THE DISCUSSION ON THE PROGNOSTIC FACTORS OF PATIENTS WITH INTRAHEPATIC MASSFORMING CHOLANGIOCARCINOMA AND THE RELATIONSHIP WITH THE IMAGING FEATURES OF ARTERIAL BLOOD SUPPLY OF TUMOR

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ABSTRACT

Objective*: To discuss the prognostic factors of patients with Intrahepatic massforming cholangiocarcinoma and the relationship with the imaging features of arterial blood supply of tumor.*

Methods: *From January 2010 to June 2020, a total of 184 Intrahepatic massforming cholangio-carcinoma patients admitted to our hospital treated with enhanced CT scan or MRI were included in this study. The clinical data were collected for a retrospective analysis, and they were grouped based on tumor blood supply status in the arterial phase of enhanced CT scan or MRI. Clinical features and prognostic indicators were analyzed. A regression model was performed to evaluate factors affecting the prognosis of patients with Intrahepatic massforming cholangiocarcinoma.*

Results: *Through the comparison of lymphadenectasis, the largest diameter of the primary lesion, the level of CA19-9, the treatment program, and the abnormalities of perfusion enhancement in the combined arterial phase between two groups, the differences were statistically significant (P<0.05); the 1-year overall survival rate, 3-year overall survival rate and 5-year overall survival rate of rich blood supply group were significantly higher than those of the poor blood supply group (P<0.05); univariate analysis results showed that CA19-9>200U/ml, combined lymphadenectasis, the abnormalities of perfusion enhancement in the combined arterial phase, insufficient arterial blood supply were related to the prognosis of patients with Intrahepatic massforming cholangiocarcinoma (P<0.05); multivariate analysis results showed that combined lymphadenectasis and insufficient arterial blood supply were independent factors affecting the prognosis of patients with Intrahepatic massforming cholangiocar-cinoma (P<0.05).*

Conclusion: *The prognosis of patients with Intrahepatic massforming cholangiocarcinoma is related to the presence of combined lymphadenectasis and the blood supply status in arterial phase; imaging features of arterial blood supply of tumor can be used to predict the prognosis of patients with Intrahepatic massforming cholangiocarcinoma.*

Keywords: *Intrahepatic massforming cholangiocarcinoma, prognosis, influencing factors, imaging, blood supply.*

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Introduction

Intrahepatic cholangiocarcinomaas (ICC) one of highly malignant primary liver tumors is common in clinical practice, among which Intrahepatic massforming cholangiocarcinoma (IMCC) accounts for the highest proportion (60%~75%)[(1)]. Currently, a lot of reports on the prognostic factors of ICC are available, generally with the opinion that the diameter, number, and distant metastasis of tumor, lymphatic metastasis, vascular or perihepatic invasion are possibly associated with survival time; while the increase in the level of CA19-9 and combined liver fibrosis often indicates bad prognosis[(2, 3)]. As a critical step of preoperative evaluation of ICC patients, imaging examination still has some deficiencies in clinical practice. First, during lymphatic metastasis, false positive or false negative results account for

high proportions, and it is easy to omit micro-metastases. Microvascular invasion and the degree of liver fibrosis cannot be accurately determined[4]. It has been re-ported that the blood supply of tumor cells in patients with IMCC is different from the delayed enhancement features of conventional interfibrillar substance[5]. For both, a significant signal contrast can be formed in the arterial phase. Therefore, it is theoretically feasible to assist in the evaluation of patient clinical prognosis by analyzing the enhancement features in the arterial phase. In this paper, a total of 184 IMCC patients admitted to our hospital treated with enhanced CT scan or MRI from January 2010 to June 2020 were included.

The clinical data were collected to perform a retrospective analysis. Patients were grouped based on the tumor blood supply status in the arterial phase of enhanced CT scan or MRI, aiming to discuss the prognostic factors of patients with IMCC and the relationship with the imaging features of arterial blood supply of tumor. Now it is reported as follows.

Materials and methods

General data

A total of 184 IMCC patients treated with enhanced CT scan or MRI in our hospital from January 2010 to June 2020 were included in this study, of which 52 patients received liver enhanced MRI, 24 patients received liver enhanced CT scan, and 108 patients received liver CT scan and enhanced MRI simultaneously, with an interval between both examinations of less than 7 days; patients were divided into a rich blood supply group and a poor blood supply group based on the tumor blood supply status in the arterial phase.

Inclusion criteria:

• Those ICC was diagnosed as IMCC by histopathological examination;

• Those received liver MRI or enhanced CT scan before operation;

• Those with complete clinical data.

Exclusion criteria:

• The lesion was located in the hilar of the liver;

• Infiltration perivascular or intraductal infiltration;

• Combined with other types of malignant tumors;

• Combined with hepatocellular carcinoma;

• Image quality is not available for evaluation;

• Non-tumor death.

The design of the study protocol complies with the requirements of the Declaration of Helsinki. All participants were knowing-agreeing and signed an informed consent form.

Imaging examination

CT scan

During the examination, US GE LightSpeed 16 -row CT scanner was used as the scanning instrument, and parameters were set as follows: tube voltage=120kV, tube current=150mA, layer thickness of 5.0mm and layer spacing of 2.5 5mm respectively. Iohexol was used as the contrast media (iodine content of 300 mg/ml), the total dose of 2ml/kg, the flow rate of 3.0ml/s; it was delayed by 25s, 60s, and 190s, respectively to complete the scan in arterial phase, portal vein phase and equilibrium phase.

MRI scan

In MRI examination, US GE 1.5T Signa HDxt MR imager was used, T2WI parameters were as follows: TR=3300~3400ms, TE=90~98ms, FOV=38×38cm, matrix=320×320, layer thickness of 6mm and layer spacing of 1mm respectively; double echo T1WI parameters were: TR= 120ms, TE=4.8ms, FOV=38×38cm, matrix=256×256, layer thickness of 6mm and layer spacing of 1mm respectively; DWI parameters were: b=800mm2/s, TR=3800~5800ms, TE=60~70ms, FOV=38×38cm, matrix=128×128, layer thickness and layer spacing are 6mm and 1mm respectively; enhanced scanning adopts horizontal axis breath-hold 3D volume interpolation, parameters as follows: TR=4.0ms, TE=1.8ms, Symphony scan TR=120ms, TE=10ms, FOV=38×38cm, matrix=320×320, reconstruction slice thick-ness of 5mm and slice spacing of 1mm respectively; Gd-DTPA was used as con-trast media, the total dose of 0.1mmol/kg, injection flow rate of 2ml/s, the delay was 25s, 60s and 190s, to complete the scan in arterial phase, portal vein phase and equi-librium phase.

Indicators for observation

Two diagnostic imaging physicians with the title of associate professor and above reached a consensus after observing scan images together, and evaluated the maximum-diameter lesion of patients with several lesions in the liver. The number, location, the maximum diameter of the lesion, the blood supply of the primary lesion in arterial phase, the abnormalities of perfusion enhancement in arterial phase, and the lymphadenectasis were recorded. The criterion of judging rich blood supply of primary lesion in arterial phase: obvious enhancement occurs

most layers of lesion with an area >50% of the same layer of lesion; the criterion of judging abnormalities of perfusion enhancement in arterial phase: wedge-shape, flake-shape and annular transient abnormal enhancement can be seen in liver tissue directly adjacent to the lesion and outside the lesion[6].

Follow-up

Follow-up was performed via telephone or outpatient case review, with the frequency of every 3 to 6 months once, deadline until December 2020; overall survival rate (OS) refers to the end of treatment until death, loss to follow-up or the end of follow-up.

Statistical processing

SPSS22.0 software and R software were adopted to complete data processing; Kolmogorov-Smirnov was adopted for test of normality, t test analysis was used for comparison of measurement data con-forming to normal distribution, expressed as ($\bar{x}\pm s$); χ^2 test or Fisher exact probability Method was used as count data, expressed as %; Kaplan-Meier method was adopted for survival analysis; Cox regression model was performed for multivariate analysis; P<0.05 represents that the difference is statistically significant.

Results

Analysis of clinical features

Through the comparison of lymphadenectasis, the largest diameter of the primary lesion, the level of CA19-9, the treatment program, and the abnormalities of perfusion enhancement in the combined arterial phase between two groups, the differences were statistically significant (P<0.05); through the comparison of other clinical features between the two groups, the differences had no statistical significance (P>0.05); see Table 1.

Analysis of prognosis

All patients in rich blood supply group received surgical treatment. The median follow-up time was 42.0 months, and 8 cases died. The 1-year, 3-year and 5-year OS were 94.37%, 87.16%, and 86.80%, respectively. 62 patients in poor blood supply group received surgical treatment, 88 patients received conserva-tive treatment, and 120 patients died. The 1-year, 3-year, and 5-year survival rates were 31.78%, 18.26%, and 15.64%, re-spectively; the 1-year, 3-year, and 5-year OS of patients in rich blood supply group who were given follow-up were significantly higher than those of poor blood supply group (P<0.05).

Indicators	Rich blood supply group (n=34)	Poor blood supply group (n=150)	*P*
Age (year)	58.54±5.40	71.31±6.86	0.40
Male (case)	26	92	0.31
Combined with chronic hepatitis B (case)	16	38	0.11
Increased AFP level (case)	0	14	0.47
CEA level (case)			0.24
≤50ng/ml	34	132	
>50ng/ml	0	38	
Location of primary lesion (case)			0.09
Left liver	10	78	
Right liver	22	58	
Caudate lobe	2	2	
2 or more involved liver lobes	0	12	
Lymphadenectasis (case)	6	90	0.00
Number of lesions in liver (case)			0.23
Single	28	96	
Multiple	6	54	
Maximum diameter of primary lesion (cm)	3.26±1.35	6.60±2.17	0.00
Combined with extrahepatic invasion (case)	2	10	1.00
Combined with liver cirrhosis (case)	16	58	0.65
CA19-9 level (case)			0.00
≤200U/ml	32	50	
>200U/ml	2	100	
Treatment program (case)			0.00
Surgical treatment	34	62	
Conservative treatment	0	88	
Combined with abnormalities of perfusion enhancement in arterial phase (case)	14	124	0.00

Table 1: Analysis of clinical features.

Cox regression model analysis of prognostic factors of patients with IMCC

Univariate analysis results showed that CA19-9 >200U/ml, combined lymphadenectasis, the abnormalities of perfusion enhancement in the combined arterial phase, insufficient arterial blood supply were correlated with the prognosis of patients with IMCC (P<0.05); multivariate analysis results showed that combined lymphadenectasis and insufficient arterial blood supply were independent factors affecting the prognosis of patients with IMCC (P<0.05). See table 2.

Indicators	Univariate			Multivariate		
	P	*HR*	95%CI	*P*	*HR*	95%CI
CA19-9 >200U/ml	0.00	2.28	1.65~6.31	-	-	-
Combined lymphadenectasis	0.01	1.90	1.36~4.82	0.04	4.23	1.09~7.97
Abnormalities of perfusion enhancement in the combined arterial phase	0.04	1.97	1.05~2.38	-	-	-
Insufficient arterial blood supply in the arterial phase	0.00	2.46	1.60~5.02	0.04	3.18	1.22~6.50

Table 2: Cox regression model analysis of prognostic factors of patients with IMCC.

Discussion

According to the results, the 1-year, 3-year, and 5-year OS of patients in rich blood supply group who were given fol-low-up were significantly higher than those of poor blood supply group (P<0.05), suggesting that there are significant prognostic differences in patients with IMCC with different features of blood supply in arterial phase. Through the comparison of lymphadenectasis, the largest diameter of the primary lesion, the level of CA19-9, the treatment program, and the abnormalities of perfusion enhancement in the combined arterial phase between two groups, the differences were statistically significant (P<0.05), suggesting that IMCC patients with rich blood supply have higher CA19-9 levels, lower proportion of lymphadenopathy and abnormalities of perfusion enhancement in the arterial phase, and smaller maximum diameter of the primary lesion than those with insufficient blood supply. Therefore, they can obtain more opportunities for surgical resection. The multivariate analysis results showed that insufficient blood supply in the arterial phase was an independent prognostic factor in IMCC patients (P<0.05), which proved that the IMCC patients with rich blood supply had better clinical prognosis.

As recommended by AACR guide-lines, ICC patients should refer to the CA19-9 level for diagnosis and prognostic evaluation, among which patients with a CA19-9 level >200U/ml have a poorer prognosis[7, 8]. There was no significant difference between the two groups of patients in the proportion of patients with chronic hepatitis B (P<0.05). According to previous reports, IMCC patients with chronic viral hepatitis account for a higher proportion of atypical enhancement, while IMCC with significant enhancement in arterial phase are less likely to be invaded and have a better prognosis, which does not conform to the results of this study[9, 10].

Therefore, subsequent studies are required for further confirmation.

It is believed by foreign scholars that the imaging enhancement mode of patients with IMCC may be associated with the clinical prognosis, which is merely classified into typical enhancement and atypical enhancement. At the same time, whole-shape, thick annular shape, grid shape and no enhancement were included in atypical enhancement includes, which were not accurate[11, 12].

Other studies have proved that the enhancement mode of lesions in the arterial phase can independently affect the clinical prognosis of patients with ICC[13, 14], among which OS of patients with obvious enhancement in the arterial phase was more than 99% in the 3-year follow-up, and the 5-year follow-up OS was close to 90%; according to the results of this study, the median follow-up time of rich blood supply group was 42.0 months and 8 patients died. The 1-year, 3-year, and 5-year OS were 94.37%, 87.16%, and 86.80%, respectively, which were consistent with the above reported results. Nevertheless, in previous studies, those with no obvious enhancement of tumor in the arterial phase but the surrounding liver tissue showed mild enhancement as arterial enhancement were included in arterial enhancement, which is controversial; for such enhancement, there exist abnormal factors of perfusion en-hancement in arterial phase, which may affect prognostic analysis[15].

For patients with ICC, the invasion of normal hepatic blood vessels, blood stealing, combined liver fibrosis, and lymphocyte infiltration around the lesion may lead to the abnormalities of perfusion enhancement in arterial phase, and the combined hepatic vascular invasion and liver fibrosis are non-lesion related prognostic factors[16, 17]. This study proved that the abnormalities of perfusion enhancement in arterial phase is a prognostic risk factor for patients with IMCC.

There exist certain shortcomings in this study: It is a monocentric small-sample retrospective report, in which the bias of sample selection cannot be avoided; The study failed to analyze other enhanced phase diagrams and se-quences beyond the arterial phase. In addition, due to the small number of patients with rich blood supply in the arterial phase, subgroup analysis could not be performed. Therefore, the conclusions await further confirmation by subsequent studies.

To sum up, the prognosis of patients with IMCC is correlated with whether it is related to lymphad-

enectasis and the blood supply status in the arterial phase; imaging features of arterial blood supply of tumor can be used to predict the prognosis of patients with IMCC.

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