RESEARCH COMMUNICATION

Hepatocellular Carcinoma: The Role of Screening

Xin-Da Zhou, Zhao-You Tang, Bing-Hui Yang, Bo-Heng Zhang

Abstract

Objective: To determine whether screening can lead to early detection of hepatocellular carcinoma (HCC) and improvement of long-term outcome. Methods: Alpha-fetoprotein (AFP) serosurvey plus ultrasonography have been employed as the principal screening approach for early detection of subclinical HCC. Results: During January 1971-December 1997, 2742 patients with pathologically proven HCC were retrospectively reviewed. Comparison between screening patients(n=1019) and clinical patients(n=1723), revealed the former to have a higher proportion of subclinical stage(74.1% vs 5.3%), a smaller tumor size (<5cm, 52.1% vs 17.8%), a higher proportion of single tumors (71.6% vs 55.4%), a higher proportion of encapsulated tumors(65.5% vs 43.1%), a lower proportion of tumor emboli in the portal vein (6.8% vs 10.8%), a lower r-GTP level (<6 units, 44.5% vs 28.3%), a lower preoperative AFP level(<400ng/ml, 30.0% vs 25.0%), a higher resection rate (81.1% vs 58.0%), a higher radical resection rate(72.4% vs 66.6%), a lower operative mortality rate (2.5% vs 4.8%), a higher postoperative normalization of AFP level (37.5% vs 24.0%) and higher survival rates (5-year, 49.9% vs 32.5%; 10-year, 34.4% vs 24.0%). Conclusions: The significance of the role of screening for HCC is clear. It provides a hopeful chance of cure of HCC, has proven to be an important approach to improve overall prognosis, and has also led to changing concepts in clinical research into HCC.

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Key words: Hepatoma, Screening, Resection, Prognosis

Introduction

Hepatocellular carcinoma (HCC) is one of the world's commonest malignant neoplasms. It is most prevalent in southeast Asia and portions of Africa, and a relatively rare malignancy in the western world. HCC has become the second cancer killer in China(Center of Health Statistics Information, Ministry of Public Health, Peoples Republic of China, 1991). HCC every year causes 315000 deaths in the world and 137000 (43.7%) deaths in China(Parkin et al., 1993). Recent implementation of screening programmes using alpha-fetoprotein(AFP) and ultrasonography in high-risk populations identified increasing numbers of patients with subclinical(asymptomatic) HCC(Chalasami et al., 1999; Shen and Zhou, 1995; Tanikawa, 1993). We previously reported 100 cases of subclinical HCC, 76 cases being discovered by AFP detection during a mass survey, 22 cases by AFP monitoring in subjects with a history of hepatitis, and only two cases clinically. It is especially worth noting that a 5-year survival rate of 72.9% has been achieved after resection of tumors in subclinical patients(Tang, 1985). Recently, we demonstrated that screening a high-risk population for HCC with a serum AFP and real-time ultrasound examination can detect patients in early stages, increase the resection rate and prolong the survival time(Yang et al., 1997). This paper summarizes our data on a large number of patients during the past 27 years, with a comparison between the screening group (n=1019) and the clinical group(n=1723) and a determination of the resectability and long-term survival rates.

Materials and Methods

From January 1971 to December 1997, a total of 2742 patients with pathologically proven HCC were admitted to the Liver Cancer Institute, Zhong Shan Hospital of Shanghai Medical University. The median age of the entire series was 48 years (range, 10-82 years), and the male/female ratio was 8.0:1. The tumors were asymptomatic in 37.2%(1019/2742) and detected by AFP screening and/or ultrasonography either in the natural population in the early years of the study or in a high-risk population in more recent years (screening group).

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The criteria for the high-risk population were defined as having a history of hepatitis, liver cirrhosis and /or serum hepatitis B surface antigen (HBsAg) when aged 35-55 years. A total of 1723 patients (62.8%) were discovered clinically with obvious symptoms and signs (clinical group).

In the screening group, an AFP test and a real-time ultrasound examination were performed about every 6 months. If at the time of screening the AFP was elevated above the normal level (>20ng/ml, radioimmunoassay) and ultrasound revealed no space-occupying lesion in the liver, a more extensive ultrasound examination was performed by a senior physician or a CT examination was performed. If a subject had a positive AFP and the imaging examination did not locate a new mass, this person was followed up closely, until a diagnosis of HCC was confirmed or excluded(Yang et al., 1997).

The liver disease background was noted: 54.8% of the patients (1502/2742) had a history of hepatitis. Of these, 84.2%(1268/1502) had a hepatitis history of more than 5 years. The HCC was coexistent with liver cirrhosis in 78.2% of the patients(2143/2742). Serum HBsAg by reverse passive hemagglutination (RPHA) was observed in 77.1% of patients tested(1858/2411). However, the positive rate for serum anti-hepatitis C virus(HCV) was only 8.2%(31/376). Because not all these clinical background items were consistently available, the numbers in some of the items reported here do not equal the total number of cases.

Pertinent abnormal findings were: AFP(>20ng/ml,) 72.1%(1976/2742) and gamma glutamyl transpeptidase (r-GTP>6U, Orlowski method) 65.7% (1802/2742).

The types of resection employed in the 1825 patients (66.6%) were: limited resection in 1361(74.6%), left lateral segmentectomy in 210(11.5%), left hemihepatectomy in 181(9.9%), left trisegmentectomy in 15(0.8%), right hemihepatectomy in 55(3.0%), and right trisegmentectomy in 3(0.2%). Radical resection was done in 1263 patients(69.2%). Radical resection refers to complete removal of the tumor, with no macroscopically identified tumor emboli in the portal vein, and no tumor residue in the remaining liver tissue or on the cut surface.

Surgical technique: a right subcostal incision is preferred either with an extension cranial to the exiphoid process or with a left extension in a chevron fashion for the resection of a tumor of the left lobe. Right thoracic extension is rarely used. In recent years, intraoperative ultrasound has been used to exclude previously undetected lesions or/ and localize non-palpable tumors situated under the liver surface. For control of bleeding during transection of the hepatic parenchyma, temporary occlusion of the portal pedicle(Pringle's manoeuver) was frequently used in this series. Generally the occlusion time should not exceed 20 min for mild to moderate cirrhosis and 15 min for severe cirrhosis. Repeated occlusion was sometimes needed for a complicated resection with 3-5 min of intervening perfusion. The raw surface of the liver is either sutured side to side to reduce the raw area and to provide a tamponade effect on the smaller vessels, or covered with a piece of momentum or faciform ligament. Adequate drainage is important.

Indications for surgery included patients with compensated liver function, including serum bilirubin below 20mg/dl, prothrombin time above 50% of the normal value, a preserved albumin/globulin ratio, no distant metastasis and a good general condition.

If resection is not indicated, various other surgical modalities, including cryosurgery with liquid nitrogen, hepatic artery ligation or/and hepatic artery cannulation for chemotherapy, microwave and laser treatment can be employed (Zhou et al., 1993; Zhou et al., 1996a; Zhou and Tang, 1998). Chemotherapeutic agents commonly used in this series included cisplatin, adriamycin or epirubicin, mitomycin C, 5-fluorouracil or flurodeoxyuridine. Operative mortality was concluded into death within 30 days of the operation.

A microcomputer was used for the storage, analysis, and statistical treatment of clinical data. Survival rates, excluding the 30-day postoperative deaths, were calculated according to the life table method. Statistical differences were tested by the log rank method.

Results

Treatment

The treatment modalities of 1019 screening cases included resection in 826 cases(81.1%), various surgical operations other than resection(cryosurgery, hepatic artery ligation or / and cannulation, microwave, laser) in 156 cases(15.3%) and conservative treatment because of uncompensated liver function and poor general condition in 37 cases(3.6%). When compared with clinical HCC, screening HCC had a higher resection rate (81.1% vs 58.0%, P<0.01), a higher radical resection rate (72.4% vs 66.6%, P<0.01), and a lower operative mortality (2.5% vs 4.8%, P<0.01). A limited resection (any kind of nonsegment resection) was performed more frequently for patients with screening HCC (84.9% vs 66.1%, P<0.01). (Table l and Table 2)

Laboratory findings

In comparison with clinical HCC, screening HCC had a lower rate for r-GTP level (<6 U, 44.5%, 453/1019 vs 28.3%, 487/1723, P<0.01), and a lower preoperative AFP level(<400ng/ml, 30.0%of patients with positive AFP(228/761) vs 25.0% of patients with positive AFP(304/1215), P<0.01), and a higher postoperative normalization of AFP level (<20ng/ml, 37.5%, vs 24.0%, P<0.01).

Tumor pathology

In comparison with the clinical HCC, screening HCC had a higher incidence of small tumor size (<5cm, 52.1% vs 17.8%, P<0.01), a higher percentage of single-nodule tumors (71.6% vs 55.4%, P<0.01), a higher proportion of well encapsulated tumors (65.6% vs 43.1%, P<0.01), and less tumor emboli in the portal vein (6.8% vs 10.8%, P<0.01). In this series, however, there was no significant difference in the differentiation of cancer cells between screening HCC

Table 1. Therapeutic Patterns with Screening HCC and Clinical HCC

Treatment	Screening HCC (n=1019)(%)	Clinical HCC (n=1723)(%)
Resection	81.1 (826/1019)	58.0 (999/1723)
Surgery other than resection	15.3 (156/1019)	27.5 (474/1723)
Conservative therapy	3.6 (37/1019)	13.9 (239/1723)
No treatment	0	0.6 (11/1723)

HCC: hepatocellular carcinoma
P<0.01

Table 2. Type of Resection for Screening HCC and Clinical HCC

Resection	Screening HCC (n=826)(%)	Clinical HCC (n=999)(%)
Limited resection*	84.9 (701/826)	66.1 (666/999)
Left lateral segmentectomy	10.3 (85/826)	12.5 (125/999)
Left hemihepatectomy	4.1 (34/826)	14.7 (147/999)
Left trisegmentectomy	0.2 (2/826)	1.3 (13/999)
Right hemihepatectomy	0.5 (4/826)	5.1 (51/999)
Right trisegmentectomy	0	0.3 (3/999)
Radical resection**	72.4 (589/826)	66.6 (665/999)
Operative mortality***	2.5 (21/826)	4.8 (48/999)

*Limited resection: any kind of nonsegment resection, P<0.01
**Radical resection: complete removal of the tumor with no macroscopically identified tumor emboli in the portal vein, and no tumor residue in the remaining liver tissue or on the cut surface, P<0.01
***Operative mortality: death within 30 days of the operation, P<0.01

Table 3. Pathological Findings for Screening HCC and Clinical HCC

Characteristics	Screening HCC (n=1019)(%)	Clinical HCC (n=1723)(%)
Tumor≤5cm*	52.1 (531/1019)	17.8 (306/1723)
Single nodule tumor *	71.6 (730/1019)	55.4 (954/1723)
Well-encapsulated tumor*	65.6 (573/874)	43.1 (569/1321)
Tumor emboli in the portal vein*	6.8 (68/999)	10.8 (178/1647)
Edmondson's grade		
I	5.8 (48/821)	3.9 (48/1222)
II	78.9 (648/821)	78.6 (960/1222)
III	15.1 (124/821)	17.1 (209/1222)
IV	0.1 (1/821)	0.4 (5/1222)

*P<0.01

and clinical HCC (see Table 3)

Long-term survival

The overall 1-,3-, 5- and 10-year survival rates were 70.0%, 48.7%, 39.5% and 28.2%, respectively, for the whole series(n=2742). The 1-,3-,5- and 10-year survival rates were 81.7%, 60.2%, 49.9% and 34.4%, respectively, for the screening patients (n=1019), and were 86.6%, 67.5%, 56.4% and 40.4% respectively for the patients who had resection of screening HCC(n=826). When compared with patients with clinical HCC, the survival rates were significantly better: the 1-, 3-, 5- and 10-year survival rates were 62.8%, 41.3%, 32.5% and 24.0%, respectively, for patients with clinical HCC (n=1723, P<0.01) and were 80.4%, 57.3%, 47.0% and 36.1%

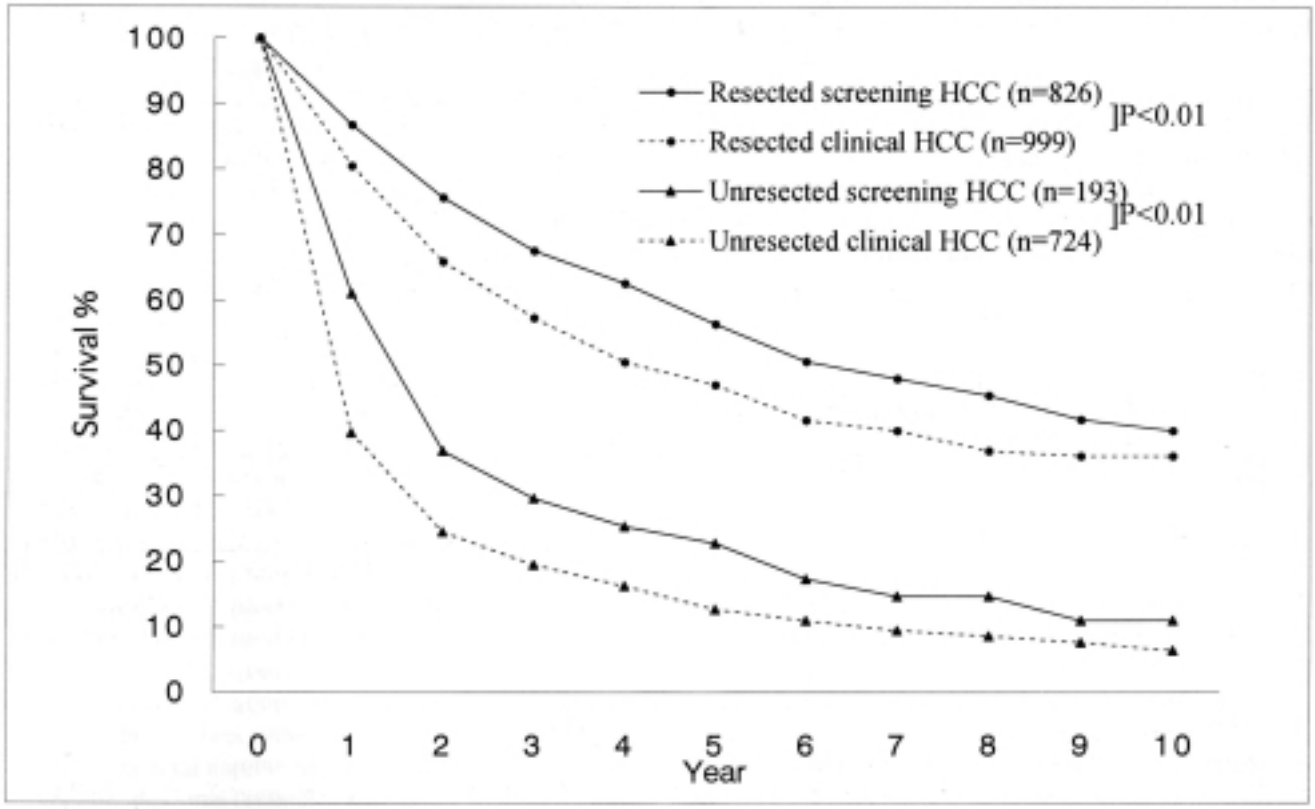

Fig.1. Survival of HCC patients in relation to resection with screening HCC and clinical HCC

respectively for the patients who had resection of clinical HCC (n=999, P<0.01).

Figure 1 illustrates the survival rates in relation to resection in the screening and clinical groups. The difference between the unresected groups was significant (P<0.01). Patients with resected screening HCC also had a significantly better prognosis than those with resected clinical HCC(P<0.01).

Discussion

HCC has long been regarded as a hopeless illness, owing to the great difficulties in early detection and effective treatment. In 1974, 3254 cases with primary liver cancer (PLC) in China were analyzed, with an extremely high proportion of late stage patients(52.6%), an extremely low resection rate (5.3%), and a dismal ultimate outcome(1-year survival, 8.6%)(Tang and Yang, 1974). The discovery of subclinical HCC in the early 1970s, however, has opened new scope for treatment modalities. Recently, rapid progress has been made in clinical research of HCC. Viral hepatitis B or C (particular B type), aflatoxin intake, and contamination of drinking water in rural areas (such as with microcystin-a promotor) are the most common causative factors of HCC in China(Yu, 1995). It was reported that in high-incidence regions, the chance of developing HCC was 160 times greater in hepatitis B virus carriers than in persons not infected with hepatitis B virus(Izzo et al., 1998). In Qidong, a high-incidence area of HCC in China, the detection rate was 38.1/100000 in the natural population. However, it increased to 984.6/100000 in the population with a background of liver disease((Zhu and Lu, 1983). Moreover, it should be emphasized that patients with subclinical HCC usually have AFP levels lower than those found in patients with clinical HCC. In this series, 30.0% of the screening patients with positive AFP had AFP levels lower than 400ng/ml. However, it was 25.0% in the clinical patients with positive AFP.

Studies from areas of the world with a moderate to high incidence of HCC have indicated that real-time transabdominal ultrasonography combined with serum AFP determination is an accurate and relatively inexpensive method to screen chronically infected hepatitis B or C virus patients (Izzo et al., 1998; Liaw et al., 1989; Unoura et al., 1993). Our results are consistent with the findings in these studies that only 74.7% of screening patients(761/1019) had elevated serum AFP levels. Thus, ultrasound is of value for early detection of AFP-negative asymptomatic HCC. Recently, diagnostic accuracy in detecting early stage HCC has been improved with employment of high-resolution abdominal CT scans, CT angioportography, and MRI in patients with borderline ultrasonography findings or AFP elevation.

Screening high-risk populations with ultrasonography and serum AFP levels leads to a diagnosis of resectable HCC in 40% to 60% of the HCC patients(Liww et al., 1989; Unoura et al., 1993). In our series, comparing with clinical HCC, screening HCC had a higher resection rate (81.1% vs 58.0%), a higher radical resection rate(72.4% vs 66.6%), a lower operative mortality rate(2.5% vs 4.8%) and a higher postoperative normalization of AFP level (37.5% vs 24.0%).

We attribute the remarkable decrease in operative death mainly to improvements in liver surgery, including the appropriate evaluation of hepatic functional reserve; better pre-and post-operative management; and new surgical techniques; as well as to earlier diagnosis. Furthermore, limited resections, which were performed widely in the present study (74.6% of the patients, 1361/1825) mainly because most HCC cases were associated with severe cirrhosis, contributed to lowering the operative mortality. At present, these are our indications for liver resection in patients with cirrhosis (Zhou et al., 1992; Zhou et al., 1994a; Zhou et al., 1994b): (1) In the presence of micronodular cirrhosis(cirrhotic nodules <0.3cm), left hemihepatectomy can be performed. However, right hemihepatectomy is justified only when there is no impairment of liver function and the left lobe is hypertrophic. (2) In patients with macronodular cirrhosis(cirrhotic nodules ≥0.3cm), hepatic lobectomy for either lobe is contraindicated. (3) If the cancer-free lobe is macroscopically normal, both right and left hemihepatectomy are indicated. In regard to small HCC in the right lobe in a cirrhotic liver, limited resection is recommended, since right hemihepatectomy involves extensive resection of normal liver parenchyma and higher risk of post-operative liver failure. Shimada also demonstrated that a major hepatectomy in cirrhotic liver is not recommended for patients with solitary small HCC measuring 3 cm or less in diameter (Shimada et al., 1999).

It is generally accepted that survival after resection of asymptomatic HCC is significantly higher than that following resection of clinical HCC. In this series, the 5-year survival was 49.9% in the screening group and 32.5% in the clinical group($P<0.01$), and the 10-year survival was 34.4% in the screening group and 24.0% in the clinical group($P<0.01$).

As we have reported previously(Zhou et al., 1991), factors influencing the long-term prognosis can be mainly summarized into two categories: early detection of asymptomatic HCC(including tumor ≤5cm, single tumor nodule, well-encapsulated tumor, and no tumor emboli in the portal vein) and radical resection. This study supports that opinion: compared with clinical HCC, screening HCC had a higher proportion of tumor size ≤5cm(52.1% vs 17.8%), a higher percentage of single tumor nodules(71.6% vs 55.4%), a higher proportion of well-encapsulated tumors(65.5% vs 43.1%), a lower proportion of tumor emboli in the portal vein (6.8% vs 10.8%) and a higher radical resection rate (72.4% vs 66.6%). Our findings are consistent with those reported in the literature(Tang et al., 1998).

Regarding the cost-benefit of screening in high-risk population for HCC, as we reported previously, it cost RMB 12600 yuan (US$1500) to detect a case of HCC, including the cost of screening, the cost of confirming the diagnosis when it was suspected, and the cost of travel to hospital. The indirect costs were not included because it was too difficult to estimate them (Yang et al., 1997). The cost is much less than reported in Singapore (Kang et al., 1992), Italy (Bolondi et al., 1997) and United States (Larcos et al., 1998)

Conclusions

It is our opinion, from the practical point of view, that in China and possibly in other countries of Asia, an AFP serosurvey plus ultrasonography in a population with a background of liver disease is so far the best approach to detecting asymptomatic small HCC. Resection of such small HCC may result in a favourable long-term outcome.

Problems remaining to be solved include: new tumor markers for early detection of AFP-negative HCC; positive scanning by using isotope-labeled specific antibodies for localization of small HCC; effective conservative treatment of HCC with noncompensated cirrhosis; and measures for preventing the recurrence and metastasis of HCC after radical resection.

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He has been a recipient of many academic awards regarding liver cancer research, including 1st Prize of National Award in 1985, 3rd Prize of National Award in 1991, and 1st Prize of Ministry of State Education Award in 1995. He has attended more than 50 international scientific meetings and given more than 40 lectures at the invitation of institutions in the United States, Europe, Australia, and Asia.