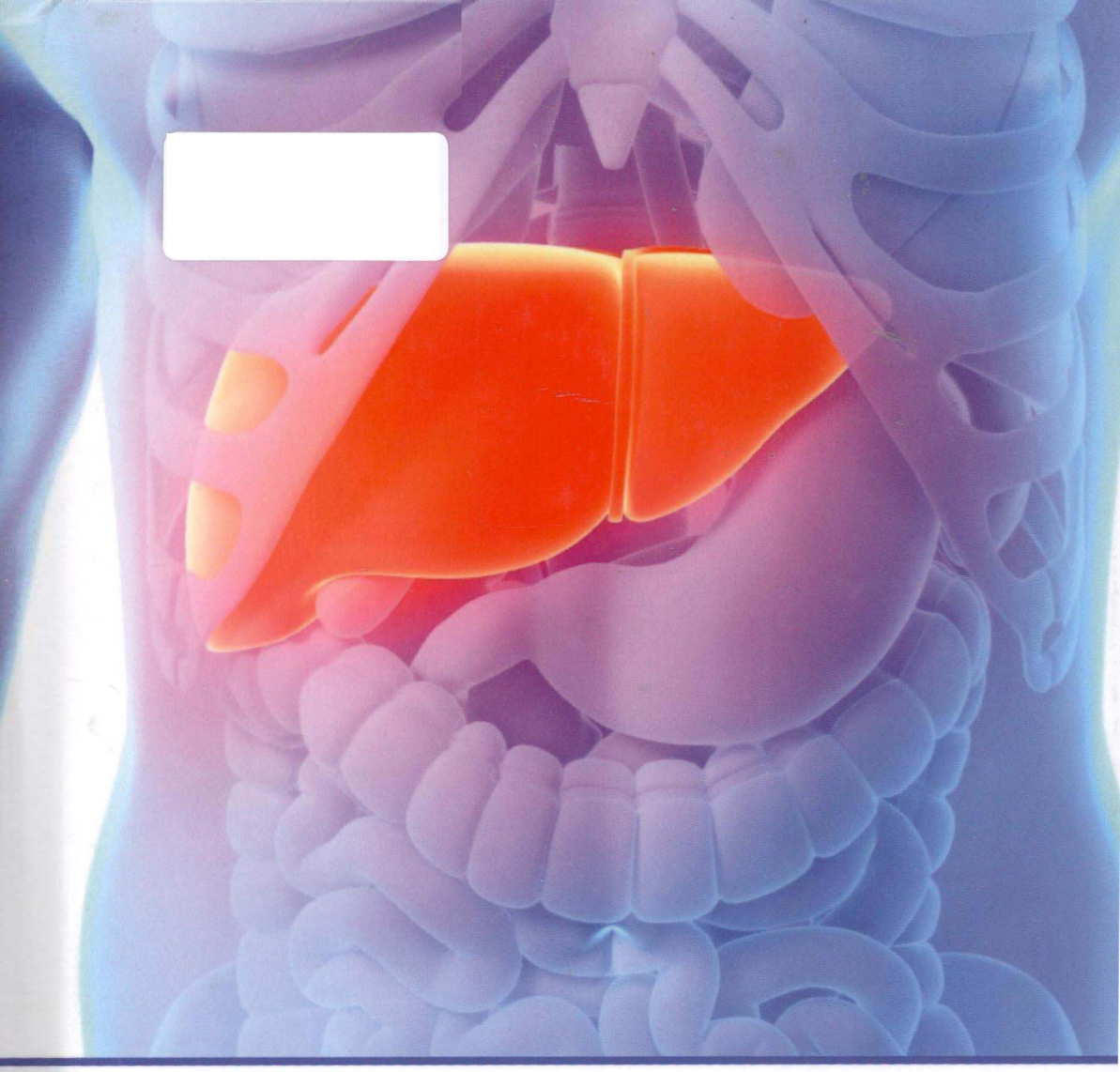

Hepatocellular Carcinoma

Clinical Findings

Jay Amsel

Hepatocellular Carcinoma: Clinical Findings

Edited by **Jay Amsel**

FOSTER ACADEMICS

New Jersey

Published by Foster Academics,
61 Van Reypen Street,
Jersey City, NJ 07306, USA
www.fosteracademics.com

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International Standard Book Number: 978-1-63242-228-6 (Hardback)

Printed in the United States of America.

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Preface

This book aims to highlight the current researches and provides a platform to further the scope of innovations in this area. This book is a product of the combined efforts of many researchers and scientists, after going through thorough studies and analysis from different parts of the world. The objective of this book is to provide the readers with the latest information of the field.

Hepatocellular carcinoma is the most common type of liver cancer and is also known as malignant hepatoma. This book discusses the clinical features of hepatocellular carcinoma. It is a collective effort of experts from around the globe and showcases the most updated information on the clinical characteristics of hepatocellular carcinoma. This book presents major aspects including Differential Diagnosis, Surgical Treatment, and Non-surgical Treatment. It is a well-researched compilation and discusses various important topics like new diagnostic techniques, molecular targeted therapy, transarterial radioembolization, hepatic lesions imitating hepatocellular carcinoma, laparoscopic liver resection and hepatectomy without allogeneic blood transfusion among others. It will play a vital role in providing a reference for the clinical management of patients with hepatocellular carcinoma. This book will cater to professionals involved in treatment and management of hepatocellular carcinoma, as well as hepatologists, liver surgeons, interventional and diagnostic radiologists and pathologists. Medical trainees, hospital managers and also drug producers will find this book helpful as a reference source.

I would like to express my sincere thanks to the authors for their dedicated efforts in the completion of this book. I acknowledge the efforts of the publisher for providing constant support. Lastly, I would like to thank my family for their support in all academic endeavors.

Editor

Contents

Part 1

Diagnosis / Differential Diagnosis

1

Hepatocellular Carcinoma: Epidemiology and Etiology

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1. Introduction

Hepatocellular carcinoma (HCC) is a major public health problem, accounting for about 600,000 deaths in the world in 2004 (WHO, 2008). HCC is the sixth most common cancer worldwide with about 500,000 new cases annually, representing the third largest cause of cancer-related death (Parkin, 2005; Ferlay et al., 2010). A slight decrease in the HCC incidence has been reported in high-rate areas, such as China and Japan (McGlynn et al., 2001). However, a steadily increasing trend has been reported in historically low-rate countries, particularly the United States and some European countries, such as Italy, France, UK and Germany (IARC, 2008a; El-Seragh et al., 2007). In particular, HCC incidence rates doubled in the United States in the period 1985-2002, an earlier age of onset has been observed (with a shift towards 45-60 years old), and HCC has become the fastest growing cause of cancer-related death in men (El-Seragh et al., 2004). Interestingly, it has been reported that in the United States 15-50% of HCC patients had no established risk factors, such as viral hepatitis infections, heavy alcohol consumption or aflatoxin B1 exposure (El-Seragh et al., 2007). Moreover, approximately 10% of all HCC cases in the USA occur in patients with non-cirrhotic livers (Shaw & Shah, 2011). In Europe an analysis of mortality rates from HCC trends in the last 20 years has shown increasing rates for men in 11 countries and for women in 6 countries out of 17 whose data were considered (Bosetti et al., 2008).

The observed increase in the incidence rates of HCC has been concomitant with the obesity epidemic observed in the last 30 years in western countries. Obesity is one of the clinical

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manifestations of metabolic syndrome and, in the last decade, epidemiological and experimental studies have shown that metabolic syndrome and high fat diets are associated with an increased risk of HCC incidence/mortality (Bugianesi 2007; Starley et al., 2010; Welzel et al., 2011). However, other causes may be involved in the increased incidence of HCC and chemical-induced liver carcinogenesis appears to be a less considered etiology. In this chapter, we will review recent acquisitions in epidemiology and experimental studies on HCC and will focus on chemical risk factors and possible new mechanisms of liver carcinogenesis, in particular those concerning metabolic disruption.

2. Chemical risk agents of hepatocellular carcinoma

Most human HCC occurs following viral hepatitis (mainly HBV or HCV) infections or aflatoxin B1 exposure caused by ingestion of contaminated food (IARC 2008a). However, the epidemiological evidence shows that the human liver is susceptible to chemical-induced carcinogenesis (Blonski et al., 2010; Degli Esposti et al., 2009) and the increased incidence of HCC in patients not having established risk factors (El-Seragh et al., 2007) suggests that some underestimated or new but still not recognized risk factors exist (Blonski et al., 2010). In particular, many natural and artificial agents have been shown by experimental or epidemiological studies to induce HCC (Table 1). In this section we will review the chemical risk factors of HCC as emerging from the epidemiological and experimental data.

2.1 Human hepatocarcinogens

Various classes of chemicals are reported to induce HCC in humans: drugs or hormonal therapies (azathioprine, tamoxifen and estrogen-progesteron oral contraceptives) (IARC, 2011); radioisotopes or heavy metals (Plutonium-239, Radium-224, Thorium-232; arsenic in drinking water) (IARC, 2001; IARC, 2004b); complex mixtures of polyaromatic hydrocarbons (PAH) and combustion products (soots and tobacco smoking)(IARC, 1987; IARC, 2004a); organochlorines such as vinyl chloride monomer (VCM) or 2,3,7,8 tetrachloride-dibenzo-para-dioxin (TCDD) (IARC, 2008b, IARC, 1997); and plant derivatives (betel or *Areca catechu*) (IARC, 2004c). Recently, some psychoactive substances, like cannabinoids, have been reported to worsen liver steatosis and fibrosis, in particular in the presence of HCV infections (Hézode et al., 2008, Parfieniuk & Flisiak, 2008). However, no evidence of carcinogenicity has been shown for delta 9-tetrahydrocannabinol (the principal psychoactive ingredient in marihuana) in rats and mice (Chan et al., 1996). More research is warranted to assess the long-term carcinogenic or co-carcinogenic effects of cannabinoids, particularly in the liver, as assumption of them during cannabis smoking may result in cannabinoid exposure for a large population. Finally, recent reviews have focused on a possible underestimation of non-viral causes of HCC (Blonski et al., 2010; Degli Esposti et al., 2009). In particular, metabolic disorders (Non-Alcoholic Fatty Liver Disease (NAFLD), obesity and diabetes), hormonal drugs (oral contraception, tamoxifen), organochlorine compounds, polycyclic aromatic hydrocarbons, tobacco smoking, betel quid chewing and dietary exposures (in particular arsenic in drinking water and aflatoxin B1, a well known hepatocarcinogen) are indicated as important contributing factors for HCC (Blonski et al., 2010; Degli Esposti et al., 2009).

Agents		Human exposure	Evidence of carcinogenicity		References
Category	Type		Humans	Experimental animals	
Natural	1. Aflatoxins	food contaminant (rice, peanuts, etc.)	+	+	Wogan and Newbern 1967; Wogan et al. 1974; Yeh et al. 1985; Olsen et al. 1988; IARC 1993; Soffritti et al. 1988
	2. Alcohol	lifestyle dependent	+		Hakulinen et al. 1974; Adelstein and White 1976; Hirayama 1981; IARC 1988
	3. Hepatitis B virus	blood transfusion	+	+	Snyder et al. 1982; Buendia 1992
	4. Sterigmatocystin	food contaminant (grain, legumes)		+	Purchase and van der Watt 1970
	5. Luteoschirina	food contaminant rice		+	Uraguchi et al. 1972
	6. Cycloclorotina	food contaminant rice		+	IARC 1976
	7. Pyrazolidinic Alkaloids	plants contaminant		+	Swoboda and Reddy 1972
	8. Cycasin	alimentary exposure		+	Laquer et al. 1963
	9. Safrole	flavouring substance		+	Long et al. 1963; Hagan et al. 1965

+ = strong evidence; (+) = limited evidence

Table 1. Agents inducing Hepatocellular Carcinoma based on experimental/epidemiological evidence (Part I)

Agents		Human exposure	Evidence of carcinogenicity		References
Category	Type		Humans	Experimental animals	
Artificial	1. Thorotrast	iatrogenic	(+)	+	Guimares et al. 1955; Commission of European Communities (CEC) 1984
	2. Radioactive colloidal gold	iatrogenic		+	Upton et al. 1956
	3. Gamma radiation	occupational or accidental		+	Upton et al. 1968
	4. Vinyl Chloride	occupational	(+)	+	Gokel et al. 1976; Koischwitz et al. 1981; Evans et al. 1983; Maltoni et al. 1984; Dietz et al. 1985, Pirastu et al. 1990
	5. Benzidine	occupational		+	IARC 1982
	6. 2-Acetylamino-fluorene	occupational		+	Wilson et al. 1941; Teebor and Becker 1971
	7. 4-Diethylamino-azobenzene	occupational		+	Kinosita 1936 Terayama 1967
	8. Dimethyl-nitrosamina	occupational		+	Magee and Barnes 1956
	9. Diethylnitrosamina	occupational		+	Schmal et al. 1960
	10. Steroidal oral contraceptives	iatrogenic	(+)	(+)	Klatskin 1977; Jick and Hermann 1978; IARC 1979
	11. Androgen steroids	iatrogenic	(+)		Johnson et al. 1972

+ = strong evidence; (+) = limited evidence

Table 1. Agents inducing Hepatocellular Carcinoma based on experimental/epidemiological evidence (Part II)

The diversity of chemical agents that induce liver tumors in humans may be at least partially explained by the multiplicity of molecular pathways that have been found altered both in human and animal hepatic tumors (Degli Esposti et al., 2009; Saffroy et al., 2007).