

# Changed clinical aspects of primary liver cancer in China during the past 30 years

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**BACKGROUND:** Primary liver cancer (PLC) is one of the most frequently seen tumors in China. Thirty years ago, patients with PLC were often detected at relatively late stage, with a palpable mass or marked clinical symptoms and poor prognosis. In the past 30 years, the diagnosis and treatment of PLC have been greatly improved with better prognosis.

**METHODS:** In order to study the changes of PLC during the 30 years, the clinical data of 3250 patients with PLC from 10 medical institutions of China were collected, analyzed, and compared with those of 3254 PLC patients before the 30 years.

**RESULTS:** In the 3250 patients aged 1-80 years, with an average age of 49.1 years, the male to female ratio (2.3:1) was lower than that before the 30 years. 73.5% of the 3250 patients sought medical advice within 3 months after the onset of the disease in contrast to 63.8% before the 30 years. Compared with those patients before the 30 years the symptoms and signs were alleviated generally. The HBsAg positive rate was 81.0%, but the HCV-Ab positive rate was 13.2%. The AFP level in 75% of patients was elevated, but in the remaining 25% was normal. 1912 patients (58.8%) were confirmed pathologically. Among them 1755 patients (91.8%) had hepatocellular carcinoma. The overall resection rate was 46.3%. Those who had early, middle, late stage carcinoma accounted for 29.9%, 51.5%, and 18.6%

respectively in contrast to 0.4%, 47.0%, and 52.6% reported before the 30 years. The 1-, 3-, 5-year survival rates of the patients were 66.1%, 39.7%, and 32.5% respectively, whereas 93.5%, 70.1%, and 59.1% for the early stage patients, and 65.3%, 30.5%, and 23.5% for the middle stage patients. The half and 1-year survival rates of the late stage patients were 52.5%, and 14.7%, respectively.

**CONCLUSION:** Comparison with the clinical data before and after the 30 years show that PLC can be diagnosed early. More PLC patients tend to undergo resection while receiving a better conservative treatment, which ensures a prognosis.

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**KEY WORDS:** primary liver cancer; diagnosis; therapy; survival rate

## Introduction

Primary liver cancer (PLC) is one of the most frequently seen tumors in China.<sup>[1-5]</sup> Thirty years ago we collected the clinical data of 3254 PLC patients from 21 medical institutions in 10 different regions of this country and the results were published in 1974, which were later frequently cited in the clinical research of PLC.<sup>[6]</sup> In the recent 30 years, great progress has been made in clinical and basic research of PLC following the development of medical science and technology.<sup>[7-10]</sup> We collected the clinical data of 3250 patients with PLC (this series) from 10 similar cities or provinces in China and compared with those of 3254 PLC patients reported 30 years ago in an attempt to find their differences in diagnosis and management.

## Methods

The patients with PLC enrolled from September 2001 to February 2002 met the following criteria: patients treated from 1996 to 1998; patients treated at Departments of Medicine, Surgery and Oncology of the 10 medical institutions; patients with PLC at different tumor stages;

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patients with PLC treated with different methods after clinical and pathological diagnosis according to the criteria issued by the Anti-cancer Association of China,<sup>[11]</sup> and patients followed up to December 2001.

The diagnostic criteria of the Anti-cancer Association defined no clinical symptoms and physical signs for early stage of PLC, jaundice, ascites and metastasis for late stage, and the rest for middle stage.

Statistical analysis was performed by a SPSS software. The survival rate was calculated with the life table method and survival rates were analyzed using the Log-rank method.

## Results

Of 3489 PLC patients enrolled from the 10 institutions, 239 were ruled out because of incomplete clinical data. In the remaining 3250 patients, 1238 were from the Liver Cancer Institute, Zhongshan Hospital of Fudan University, 829 from the Tumor Hospital, Medical Center of Zhongshan University, 592 from the Tumor Hospital of Guangxi Medical University, and 100-200 from each of the other hospitals.

### Symptoms, signs, liver function and tumor stage

Patients without symptoms accounted for 29.9% in this series in contrast to 0.3% 30 years ago. Other symptoms and signs were alleviated in the patients of this series compared with those of the patients 30 years ago. The abnormal liver function and late stage patients were more often encountered 30 years ago (Table 1).

### Imaging techniques

Nuclear scanning was rarely used nowadays, but its positive diagnostic rate was 73.4%. The positive diagnostic rate of other imaging techniques ranged from 94.8% to 98.7% (Table 2).

### Other clinical data

In the 3250 patients aged 1-80 years (mean 49.1 ± 11.5 years), of whom one third were 40-49 years old, the ratio of male to female was 2.3:1. The interval between diagnosis and treatment was less than 1 month in 2.4% of the patients, 1-3 months in 71.1%, 3-6 months in 15.3%, greater than 6 months in 11.2%. Of the patients, 63.0% had hepatitis for an average of 14.3 years, 4.9% liver cirrhosis, and 13.3% alcohol addiction. 9.7% of the patients had a family history of PLC. A positive rate of HBsAg was noted in 81.0% of the patients and a positive rate of HCV in 13.2%. AFP level was normal ( $\leq 20 \mu\text{g/L}$ ) in 25.0% of the patients, and elevated ( $> 20 \mu\text{g/L}$ ) in 75.0% (21-200  $\mu\text{g/L}$  22%, 201-400  $\mu\text{g/L}$  8.4%, and  $> 400 \mu\text{g/L}$  44.6%). X-ray showed elevation, distention or movement-restriction of the right diaphragm in 14.9% of the patients, esophageal

**Table 1.** Clinical data of PLC patients in this series and those of 30 years ago

Clinical data	This series (%, n=3250)	30 years ago (%, n=3254)
<b>Symptoms</b>		
No symptoms	29.9	0.3
Upper abdominal mass	4.7	37.0
Anorexia	6.7	34.2
Hypodynamia	6.2	27.9
Emaciation	6.9	26.4
Abdominal distention	15.3	24.4
Fever	1.7	10.3
Diarrhea	0.9	5.8
Acute abdominal pain	0.6	3.4
<b>Signs</b>		
Liver enlargement	42.7	94.0
Spleen enlargement	9.7	38.1
Jaundice	9.0	37.5
Ascites	9.3	43.3
Poor appearance	8.6	38.5
<b>Abnormality of liver function</b>		
Total bilirubin	25.0	/
Serum albumin	16.8	/
ALT	44.4	36.4
$\gamma$ -GT	65.2	91.2
ALP	38.6	84.3
<b>Tumor stage</b>		
Early	29.9	0.4
Middle	51.5	47.0
Late	18.6	52.6

**Table 2.** Positive findings of imagings

Imagings	Patients	Positive rate (%)
B-ultrasound	2875	97.6
CT	2660	98.7
MRI	345	94.8
Angiography	981	95.5
Nuclear scanning	15	73.4

varices in 3.1%, and lung metastasis in 9.0%. Extrahepatic metastases were found in 422 patients (12.9%), lung metastases in 69.4%, bone metastases in 2.6%, renal metastases in 0.5%, brain metastases in 0.5%, lymph nodes metastases in 8.3%, and others 18.7%. Of the 3250 patients, 1777 died during follow-up of exhaustion (51.6%), liver coma (21.8%), upper gastrointestinal bleeding (10.9%), tumor rupture (0.3%), and other causes (15.4%).

### Pathological diagnosis

In 1912 patients (58.8%) who were subjected to pathological examination, 91.8% (1755 patients) had hepatocellular carcinoma, 2.7% cholangiocarcinoma, 1.4% combined hepatocellular and cholangiocarcinoma, and 4.1% unknown tumor. 95.5% of the tumor tissues

for pathological diagnosis were obtained by surgery, 3.7% by puncture, and 0.3% by biopsy of metastasized lesions.

**Treatment**

The early and middle stage patients were divided into 6 groups according to different treatments, liver resection, hepatic ligation (HAL) plus hepatic intubation (HAI), transcatheter arterial chemoembolization (TACE), microwave and cryosurgery, radiotherapy and others.

Liver resection group consisted of 1505 patients (46.3%) who had received resection of PLC. TACE group comprised 684 patients (21.0%), including those who had undergone TACE after open-close operation (without HAL+HAI). HAL+HAI group was composed of 256 patients (7.9%) who had received hepatic arterial ligation and/or portal vein intubation. Cryosurgery and microwave group consisted of 16 patients (0.5%) who had had cryosurgery or microwave therapy. Radiotherapy group consisted of 23 patients (0.7%) who had had radiotherapy. Other treatment group included 158 patients (4.9%) who had received immune therapy or Chinese herbal medicine. Most of late stage patients could only tolerate palliative or Chinese medicine therapy, but few received chemotherapy. Because percutaneous ethanol injection (PEI) was mostly performed in out-patient department, the data were not collected in this study.

**Survival rate**

The overall 1-, 3-, 5-year survival rates were 66.1%, 39.7%, and 32.5% respectively in this group. The survival rates of patients at different tumor stage are

**Table 3.** Survival rates of different stage patients

Stage	Patients	Survival rate (%)				Median survival time (mon)
		0.5-year	1-year	3-year	5-year	
Early	972		93.5	70.1	59.1	76.0±5.1
Middle	1674		65.3	30.5	23.5	16.8±0.7
Late	604	52.5	14.7	0.3	/	6.0±0.2

**Table 4.** Efficacy of different treatments for early and middle stage patients

Treatment	Patients	Survival rate (%)		
		1-year	3-year	5-year
Liver resection	1505 *	88.1	62.4	51.6
HAL+HAI	256 *	74.1	38.3	28.5
TACE	684 *	58.4	16.8	12.8
Cryosurgery/Microwave	16	79.3	52.9	52.9
Radiotherapy	23	58.8	35.3	35.3
Other therapy	158	37.3	18.8	18.8

\* :  $P < 0.01$  between groups.

**Table 5.** Efficacy of different treatments in early and middle stage patients

Treatment	Patients	Survival rate (%)		
		1-year	3-year	5-year
Liver resection				
Early	761	93.4	72.4	61.0
Middle	744	82.4	51.2	40.6
HAL+HAI				
Early	61	95.0	65.9	49.5
Middle	195	67.3	28.7	21.8
TACE				
Early	109	98.0	61.0	52.7
Middle	575	51.0	7.5	3.6

In middle stage patients, statistical significance was shown between different treatment groups ( $P < 0.01$ ), but no statistical significance in early stage ( $P > 0.05$ ).

summarized in Table 3.

**Efficacy of different treatments**

The efficacy of different treatments for early and middle stage patients is shown in Table 4. The Log-rank analysis revealed significant difference between the groups of liver resection, HAL+HAI, and TACE ( $P < 0.01$ ). The efficacy of different treatments is statistically significant between the groups of liver resection, HAL+HAI, and TACE in the middle stage patients ( $P < 0.01$ ), whereas it was not significant in the early stage ones ( $P > 0.05$ , Table 5).

**Discussion**

The clinical data from the 10 medical institutions of China contained complete records of PLC diagnosis and treatment of 3254 patients in the period of 1996-1998. They included the data of follow-up in patients at early, middle and late stage as well as their different treatment. Because 6.9% of the patients lost to follow up, these data showed an overview of PLC patients in China though in-hospital clinical data couldn't represent the full view of the PLC patients. Since the data were also from in-hospital patients 30 years ago, it would be possible to compare the clinical data of 3254 patients 30 years ago with those of 3250 patients in this series.

**Changes of clinical aspects**

The average age of the patients increased from 43.7 to 49.1 years, indicating the boost of immunity of the Chinese people or the effective control of basic diseases including hepatitis B. The decrease of the male to female ratio from 7.7:1 to 2.3:1 indicated that female patients have received more clinical treatment in the recent years.

The shortened interval between the onset of the

disease and therapy suggested the awareness for medication in patients and the accessibility of medical service in the past 30 years in China.

The data of this group showed that the symptoms and signs were alleviated. The following variables of symptoms were decreased of upper abdominal mass from 37.0% to 4.7%, anorexia from 34.2% to 6.7%, hypodynamia from 27.9% to 6.2%, emaciation from 26.4% to 6.9%, abdominal distention from 24.4% to 15.3%, fever from 10.3% to 1.7%, diarrhea from 5.8% to 0.9%, and acute abdominal pain from 3.4% to 0.6%, except the increase of percentage of patients with no symptoms from 0.3% to 29.9%. In signs, liver enlargement dropped from 94.0% to 42.7%, spleen enlargement from 38.1% to 9.7%, jaundice from 37.5% to 9.0%, ascites from 43.3% to 9.3%, and poor appearance from 38.5% to 8.6% (Table 1).

The most significant changes took place in the composition of tumor stages of the patients. During the past 30 years, percentages of patients at early, middle and late stage have changed from 0.4%, 47.0%, and 52.6% to 29.9%, 51.5%, and 18.6%, respectively. Significant increase of early stage patients and marked decrease of late stage patients have contributed to the improved prognosis of the disease.

The causes of death changed markedly. The percentages of patients who died of liver coma were decreased from 34.9% to 21.8%, of upper gastrointestinal bleeding from 15.1% to 10.9%, and of rupture of hepatoma from 9.0% to 0.3% respectively. But the percentages of patients who died of tumor exhaustion and other reasons unrelated to liver cancer were increased from 39.1% to 51.6%, and from 5.9% to 15.4% respectively, indicating the decrease of complications after therapy and the prolongation of survival time.

In this series, the percentages of patients with positive hepatitis and PLC family history increased from 15.2% to 63.0% and from 3.8% to 9.7% respectively, showing the accuracy in the diagnosis of the two diseases.

### Improvement of diagnosis

AFP testing and mass screening found a batch of patients without symptoms in their early stage.<sup>[12,13]</sup> Comparison with the data of the patients 30 years ago showed a decrease of AFP positive rate ( $> 400 \mu\text{g/L}$ ) from 65.7% to 44.6%, suggesting the progress and wide use of imaging techniques.

Great progress and application of imaging techniques<sup>[14-18]</sup> including CT, MRI and hepatic angiography have increased the positive rate of diagnosis up to 95%. Nuclear scanning was rarely used in this series except 15 patients with a positive rate of 73.4%, which was lower than that of other methods, and also lower than that (89.4%) reported 30 years ago. This may be due to the increase of the percentage of small liver cancer in recent

years.

The percentage of patients examined pathologically increased from 38.1% (1293/3254) to 58.8% (1912/3250) because of the increase of operative patients.

### Improvement of treatment

The increase of early stage patients has been possible to select different therapeutic methods, especially operation. The operative rate has been increased from 6.1% 30 years ago to 46.3% at present ( $P < 0.01$ ). And non-operative patients could receive efficient therapies, such as TACE, HAL, HAI, and radiotherapy.

The 1-, 3-, and 5-year survival rates in the operation group were 88.1%, 62.4%, and 51.6%, in the HAL+HAI group 74.1%, 38.3%, and 28.5%, and in the TACE group 58.4%, 16.8%, and 12.8% respectively. Significant differences were shown between the groups by the Log-rank test. The HAL+HAI group showed a better prognosis than did the TACE group because these patients in their early stage and with better general conditions were suitable for operation.

In our study the three different treatments for middle stage patients showed different prognosis. No significant differences were observed between early stage patients who received surgery, HAL+HAI, or TACE ( $P > 0.05$ ), suggesting the progress of effective non-surgical treatments during these years. Moreover, the 1-, 3-, and 5-year survival rates of the above three treatments which were significantly different in middle stage patients ( $P < 0.01$ ) indicated the need of further study and the superiority of surgery. In this study, the patients who had been treated with PEI were not included. But PEI is an effective local therapy for PLC especially for small tumors.<sup>[19-21]</sup> The newly introduced therapies such as radiofrequency,<sup>[22,23]</sup> microwave,<sup>[24,25]</sup> liver transplantation,<sup>[26,27]</sup> cryosurgery,<sup>[28]</sup> intrahepatic radiation,<sup>[29,30]</sup> and combined therapy<sup>[31]</sup> have been employed, so it is expected to get even better outcome in the near future.

### Improved prognosis of PLC patients

In this series, the overall 1-, 3-, and 5-year survival rates were 66.1%, 39.7%, and 32.5%, respectively, but those of the early-middle group were 93.5%, 70.1%, and 59.1%. The half- and 1-year survival rates were 36.1% and 13.5% which were similar to those (52.5% and 14.7%) of the late stage group, and those patients without treatment.<sup>[32]</sup> The improvement of prognosis for PLC patients is ascribed to early diagnosis, more operative chances, and effective non-surgical therapies including HAL and TACE.

In conclusion, the advances in clinical study of PLC in the past 30 years have been attributed to the improvement of diagnosis and medical service for early stage patients and the decreased number of late stage patients. The increased resection rate and improved non-surgical treatments have prolonged the survival time of

patients. Since PLC is no longer incurable, a few patients can survive for a long period.

### Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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