II and grade III HCC were significantly higher compared with that of patients with grade I HCC ($P<0.05$) (Fig. 5). The median recurrence time of the low $T_{1(L-H)}/H\%$ value group (n=17), the medium group (n=22) and the high group (n=37) were undefined, 530 days and 447 days, respectively. Recurrence rates also increased with increasing $T_{1(L-H)}/H\%$ from the low group to the medium and from the low to the high groups in the 20-min HBP ($P<0.05$). The patients with HCC classified with low $T_{1(L-H)}/H\%$ values had lower cumulative recurrence rates compared with that in patients classified as medium and high value groups ($P=0.028$ and $P=0.001$, respectively). The cumulative recurrence rates of the patients with medium $T_{1(L-H)}/H\%$ values were lower compared with that of the high value group, but the results were not significantly different ($P>0.05$) (Fig. 6).

**Discussion**

In the present study, Gd-EOB-DTPA-enhanced $T_1$ mapping was used to quantitatively evaluate HCC. The results demonstrated that $T_{1(L-H)}/H\%$ was positively correlated with the Edmondson-Steiner grade of HCC. Gd-EOB-DTPA-enhanced $T_1$ relaxation time-based parameter performed accurate diagnostic grading of HCC. Gd-EOB-DTPA has a $T_1$ shortening effect and highlights the lesions in the liver. $T_1$ relaxation time is an objective quantitative parameter. The $T_1$ relaxation time was measured on the basis of the MR relaxation technique and is directly correlated with the concentration of Gd-EOB-DTPA (24). In the present study, the majority of patients with HCC had a history of chronic liver disease. The increment rate of the $T_1$ value, which increased in the lesions relative to the non-tumorous liver parenchyma $[T_{1(L-H)}/H\%]$, reflects the true $T_1$ relaxation time of the lesion. $T_{1(L-H)}/H\%$ was positively correlated with the Edmondson-Steiner grade of HCC. Due to the higher grade of HCC, the differences in liver function between tumor and normal liver parenchyma were more visible and the differences in the concentration of the Gd-EOB-DTPA in the tissue were markedly visible in the three grades of HCC at 5 min, 10 min and 20 min HBP after enhancement, respectively, leading to a higher rate-of-change of $T_1$ values in the lesions when compared with that in non-tumorous liver parenchyma. Kogita et al (11) also confirmed that the concentration of Gd-EOB-DTPA uptake in HCC was positively associated with the degree of HCC differentiation. Moreover,
the $T_{1\text{L-H:H}}$ (%) was highest at the 20 min HBP in the present study, as the concentration of Gd-EOB-DTPA reached a peak value at 20 min after enhancement, while the concentration of the contrast agent in HCC cells remained lower.

In the present study, the $T_1$ value of the non-tumorous liver parenchyma, especially on pre-contrast, was lower with a higher malignant degree of HCC ($P<0.05$) and reached a peak at 20 min, which was similar to the result found in a previous study (11). The $T_1$ value of grade I HCC was lowest at 5 min, and increased gradually at 10 and 20 min, with partly overlapping values in grade II and grade III HCC; however, the $T_{1\text{L-H:H}}$ (%) of the three grades of HCC showed significant differences at pre-contrast, 5 min, and 20 min HBP, respectively. This result might be due to the liver background affecting the $T_1$ value of the tumor. These results suggest that higher grades of HCC will uptake smaller amounts of Gd-EOB-DTPA, and that the absorption rate of the contrast agent is significantly different between HCC and non-tumorous liver parenchyma at different time points. This may be due to the absence of normal liver function for patients with HCC and due to the fact that Gd-EOB-DTPA is mainly observed in the extracellular space and intravascular area at the beginning of enhancement. Furthermore, the HCC cells uptake the contrast agents slowly, resulting in less uptake of the contrast agents into the cells, and the concentration of Gd-EOB-DTPA in the intracellular area increases gradually post-contrast. By contrast, the non-tumorous liver parenchyma uptakes Gd-EOB-DTPA faster than HCC, leading to two types of $T_1$ value-time curves (Fig. 3B and C).

With a higher degree of malignancy, new blood vessels are formed, which are more likely to invade the surrounding liver parenchyma, leading to recurrence (25). Previous studies have reported that HCC recurrence is related to heterogeneity, multicentric type and expression of vascular endothelial growth factor of the tumor (26,27). In the present study, the patients with a higher grade of HCC had a higher
Patients with grade I HCC had the lowest cumulative recurrence rates compared with that of grade II HCC (P=0.023 and P=0.006, respectively). Patients with grade III HCC had higher recurrence rates compared with patients with grade II HCC, at 800 days after resection, but the differences were not significantly different (P>0.05). HCC, hepatocellular carcinoma.

The recurrence rate. Patients with grade I HCC had the lowest cumulative recurrence rates compared with patients with grade II and III HCC. Patients with grade III HCC had a higher but indistinctive recurrence rate compared with that in patients with grade II HCC, which was ~800 days after resection. We hypothesized that the absence of a significant difference may be due to the small sample size for grade III HCC compared with that of grade II HCC, therefore, studies with a larger sample size are required in the future. This may also be due to tumorous microvascular invasion and the histological grade of the cirrhosis (28). It is possible that the recurrent tumor may invade the surrounding liver parenchyma, promote cellular density and increase the formation of new vessels. If the tumor invades the microvasculature of the surrounding liver parenchyma and local liver function is damaged, the excretion of Gd-EOB-DTPA can be blocked (29,30). In addition, Zhou et al (4) reported that the Edmondson-Steiner grade of HCC was an independent risk factor for recurrence after resection. Mori et al (31) also demonstrated that poorly differentiated HCC was more likely to have intrahepatic metastasis and recurrence compared with well-/moderately differentiated HCC. The results from the present study revealed that the HCC patients with lower T_{1(L-H)/H} (%) values had lower cumulative recurrence rates compared with those patients with higher T_{1(L-H)/H} (%) values at the 20-min HBP. Shen et al (32) also recently found that a poorly differentiated tumor had a negative impact on the recurrence and long-term survival of patients with solitary HBV-associated HCCs after curative hepatectomy. This suggests that the lower the differentiation of HCC is, the more likely it is to recur, which was partly consistent with the study by Shen et al (32). Hence, if Gd-EOB-DTPA-enhanced MRI could be used to detect small lesions with high sensitiviy, and grade HCC with Gd-EOB-DTPA-MRI T₁ mapping before surgery, it will contribute to a more appropriate therapy for patients with HCC. Precise preoperative information regarding the characterization, prognosis and staging of HCC is essential.

However, the present study has several limitations. Firstly, the sample size is small, particularly for well- and poorly differentiated HCC. A further study with a larger sample size and longer follow-up time is required. Secondly, due to the small number of recurrent HCC patients, the effect of liver function, liver fibrosis and other liver backgrounds on the recurrence of HCC were not analyzed.

In conclusion, the parameters of T₁ mapping, T_{1(L-H)/H} (%) are positively correlated with the degree of malignancy of HCC. Higher grade HCC has a higher recurrence rate. The recurrence rate of HCC patients with high T_{1(L-H)/H} (%) was consistently significantly higher compared with that of patients with low T_{1(L-H)/H} (%). Although a larger-scale prospective study is required to confirm these findings, the results showed that T₁ mapping on Gd-EOB-DTPA-enhanced MRI was beneficial in HCC applications and provided valuable information for HCC grading and recurrence prediction.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors’ contributions

TFY conceived the study design and drafted the manuscript. ZKH provided the concept of the study and reviewed the manuscript. YJG collected the samples and researched the literature. XLQ was involved in data acquisition, statistical analysis, manuscript preparation and editing. ZPZ participated in the data analysis. WML, MZW and XYZ interpreted the data and revised the manuscript. LLL made substantial contributions to conception and design and guaranteed that any questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved. All the authors have read and approved the final manuscript.
Ethics approval and consent to participate
Retrospective data and tissue collection and analysis were approved by the Institutional Review Board of The First Affiliated Hospital of Guangxi Medical University (approval no. 2012-KY-223).

Patient consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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