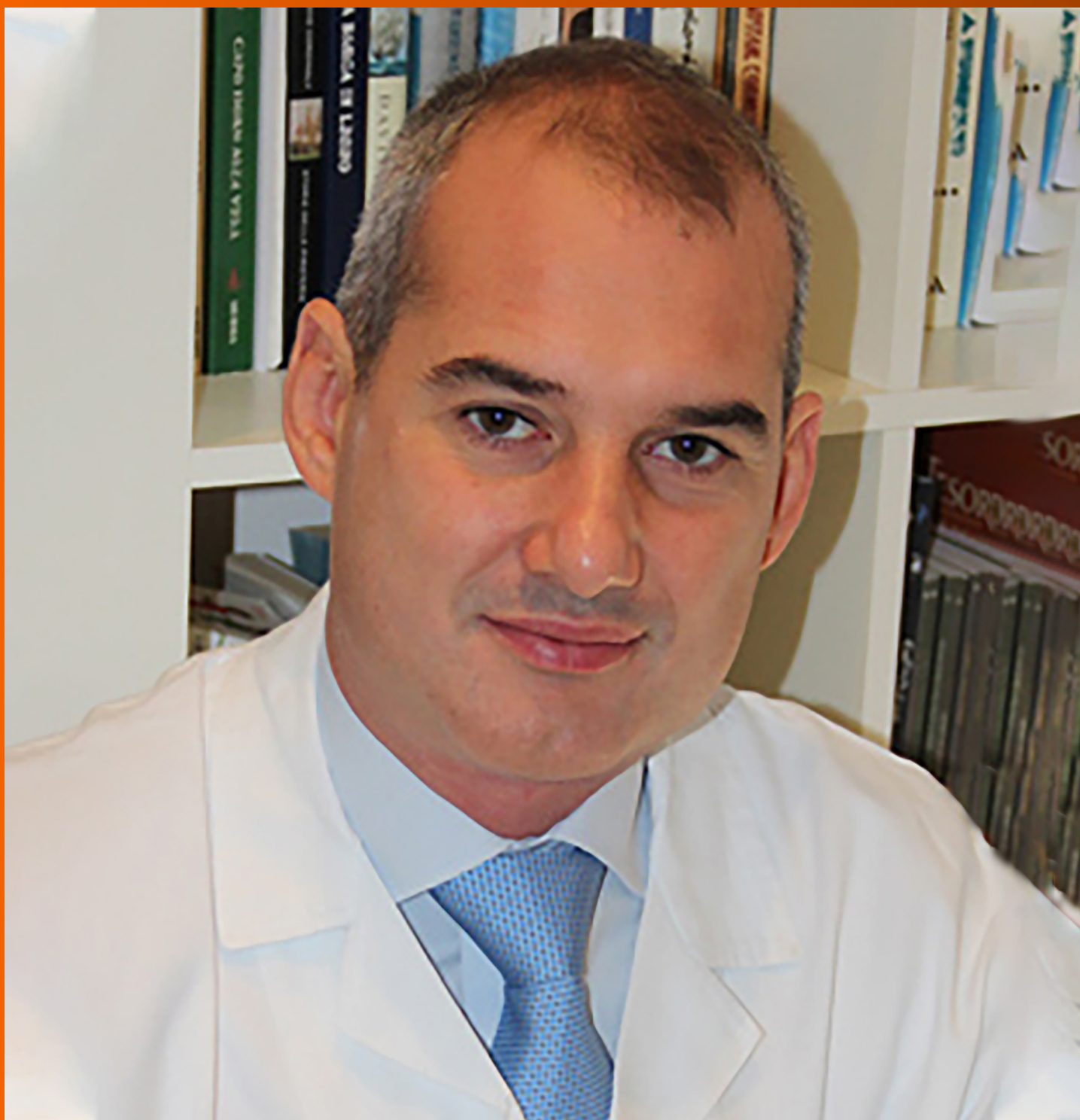


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Retrospective Study

Expression of caspase-3 and hypoxia inducible factor 1 α in hepatocellular carcinoma complicated by hemorrhage and necrosis

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) is a malignant tumor that occurs in the liver. Its onset is latent, and it shows high heterogeneity and can readily experience intrahepatic metastasis or systemic metastasis, which seriously affects patients' quality of life. Numerous studies have shown that hypoxia inducible factor1 α (HIF-1 α) plays a significant role in the occurrence and development of tumors, as it promotes the formation of intratumoral vessels and plays a key role in their metastasis and invasion. Some studies have reported that caspase-3, which is induced by various factors, is involved in the apoptosis of tumor cells.

AIM

To investigate the expression of caspase-3 and HIF-1 α and their relationship to the prognosis of patients with primary HCC complicated by pathological changes of hemorrhage and necrosis.

METHODS

A total of 88 patients with HCC complicated by pathological changes of hemorrhage and necrosis who were treated at our hospital from January 2017 to December 2019 were selected. The expression of caspase-3 and HIF-1 α in HCC and paracancerous tissues from these patients was assessed.

RESULTS

The positive expression rate of caspase-3 in HCC tissues was 27.27%, which was significantly lower than that in the paracancerous tissues ($P < 0.05$), while the positive expression rate of HIF-1 α was 72.73%, which was significantly higher than that in the paracancerous tissues ($P < 0.05$). The positive expression rates for

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caspase-3 in tumor node metastasis (TNM) stage III and lymph node metastasis tissues were 2.78% and 2.50%, respectively, which were significantly lower than those in TNM stage I-II and non-lymph node metastasis tissues ($P < 0.05$). The positive expression rates of HIF-1 α in TNM stage III, lymph node metastasis, and portal vein tumor thrombus tissues were 86.11%, 87.50%, and 88.00%, respectively, and these values were significantly higher than those in TNM stage I-II, non-lymph node metastasis, and portal vein tumor thrombus tissues ($P < 0.05$). The expression of caspase-3 and HIF-1 α in HCC tissues were negatively correlated ($r_s = -0.426$, $P < 0.05$). The median overall survival time of HCC patients was 18.90 mo (95% CI: 17.20–19.91). The results of the Cox proportional risk regression model analysis showed that TNM stage, portal vein tumor thrombus, lymph node metastasis, caspase-3 expression, and HIF-1 α expression were the factors influencing patient prognosis ($P < 0.05$).

CONCLUSION

The expression of caspase-3 decreases and HIF-1 α increases in HCC tissues complicated by pathological changes of hemorrhage and necrosis, and these are related to clinicopathological features and prognosis.

Key Words: Hepatocellular carcinoma; Caspase-3; Hypoxia inducible factor 1 α ; Hemorrhage; Necrosis; Prognosis

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Core Tip: It was confirmed that the expression of caspase-3 in hepatocellular carcinoma (HCC) complicated by hemorrhagic and necrotic pathological changes decreased and the expression of hypoxia inducible factor 1 α (HIF-1 α) increased, and these were related to clinicopathological features and prognosis. This study explored the expression characteristics of caspase-3 and HIF-1 α in tissues, and their relationship with the biological behavior of HCC complicated by hemorrhage and necrosis. The results will provide guidance for further clinical biological behavior assessments for prognosis prediction.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is a malignant tumor that occurs in the liver. Its onset is latent, and it shows high heterogeneity and intrahepatic metastasis or systemic metastasis readily occurs, which can seriously affect patients' quality of life[1,2]. After referring to the relevant medical data regarding HCC tissues that have not yet received a pathological biopsy, tumor cells were found to show high proliferation and differentiation activity, and the pathological specimens of the liver often suffered from hemorrhage and necrosis. We hypothesized that there is a correlation between tumor hemorrhage necrosis and the malignant tumor phenotype[3]. Numerous studies have reported that[4,5] both apoptotic and inhibitory genes are involved in the occurrence and development of tumors. Hypoxia is a characteristic of the tumor microenvironment, and many studies[6] have found that hypoxia inducible factor 1 α (HIF-1 α) plays a significant role in the occurrence and development of tumors. It mainly promotes the formation of intratumoral vessels and plays a key role in the process of metastasis and tumor invasion. Some studies have reported that[7,8] caspase-3, which is induced by various factors, is involved in the apoptosis of tumor cells. At present, in patients with HCC complicated by hemorrhage and necrosis, HIF-1 α and caspase-3 levels in relation to the patient characteristics have not yet been studied in China. Therefore, this study explored the expression characteristics of caspase-3 and HIF-1 α

in HCC tissues, and their relationship with the biological behavior of HCC that is complicated by hemorrhage and necrosis. The results will provide guidance for further clinical biological behavior analysis to judge prognosis.

MATERIALS AND METHODS

Patients and tissues

A total of 88 patients with HCC complicated by pathological changes of hemorrhage and necrosis who were treated at our hospital from January 2017 to December 2019 were selected, among whom 45 were ≤ 50 years old and 43 were > 50 years old; 45 were male and 43 were female. The tumor diameter for 50 cases was < 5 cm and for 38 cases it was ≥ 5 cm. There were 52 cases in the tumor node metastasis (TNM) stage and 36 in stage III. The differentiation degree of 56 cases was medium/low and for 32 cases it was high. Forty patients had lymph node metastasis, 72 were hepatitis B surface antigen positive, and 50 had portal vein tumor thrombus. Paracancerous tissues were selected as controls. The inclusion criteria were as follows: (1) A definite pathological diagnosis; (2) Non-preoperative radiotherapy, chemotherapy, or other therapy; and (3) Complete clinical and follow-up data. The exclusion criteria were as follows: (1) Those complicated by other malignant tumors; and (2) Those with other organ diseases such as diseases affecting the heart, lung, kidney, blood system, or immune system (Table 1).

Detection method

Immunohistochemical staining was used to evaluate the expression of caspase-3 and HIF-1 α . The tumor tissues and paracancerous tissues were fixed in 4% paraformaldehyde. Afterwards, routine paraffin sections were made and dehydration, dewaxing, and staining were performed according to the requirements of the SP reagent kit. The immunohistochemical Envision two-step method was used to detect HIF-1 α [9], and the biotin-horseradish ABC three-step method was used to detect caspase-3[10]. The positive control was the photo provided by the reagent kit company, and the negative control was treated by replacing the first antibody with PBS when hatching the first antibody. After staining, tissue staining was performed, and the slides were mounted with neutral gum.

Judgment standard for positive results: Under a microscope, five clear fields of vision were randomly selected for each section, each field had 200 cells, and five fields had 1000 cells in total. No staining or less than 1% of the cells were considered negative. If cytoplasmic staining was not obvious, less than 10% of the nuclei were considered positive; when less than half of the nuclei were stained, obvious cytoplasmic staining indicated strong positive expression; when more than half of the nuclei were stained, obvious cytoplasmic staining indicated very strong positive expression[11].

The field of vision was selected as described above and the staining scoring standard was as follows[12]: No staining, 0; light yellow, 1; dark yellow, 2; and dark brown, 3. The percentage scores for positive cells were as follows: No positive cells, 0; $\leq 10\%$ positive cells, 1; $> 10\%$ but $\leq 50\%$ positive cells, 2; $> 50\%$ but $\leq 75\%$, 3; and $> 75\%$, 4.

Final result judgment[13]: The product of two items was positive when the product was greater than or equal to 3, and negative when the product was less than 3.

Statistical analysis

The SPSS22.0 software was used for statistical analyses. The expression of caspase-3, HIF-1 α , and others are expressed as n (%), and a comparison between groups was performed using the χ^2 test and Spearman correlation analysis. Prognostic multivariate analysis was performed using Cox proportional risk regression models. $P < 0.05$ indicated statistical significance.

RESULTS

Comparison of expression of caspase-3 and the HIF-1 α in HCC tissues and paracancerous tissues

The positive expression rate of caspase-3 in the HCC tissues was significantly lower

Table 1 Clinical material of patients

Clinicopathological feature	Cases
Age (yr)	
≤ 50	45
> 50	43
Sex	
Male	45
Female	43
Tumor diameter	
< 5 cm	50
≥ 5 cm	38
TNM stage	
I-II	52
III	36
Differentiation degree	
High differentiation	32
Medium/low differentiation	56
Lymph node metastasis	
Yes	40
No	48
Hepatitis B surface antigen positivity	
Yes	72
No	16
Portal vein tumor thrombus	
Yes	50
No	38

than that in the paracancerous tissues ($P < 0.05$), while the positive expression rate of HIF-1 α was significantly higher in the HCC tissues ($P < 0.05$; Table 2).

Relationship between expression of caspase-3 and HIF-1 α and clinical pathology of HCC

The positive expression rate of caspase-3 in TNM stage III and lymph node metastasis tissues were significantly lower than those in TNM stage I-II and non-lymph node metastasis tissues ($P < 0.05$), while the positive expression rate of HIF-1 α in TNM stage III, lymph node metastasis, and portal vein tumor thrombus tissues were significantly higher than those in TNM stage I-II, non-lymph node metastasis, and portal vein tumor thrombus tissues ($P < 0.05$; Table 3).

Expression correlation of caspase-3 and HIF-1 α

The expression of caspase-3 and HIF-1 α in HCC tissues was negatively correlated ($r_s = -0.426$, $P < 0.05$; Table 4).

Survival status

By June 2020, the median overall survival time of HCC patients was 18.90 mo (95% CI: 17.20–19.91).

Multivariate analysis

The clinicopathological characteristics, caspase-3, and HIF-1 α expression were taken as independent variables, and the prognosis was considered as the dependent variable for the Cox proportional risk regression model analysis. The results of the Cox propor-

Table 2 Comparison of caspase-3 and hypoxia inducible factor 1 α expression in hepatocellular carcinoma and paracancerous tissues, *n* (%)

Group	Cases	Positive expression rate of caspase-3	Positive expression rate of HIF-1 α
HCC tissues	88	24 (27.27)	64 (72.73)
Paracancerous tissues	88	72 (81.82)	28 (31.82)
χ^2		52.800	29.516
<i>P</i> value		0.000	0.000

HIF-1 α : hypoxia inducible factor 1 α ; HCC: Hepatocellular carcinoma.

Table 3 Relationship between expression of caspase-3 and hypoxia inducible factor 1 α and clinical pathology of hepatocellular carcinoma, *n* (%)

Clinicopathological feature	Cases	Positive expression rate of caspase-3	χ^2	<i>P</i> value	Positive expression rate of HIF-1 α	χ^2	<i>P</i> value
Age (yr)			0.499	0.480		0.017	0.896
≤ 50	45	5 (11.11)			33 (73.33)		
> 50	43	7 (16.28)			31 (72.09)		
Sex			0.288	0.591		0.121	0.728
Male	45	7 (15.56)			32 (71.11)		
Female	43	5 (11.63)			32 (74.42)		
Tumor diameter			0.013	0.909		1.305	0.253
< 5 cm	50	7 (14.00)			34 (68.00)		
≥ 5 cm	38	5 (13.16)			30 (78.95)		
TNM stage			4.639	0.031		5.502	0.019
I-II	52	11 (21.15)			33 (63.46)		
III	36	1 (2.78)			31 (86.11)		
Differentiation degree			0.506	0.477		0.018	0.892
High differentiation	32	4 (12.50)			23 (71.88)		
Medium/low differentiation	56	8 (14.29)			41 (73.21)		
Lymph node metastasis			7.723	0.005		11.619	0.001
Yes	40	1 (2.50)			22 (55.00)		
No	48	11 (22.92)			42 (87.50)		
HbsAg positivity			0.000	1.000		0.497	0.481
Yes	72	10 (13.89)			54 (75.00)		
No	16	2 (12.50)			10 (62.50)		
Portal vein tumor thrombus			0.013	0.909		13.617	0.035
Yes	50	7 (14.00)			44 (88.00)		
No	38	5 (13.16)			22 (52.63)		

HbsAg: Hepatitis B surface antigen; TNM: Tumor node metastasis; HIF-1 α : Hypoxia inducible factor 1 α .

tional risk regression model analysis showed that TNM stage, portal vein tumor thrombus, lymph node metastasis, caspase-3 expression, and HIF-1 α expression were factors influencing patient prognosis (hazard ratio = 1.822, 1.201, 1.143, 0.773, and 1.211, respectively, *P* < 0.05; Table 5).

Table 4 Expression correlation of caspase-3 and hypoxia inducible factor 1 α

Caspase-3 expression	HIF-1 α		r_s	P value
	Positive	Negative		
Positive	3	9	-0.426	0.000
Negative	61	15		

HIF-1 α : Hypoxia inducible factor 1 α .**Table 5 Multivariate analysis**

Index	Hazard ratio (95%CI)	P value
TNM stage	1.822 (1.322-3.154)	0.000
Portal vein tumor thrombus	1.201 (1.092-2.822)	0.000
Lymph node metastasis	1.143 (1.022-2.560)	0.000
Caspase-3	0.773 (0.573-0.882)	0.000
HIF-1 α	1.211 (1.034-2.432)	0.000

TNM: Tumor node metastasis; HIF-1 α : Hypoxia inducible factor 1 α .

DISCUSSION

The rapid growth of HCC tumors often leads to hemorrhagic necrosis at the tumor center. At present, the role of caspase-3 and HIF-1 α in the diagnosis and prognosis of patients with HCC complicated by hemorrhage and necrosis is still controversial[14]. In this study, evidence for the clinical diagnosis and treatment of the disease was provided by observing the expression of caspase-3 and HIF-1 α in patients with HCC complicated by hemorrhage and necrosis.

As a marker reflecting the hypoxic state in the tumor microenvironment, HIF-1 α can adapt to hypoxic stress conditions and is widely present in humans and mammals. The levels of HIF-1 α can be affected by many factors[15]. Furthermore, it can bind with vascular endothelial growth factor, glucose transporter 1, and other genes to promote their transcription and create a powerful microenvironment for tumor growth. HIF-1 α has also been found to be highly expressed in breast cancer, ovarian cancer, and other tumor tissues[16,17].

According to previous results, the positive expression rate of HIF-1 α in cancer tissues was significantly higher than that in adjacent normal tissues. The expression levels in samples with high tumor stages, lymph node metastasis, and portal vein tumor thrombus were higher than those in samples with a low tumor stage and no metastasis or thrombus. The pathological phenotype of hemorrhagic necrosis is related to the size, capsule, venous infiltration, and clinical stage of HCC. Due to the insufficient oxygen supply in HCC, immature tumor microvessels can cause hemorrhage and necrosis. In addition, immature vascular features provide a convenient gateway for the invasion and metastasis of pathological changes in hemorrhagic necrotic tissue cells. The microenvironments of HCC and angiogenesis are related, as angiogenesis promotes tumor metastasis. In addition, the HIF-1 α signal transduction pathway is activated, and the HIF-1 α expression level will increase if hypoxia occurs in the microenvironment, providing oxygen and energy for tumor cells, maintaining their normal physiological needs, and providing a favorable environment for cancer cell metastasis.

The results of this study showed that the positive expression rate of caspase-3 in HCC tissues was significantly lower than that in adjacent tissues, and the positive expression rate of caspase-3 in samples in TNM stage III and with lymph node metastasis was significantly lower than that of samples in stage I-II and with no lymph node metastasis. The caspase family is recognized as the core mechanism of cell apoptosis, and the hardness of the HCC extracellular matrix increases with the degree of tumor malignancy. When the extracellular matrix hardens, cell traction increases, which changes the surface tension of the cells and causes a change in the micro-

vascular structure due to the abnormal mechanics and this regulates the process of skin-interstitial transformation, which leads to tumor infiltration and metastasis[18,19].

The results showed that the median overall survival time of HCC patients was 18.90 mo, and TNM stage, portal vein tumor thrombus, lymph node metastasis, caspase-3 expression, and HIF-1 α expression were factors influencing the survival. The tumor pressure gradient in HCCs with hemorrhage and necrosis was reduced. After necrosis of the tumor, many inflammatory factors are released, which can damage the body and promote tumor metastasis. In addition, there may be different subclones in the tumor, which will also affect its proliferation and metastasis.

Previous reports have shown that[20] the caspase-3 level is low in breast cancer tissues, and its levels are closely related to the histological grade; thus, a low level may be related to a higher histological grade, a higher degree of tumor proliferation, more active metabolism, and a relatively lower proportion of apoptosis. At present, there are few reports on the relationship between HIF-1 α , caspase-3, and hemorrhagic necrosis in HCC. In this study, the positive expression rate of caspase-3 in tissues in TNM stage III with lymph node metastasis was significantly lower than that in tissues in TNM stage I-II with no lymph node metastasis. We believe that caspase-3 plays an important role in the process of HCC and is involved in bleeding and necrosis, which has important predictive significance for the prognosis of patients.

This study innovatively explored the changes in the expression levels of caspase-3 and HIF-1 α in relation to the pathological changes of HCC that are complicated by hemorrhage and necrosis. In addition, the relationship between caspase-3 and HIF-1 α expression, tumor stage, and lymph node metastasis were also analyzed. However, this study lacked *in vitro* experiments. In future investigations, we aim to explore the pathological characteristics of HCC complicated by the pathological changes of hemorrhage and necrosis using *in vitro* cell experiments to improve our understanding of the involved mechanisms.

CONCLUSIONS

In conclusion, the expression of caspase-3 is decreased and that of HIF-1 α is increased in HCC complicated by hemorrhage and necrosis, and these changes are related to the clinicopathological features and prognosis.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) is a malignant tumor that is occurring in the liver. Hypoxia inducible factor1 α (HIF-1 α) plays a significant role in the occurrence and development of tumors, which mainly promote the formation of intratumoral vessels, and plays a key role in the process of tumor metastasis and invasion. Some studies reported that caspase-3 is involved in the process of apoptosis of tumor cells and the apoptosis induced by various factors.

Research motivation

At present, in patients with HCC complicated by hemorrhage and necrosis, the HIF-1 α and caspase-3 expression levels in relation to the characteristics of patients with HCC complicated by hemorrhage and necrosis and their prognosis have not been examined in China.

Research objectives

This study aimed to investigate the expression of caspase-3 and HIF-1 α and their relationship with prognosis in patients with primary HCC complicated by the pathological changes of hemorrhage and necrosis.

Research methods

A total of 88 patients with HCC complicated by the pathological changes of hemorrhage and necrosis were selected. The expression of Caspase-3 and HIF-1 α in HCC and paracancerous tissues from these patients was detected.

Research results

The positive expression rate of caspase-3 in HCC tissues was 27.27%, which was significantly lower than that in paracancerous tissues, while the positive expression rate of HIF-1 α was 72.73%, which was significantly higher than that in paracancerous tissues. The expression of caspase-3 and HIF-1 α in HCC tissues was negatively correlated. The median overall survival time of HCC patients was 18.90 mo.

Research conclusions

The expression of caspase-3 decreases and that of HIF-1 α increases in the tissues of HCC complicated by the pathological changes of hemorrhage and necrosis, which is related to clinicopathological features and prognosis.

Research perspectives

This study may provide help for the further clinical biological behavior assessments so as to judge the prognosis.

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