

SUBCLINICAL HEPATOCELLULAR CARCINOMA

Edited by Tang Zhao-you

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To my Teachers
To the Peoples of the World

Foreword

Hepatocellular carcinoma is a relatively rare malignancy in the Western world, but one of the most frequent fatal tumors in the Far East and in sub-Saharan Africa, that means, in the areas where the majority of mankind lives. Until a few decades ago it was mainly detected at autopsy or, far less frequently, at operation. The improvement of imaging methods and the widespread use of liver biopsy have subsequently permitted earlier recognition. Still, it has only been detected when the process was far advanced and frequently only when a palpable mass or dramatic clinical symptoms encouraged thorough clinical investigation. This detection during life led to attempts at surgical removal. Nevertheless, these often far advanced tumors were usually associated with a bad prognosis and a relatively low rate of cure or prolonged survival after operation.

Several factors are responsible for the greater clinical interest in hepatocellular carcinoma in the past decade. The reproduction of the carcinoma in experimental animals has contributed greatly to the increasing interest in the understanding of carcinogenesis in general, although the extensive experimental investigations of these animal carcinomas have had relatively little impact on the clinical management of the tumor. Advancements in surgical techniques have improved the prognosis; transplantation of the liver, however, has so far proven to be of only limited therapeutic value. Chemotherapy of hepatocellular carcinoma with various drugs and various routes of administration has also resulted in some success, though it is so far barely convincing as a widely useful therapeutic modality. The interest in hepatocellular carcinoma has been conspicuously enhanced by the recognition of its relation to hepatitis B virus infection; carriers, of which there are 200 million worldwide, are at particular risk to develop the carcinoma. Cell lines established from hepatocellular carcinoma produce some specific viral antigens, particularly the surface antigen, and integration of hepatitis B viral DNA into the genome of the host has been demonstrated in the tumor, in the surrounding liver, and in carrier livers, but the oncogenicity of the hepatitis B virus is so far not established. Nevertheless, the hope exists that elimination of hepatitis B virus infection by administration of the vaccine and/or hyperimmune globulin may prevent the tumor, thus establishing the causal relation. The relation is

also supported by the observation of hepatitis and hepatocellular carcinoma in animals infected by a virus related to, but different from, the hepatitis B virus. This holds true for the woodchuck and – especially in China – for the duck. However, factors other than hepatitis B virus infection are also incriminated in hepatocellular carcinoma. They include alcohol abuse – particularly in the Western world – and, worldwide aflatoxin, though at present it cannot be excluded that even in these instances, hepatitis B infection plays a contributory role. Other chemical agents that are potent hepatocarcinogens in animals or incriminated in tumors other than the liver seem not to cause hepatocellular carcinoma, whereas sex hormones, metabolic diseases, and the Budd-Chiari syndrome seem to be infrequent causes, and a carcinogenic role of hepatitis non-A, non-B is problematic. Hepatitis B virus infection is therefore the most common factor today in hepatocellular carcinoma, particularly in the Orient and in Africa.

Probably the most compelling reason for the rising clinical interest in hepatocellular carcinoma, however, is the discovery of more or less specific serum markers, some of them oncofetal proteins, with alpha-fetoprotein the most important in practical use today. Although moderate serum elevations may accompany unrelated diseases, for instance those referable to yolk sac disorders, otherwise conspicuous and sustained elevations have permitted screening for hepatocellular carcinoma in earlier stages even if it is not necessarily present in all cases and if some elevations are found in chronic hepatitis. While this screening takes place in many locations, the most extensive and successful such attempt has been made in China. Such screening, together with or supplemented by various imaging techniques (particularly angiography and sonography), has led to the clinical detection of hepatocellular carcinoma in an early stage, before any clinical or even other laboratory abnormalities are evident. This detection of the small tumors in the early stages in Japan, but particularly in China and predominantly in Shanghai, has been rewarded with excellent chances of survival and possibly cure by surgical removal of the carcinoma, at this stage often still single.

These observations and successes have completely altered the clinical outlook in hepatocellular carcinoma and have led to the concept of subclinical hepatocellular carcinoma by the authors of this monograph. This concept represents major progress in the understanding, and particularly the management, of hepatocellular carcinoma, permitting “secondary prevention” at a time when primary prevention by immunization techniques such as vaccine and hyperimmune globulin is still a goal of the future. However, it has not yet been established whether the experiences in the Far East hold true for other parts of the world; in Africa there seems to be a tendency for more rapid growth of the hepatocellular carcinoma with less development of cirrhosis. Sufficient observational data are

not yet available for us to know whether or not this geographical difference is real, or to determine the predominant pattern in Western countries, aside from that in Oriental immigrants.

Nevertheless, this monograph, based on the study of an unusually large amount of material and its thorough laboratory evaluation, and supplemented by Chinese experiences with the basic aspects of the disease, should be of major interest to clinicians as well as to basic science-oriented physicians and other scientists all over the world, including the Western countries. It should assist them in understanding the problem and encourage them to repeat these studies in their own countries. The scientific community is indebted to Dr. Tang for making this information widely available.

New York, November 1984

Hans Popper, MD, PhD

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Abbreviations

AFP	Alpha fetoprotein
AGD	Agar gel diffusion
ALD	Active-stage liver disease
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
anti-HBc	Antibody to hepatitis B core antigen
anti-HBe	Antibody to hepatitis B "e" antigen
anti-HBs	Antibody to hepatitis B surface antigen
CHCC	Clinical hepatocellular carcinoma
CIEP	Countercurrent immunoelectrophoresis
CT	Computed tomography
γ -GTP	Gamma glutamyl transpeptidase
HA	Hepatic angiography
HBcAg	Hepatitis B core antigen
HBeAg	Hepatitis B "e" antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
LDH	Lactate dehydrogenase
OT	Skin delayed hypersensitivity reaction to old tuberculin
PLC	Primary liver cancer
RIA	Radioimmunoassay
RN	Radionuclide imaging
RPHA	Reverse passive hemagglutination
RREA	Radiorocket electrophoresis autoradiography
SCHCC	Subclinical hepatocellular carcinoma
US	Ultrasound, ultrasonography

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Contents

<i>1 Subclinical Hepatocellular Carcinoma – Historical Aspects and General Considerations (Tang Zhao-you)</i> . . .	1
I. Definition	1
A. Subclinical Hepatocellular Carcinoma	1
B. Small or Minute Hepatocellular Carcinoma	1
C. Relationship Between SCHCC and Small HCC	2
II. Historical Aspect	2
A. General History	2
B. History of Study of SCHCC and Small HCC Abroad	3
C. History of Study of SCHCC and Small HCC in China	3
D. Present Status and Latest Trend	4
III. Aim of Studying SCHCC	5
IV. Materials and Methods	6
A. Patients	6
B. Assays Employed for Laboratory Examinations	6
C. Measurements of Immunostatus of Host	6
D. Calculation of Survival Rate	7
E. Storage, Analysis, and Statistical Treatment of Data	7
V. Brief Outline of Study	7
VI. Significance of the Study of SCHCC	9
 <i>2 Early Detection of Subclinical Hepatocellular Carcinoma (Tang Zhao-you, Yang Bing-hui)</i>	 12
I. Discovery of Small HCC and SCHCC	12
A. Autopsy Findings	12
B. Clinical Findings During Operation	12
C. Serial Monitoring of AFP and/or Arteriography in Subjects with Background of Liver Disease	13
D. AFP Survey in Natural and High-Risk Populations	13
E. Measurements Employed for Early Detection	14

XII Contents

II. General Data from Authors' Series of SCHCC	14
III. Significance of AFP Survey	14
A. Marked Change in Clinical Staging Pattern	15
B. Marked Change in Therapy Pattern	16
C. Marked Change in Prognostic Pattern	16
D. The Role of Mass Survey in the Overall Series	16
IV. Factors Influencing Detection Rate in AFP Survey	17
A. Subjects Screened	17
B. Assays Employed	17
C. Interval of AFP Serosurvey	17
V. Key Links in Early Detection of SCHCC	18
A. AFP Serosurvey and Follow-up Study	18
B. Nature of Low and Gradually Increasing AFP	18
C. Renewing Diagnostic Concept	19
VI. Problem Concerning Cost-Effect Relationship	19
A. Pros and Cons	19
B. High-risk Population – Factors Involved	20
VII. Suggestions and Problems to Be Solved	20
 3 <i>New Concepts of Diagnosis of Subclinical Hepatocellular Carcinoma</i> (Tang Zhao-you, Yang Bing-hui)	 22
I. Brief History of Diagnosis of HCC	22
A. Postmortem Diagnosis	22
B. Clinical Diagnosis	22
C. Subclinical Diagnosis	22
II. Comparison of Clinical and Laboratory Findings in SCHCC and CHCC	23
III. Diagnosis of SCHCC by AFP	24
A. AFP Level	24
B. Serial Change in AFP	25
C. Alanine Aminotransferase Level	25
D. Interrelationship Between AFP and ALT Curves	26
E. Diagnostic Criteria of AFP	26
F. Key Link to Further Improvement in Diagnostic Level of SCHCC	27
IV. Role of Other Markers in Diagnosis of SCHCC	27
V. Localization of SCHCC	28
A. Hepatic Angiography	28
B. Ultrasonography	30
C. Computed Tomography	31

D. Radionuclide Imaging	32
E. Comparison of Localization Procedures	33
VI. Problems with Diagnosis of SCHCC	33
 4 <i>Real-Time B-Mode Ultrasonography in Localization of Subclinical Hepatocellular Carcinoma</i> (Xu Zhi-zhang) . .	36
I. Equipment	36
A. High Sensitivity and Low Noise	36
B. Sufficient Gray Scales	37
C. Dynamic Focused Beam Characteristics	
D. Freeze Frame	37
E. Gain Quantification and Decibel Display	37
F. Types of Real-Time B-Scan	38
II. Liver Scanning Techniques	38
A. Preparation and Posture	38
B. Ultrasound Approaches	38
III. Normal Hepatic Ultrasonogram	40
IV. Ultrasonograms of Hepatocellular Carcinoma	42
A. General Presentation of HCC	42
B. Sonograms of Small HCC	46
C. Tumor Localization	46
D. Comparison with Other Studies	47
E. Ultrasonically Guided Percutaneous Liver Aspiration Biopsy in the Diagnosis of HCC	47
F. Portal Vein Invasion	47
V. Differential Diagnosis	48
A. Liver Cirrhosis	48
B. Hemangioma	49
C. Hepatic Adenoma	49
D. Hepatic Abscess	49
E. Carcinoma of the Gallbladder	51
F. Right Adrenal Chromatocytic Tumor (Chromaffinoma)	51
G. Metastatic Liver Tumors	52

5 General Considerations on Treatment of Subclinical Hepatocellular Carcinoma (Tang Zhao-you)	54
I. Evolution in Treatment of HCC	54
II. Changing Therapeutic Pattern	55
A. Proportion of Hepatic Resection in the Overall Series	55
B. Alteration in Proportion of Various Therapeutic Modalities	56
III. Selection of Therapeutic Modality in Management of SCHCC	57
A. SCHCC with Compensated Liver Function	57
B. SCHCC with Noncompensated Liver Function	58
IV. Guidelines on Treatment of SCHCC	58
A. Early Treatment	58
B. Radical Treatment	59
C. Aggressive Treatment	59
D. Multimodality Treatment	60
V. Unsolved Problems	61
6 Surgical Treatment of Subclinical Hepatocellular Carcinoma (Tang Zhao-you)	63
I. Changing Role of Surgery in Treatment of SCHCC	63
II. Indications for Surgery of SCHCC and Preoperative Care	63
A. Indications	63
B. Preoperative Care	65
III. Anesthesia, Transfusion, and Surgical Incision	65
A. Anesthesia	65
B. Transfusion	65
C. Incision	65
IV. Localization of Small HCC During Surgery	66
V. Experience in Surgical Resection of SCHCC	66
A. Approach to Increasing Resectability Rate	67
B. Approach to Decreasing Operative Mortality	70
C. Approach to Further Prolonging Survival After Resection	71
VI. Surgical Management of Nonresectable SCHCC	73
A. Cryosurgery and Laser Beam Vaporization	73
B. Hepatic Artery Ligation or Embolization	73

C. Hepatic Artery Cannulation and Perfusion	73
D. Multimodality Treatment	73
VII. Postoperative Care and Follow-up AFP Monitoring . . .	74
A. Postoperative Care	74
B. Follow-up Studies	74
VIII. Problems to be Solved	75
 7 <i>Factors Influencing Resectability and Resection Survival Rates of Subclinical Hepatocellular Carcinoma</i> (Zhou Xin-da, Tang Zhao-you)	78
I. Clinical Data	78
II. Factors Influencing Resectability Rate	78
A. Single-Factor Analysis of SCHCC	78
B. Multivariate Analysis of HCC	80
C. Discussion	82
III. Factors Influencing Resection Survival Rate of SCHCC	83
 8 <i>Bloodless Hepatectomy and Hepatic Clamp in Resection of Small Hepatocellular Carcinoma</i> (Zhou Xin-da, Tang Zhao-you)	85
I. Bloodless Hepatectomy	85
A. Technique	85
B. Case Reports	87
C. Physiological Monitoring, Biochemical Changes, and Their Management During Surgery	90
D. Changes in Liver Function and AFP After Bloodless Hepatectomy, and Their Management	93
E. Evaluation	95
II. Hepatic Clamp in Resection of Small Hepatocellular Carcinoma	96
A. Instrument	96
B. Operative Technique	97
C. Results	97
D. Evaluation	98

XVI Contents

9 Subclinical Recurrent Hepatocellular Carcinoma: Detection and Reoperation (Yu Ye-qin)	101
I. Subclinical Recurrence Can Be Detected in Time	101
II. Determining the Site of Recurrence and Reoperability	102
III. Criteria for Reoperation	102
IV. Selection of Surgical Procedures	102
V. Clinical Material	102
VI. Critique on Reresection	103
 10 Cryosurgery for Hepatocellular Carcinoma – Experimental and Clinical Study (Zhou Xin-da, Tang Zhao-you, Yu Ye-qin)	107
I. Experimental Study	107
A. Animals and Tumor Models	107
B. Experimental Methods	107
C. Safety of Hepatic Cryosurgery	109
D. Physical Conditions	109
E. Pathological Changes	110
F. Immunological Findings	110
II. Clinical Application	111
A. Indication	111
B. Patients	111
C. Operative Procedure	111
D. Pre- and Postoperative Management	112
E. Postoperative Reactions	112
F. Survival Rates	112
G. Pathological Findings	113
H. Case Reports	113
III. Discussion	116
A. Mechanism of Cryosurgery	116
B. Factors Influencing Freezing Effects	116
C. Safety of Cryosurgery for HCC	117
D. Evaluation of Cryosurgery for HCC	117